

Deep vein thrombosis

Paul A Kyrle, Sabine Eichinger

Deep vein thrombosis and its sequelae pulmonary embolism and post-thrombotic syndrome are some of the most common disorders. A thrombus either arises spontaneously or is caused by clinical conditions including surgery, trauma, or prolonged bed rest. In these instances, prophylaxis with low-dose anticoagulation is effective. Diagnosis of deep vein thrombosis relies on imaging techniques such as ultrasonography or venography. Only about 25% of symptomatic patients have a thrombus. Thus, clinical risk assessment and D-dimer measurement are used to rule out deep vein thrombosis. Thrombus progression and embolisation can be prevented by low-molecular-weight heparin followed by vitamin K antagonists. Use of these antagonists for 3–6 months is sufficient for many patients. Those with antithrombin deficiency, the lupus anticoagulant, homozygous or combined defects, or with previous deep vein thrombosis can benefit from indefinite anticoagulation. In cancer patients, low-molecular-weight heparin is more effective than and is at least as safe as vitamin K antagonists. Women seem to have a lower thrombosis risk than men, but pregnancy or use of oral contraceptives or hormone replacement therapy represent important risk factors.

Deep vein thrombosis is a clinical challenge for doctors of all disciplines. It can complicate the course of a disease but might also be encountered in the absence of precipitating disorders. Thrombosis can take place in any section of the venous system, but arises most frequently in the deep veins of the leg. Long-term morbidity due to post-thrombotic syndrome is common and can be substantial. The major concern, however, is embolisation of the thrombus to the lung, which can be fatal. Deep vein thrombosis is highly prevalent and poses a burden on health economy. The disorder and its sequelae are also among the best examples of preventable diseases.

This Seminar will focus on deep vein thrombosis of the leg, with special emphasis on new diagnostic and therapeutic strategies. It will also discuss management of the disorder in specific groups of patients, such as women and people with cancer.

Epidemiology

Relevant data for the frequency of deep vein thrombosis derive from large community-based studies because they mainly reflect symptomatic rather than asymptomatic disease. In a systematic review, the incidence of first deep vein thrombosis in the general population was 0.5 per 1000 person-years.¹ The disorder is rare in children younger than 15 years,^{2,3} but its frequency increases with age, with incidence per 1000 person-years of 1.8 at age 65–69 years and 3.1 at age 85–89 years.⁴ Two-thirds of first-time episodes of deep vein thrombosis are caused by risk factors, including surgery, cancer, immobilisation, or admission for other reasons.^{5,6}

In a retrospective hospital discharge dataset,³ the prevalence of deep vein thrombosis was comparable in black (0.69%) and white adults (0.84%). In a British study,⁷ 25% of white and 22% of black people with suspected thrombosis were confirmed to have the disorder. The prevalence of deep vein thrombosis in Asian populations is low.⁸

Risk for first deep vein thrombosis seems to be slightly higher in men than in women.^{6,9} In a population-based cohort study, the age-adjusted incidence of first venous thromboembolism was 1.3 per 1000 person-years in men and 1.1 per 1000 person-years in women.² It is noteworthy that the risk for recurrence of this disorder is higher in men than in women.^{6,10}

Pathophysiology

In 1856, Virchow postulated that damage of the vessel wall, alterations in the flow, and hypercoagulability of the blood are the main causes of thrombus formation. This pathophysiologic notion is still valid today. Venous thrombi are formed in the setting of low flow and low shear stress and mainly consist of fibrin strands, red blood cells, and few platelets. Usually, thrombi form in the valve pockets of calf veins and extend to the proximal veins.¹¹ The raised venous and capillary pressure after thrombus formation increases the transcapillary filtration rate, resulting in oedema. In 50% of patients, venous outflow obstruction subsides within 3 months by lysis and recanalisation.¹² Patients with early oedema are most likely to have residual thrombosis, whereas late oedema is correlated with valvular incompetence.¹²

Search strategy and selection criteria

We searched the National Library of Medicine (PubMed), The Cochrane Library, MEDLINE, and the AMEDEO website. We used the search keyword “deep vein thrombosis” in combination with the terms “prevention”, “diagnosis”, “treatment”, “pregnancy”, or “cancer”. We searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Several recently published review articles were included because they provide comprehensive overviews that are beyond the scope of this Seminar.

Lancet 2005; 365: 1163–74

Medical University of Vienna,
Department of Internal
Medicine I, Währinger Gürtel
18-20, 1090 Vienna, Austria
(Prof P A Kyrle MD,
Prof S Eichinger MD)

Correspondence to:
Prof Paul A Kyrle
paul.kyrle@meduniwien.ac.at

Panel 1: Conditions associated with increased risk for deep vein thrombosis

Advancing age
 Obesity
 Previous venous thromboembolism
 Surgery
 Trauma
 Active cancer
 Acute medical illnesses—eg, acute myocardial infarction, heart failure, respiratory failure, infection
 Inflammatory bowel disease
 Antiphospholipid syndrome
 Dyslipoproteinaemia
 Nephrotic syndrome
 Paroxysmal nocturnal haemoglobinuria
 Myeloproliferative diseases
 Behçet's syndrome
 Varicose veins
 Superficial vein thrombosis
 Congenital venous malformation
 Long-distance travel
 Prolonged bed rest
 Immobilisation
 Limb paresis
 Chronic care facility stay
 Pregnancy/puerperium
 Oral contraceptives
 Hormone replacement therapy
 Heparin-induced thrombocytopenia
 Other drugs
 Chemotherapy
 Tamoxifen
 Thalidomide
 Antipsychotics
 Central venous catheter
 Vena cava filter
 Intravenous drug abuse

Risk for deep vein thrombosis

Panel 1 outlines clinical factors that are associated with increased risk for deep vein thrombosis. Some of these sources of risk are discussed below.

Surgery

Thrombotic risk depends on the type of surgery and presence of additional risk factors. Procedures with an especially high risk are orthopaedic surgery, major vascular surgery, and neurosurgery.¹³ Advancing age, obesity, previous thrombosis, cancer, or comorbid medical disorders increase the likelihood of postoperative thrombosis (table 1).^{14–16} Risk for thrombosis persists over several months post-surgery. In a clinical outcome study of patients undergoing major orthopaedic surgery,¹⁷ the 3-month incidence of symptomatic venous thromboembolism was 3·2% and of fatal pulmonary embolism, 0·1%.

Trauma

Major injury confers about a 50% risk for venographically proven deep vein thrombosis. Risk for thrombosis is high in patients with spinal injuries (62%), pelvic fractures (61%), or leg fractures (80%),¹⁸ and it is low (19%) in people with lower limb plaster casts.¹⁹

Acute medical disorders

In outpatients and people admitted with acute medical disorders, risk for thrombosis is comparable with that for general surgery. Myocardial infarction, acute heart or respiratory failure, and acute infections confer the greatest risk. Risk is increased by other factors, including advanced age, bed rest, or previous deep vein thrombosis.^{20–23}

History of deep vein thrombosis

In patients with first spontaneous deep vein thrombosis, the annual likelihood of recurrence is 5–15%, with a cumulative recurrence rate of about 25% after 4 years.²⁴ Risk is low in patients with postoperative deep vein thrombosis.²⁴

Antibodies against phospholipids

Antibodies against phospholipids, such as the lupus anticoagulant or antibodies directed against cardiolipin or β_2 glycoprotein I, interact with phospholipids or plasma proteins bound to an anionic surface. The prevalence of antibodies against phospholipids in unselected patients with deep vein thrombosis is about 5%.²⁵ Whereas the lupus anticoagulant confers a tenfold increased risk for

	Deep vein thrombosis		Pulmonary embolism	
	Calf	Proximal	Clinical	Fatal
Low risk (minor surgery in patients <40 years with no additional risk factors)	2%	0·4%	0·2%	<0·01%
Moderate risk (minor surgery and additional risk factor; surgery in patients age 40–60 years with no additional risk factors)	10–20%	2–4%	1–2%	0·1–0·4%
High risk (surgery in patients >60 years, or age 40–60 years with additional risk factors (previous venous thromboembolism, cancer, thrombophilia)	20–40%	4–8%	2–4%	0·4–1·0%
Highest risk (surgery in patients with multiple risk factors [age >40 years, cancer, previous venous thromboembolism]; hip or knee arthroplasty, hip fracture surgery; major trauma—spinal-cord surgery)	40–80%	10–20%	4–10%	0·2–5%

Modified from reference 16 with permission of the American College of Chest Physicians.

Table 1: Risk for venous thromboembolism in surgical patients without prophylaxis

first thrombosis^{26,27} and is a risk factor for recurrence,^{26,28} the association between anticardiolipins and deep vein thrombosis is weak. Only high titres of the G isotype are thrombogenic.^{26,27} The relevance of raised amounts of antibodies directed against $\beta 2$ glycoprotein I is uncertain.²⁹

Thrombophilia

Several distinct abnormalities in the coagulation system are associated with increased risk for deep vein thrombosis (panel 2). These defects are generally inherited and can be detected in about 50% of patients with first spontaneous thrombosis. Many patients have more than one risk factor, and combined defects further enhance the risk. Risk for deep vein thrombosis can increase when patients with thrombophilia are exposed to temporal risk conditions such as surgery or trauma. Aspects on thrombophilia and women's health issues, such as pregnancy or oral contraception, are addressed later in this Seminar.

Factor V Leiden

Factor V Leiden results from a point mutation in the factor V gene, which renders the protein resistant to degradation by activated protein C.³⁰ The prevalence of heterozygous factor V Leiden in white populations is 5–8%.³¹ Factor V Leiden is reported in 12–30% of patients with spontaneous deep vein thrombosis,^{32,33} and it confers a sevenfold risk for thrombosis in heterozygotes and an 80-fold risk in homozygotes.^{34,35} Factor V Leiden is not a risk factor for recurrent deep vein thrombosis.³³

Factor II G20210A

A transition at nucleotide 20210 in the 3' untranslated region of the prothrombin gene increases risk for deep vein thrombosis by unknown mechanisms. Carriers of the mutation have higher prothrombin concentrations than do non-carriers.³⁶ In white populations, prevalence of the nucleotide transition is 0.7–4.0%.³⁷ The mutation is reported in 7–18% of patients with spontaneous deep vein thrombosis, and it confers a 2.8-fold risk for the disorder in heterozygotes.^{36,38} Heterozygous carriers have a moderately enhanced risk for recurrent deep vein thrombosis.^{10,39}

Natural inhibitor deficiencies

Antithrombin is a potent inhibitor of several coagulation proteases. The frequency of antithrombin deficiency is rare in the general population (1 per 250–500 individuals)⁴⁰ and is less than 1% in unselected patients with venous thromboembolism.²⁵ Antithrombin deficiency confers a more than eightfold risk for deep vein thrombosis in an individual's lifetime and enhances risk for thrombosis during temporary risk conditions (such as surgery).^{41,42}

Protein C is a vitamin K-dependent glycoprotein that

Panel 2: Thrombophilia

Factor V Leiden
Factor II G20210A
Natural inhibitor deficiency
High factor VIII, factor IX, or factor XI
Lupus anticoagulant
High thrombin activatable fibrinolysis inhibitor
Hyperhomocysteinaemia
Dysfibrinogenaemia or hyperfibrinogenaemia
Plasminogen deficiency

circulates as a proenzyme and, on activation by thrombomodulin, inhibits factors V and VIII. Protein C deficiency arises in 1 per 200–500 people in the general population and in 3.2% of unselected patients with venous thromboembolism.^{25,43} Heterozygous protein C deficiency confers a sevenfold increased risk for deep vein thrombosis.⁴⁴

Protein S is a vitamin K-dependent glycoprotein and a cofactor for protein C. The estimated prevalence of familial protein S deficiency is between 0.03% and 0.13% in the general population.⁴⁵ This deficiency was reported in 7.3% of unselected patients with deep vein thrombosis, and it confers a more than eightfold lifetime risk for thrombosis.^{25,41}

High clotting factor levels

Raised concentration of factor VIII (>150 IU/dL), factor IX (>129 IU/dL), or factor XI (>121 IU/dL) is an independent risk factor of first spontaneous deep vein thrombosis, with adjusted odds ratios of 4.8, 2.8, and 2.2, respectively.^{46–48} The mechanisms by which increased amounts of clotting factors cause thrombosis are unclear. Whether high clotting-factor concentrations are related to a genetic background is unknown. High factor VIII (>234 IU/dL) is a potent risk factor for recurrence of thrombosis,⁴⁹ whereas risk for recurrence is moderately increased in patients with high amounts of factor IX or XI.^{50,51}

Mild hyperhomocysteinaemia

Hyperhomocysteinaemia is caused by genetic defects, most typically homozygosity for a thermolabile mutant of methylenetetrahydrofolate reductase, nutritional deficiencies in vitamin cofactors (folic acid, vitamin B6, vitamin B12), renal function impairment, or drugs.⁵² Mild hyperhomocysteinaemia is seen in about 25% of patients with deep vein thrombosis.⁵³ It confers a two to threefold increased risk for first thrombosis and is a risk factor for recurrence (relative risk 2.7).^{53,54}

Primary prevention

Primary thromboprophylaxis is effective in reducing the occurrence of symptomatic and asymptomatic deep vein thrombosis in both medical and surgical patients.^{20,55}

Prophylaxis can be achieved by physical methods (postoperative early ambulation, graduated compression stockings, or intermittent pneumatic compression) or with anticoagulant drugs (unfractionated heparin, vitamin K antagonists, low-molecular-weight heparin, or fondaparinux). Whereas physical methods alone are indicated in low-risk patients and in those with contraindications to anticoagulants, individuals at moderate-to-high risk for thrombosis need anticoagulation. Unfractionated heparin and vitamin K antagonists are inconvenient for both patients and medical staff because of frequent injections and laboratory monitoring. Thus, low-molecular-weight heparin is the drug of choice.

Low-molecular-weight heparin is effective and safe in both medical and surgical patients.¹⁶ Medical patients admitted for severe heart or respiratory failure, or those bedridden with an additional risk factor such as cancer, previous venous thromboembolism, sepsis, or acute neurological disease, should receive low-molecular-weight heparin at a prophylactic dose—eg, enoxaparin 40 mg daily or dalteparin 5000 U daily.^{16,20,21} Surgical patients with a moderate or high thrombosis risk also need low-molecular-weight heparin at a prophylactic dose.¹⁶ A high prophylactic dose of this drug (eg, enoxaparin 40 mg daily or dalteparin 5000 U daily) should be given to individuals after elective spine surgery or neurosurgery and to high-risk patients with arthroscopy, laparoscopy, major trauma, and before long-distance travel.¹⁶

In individuals undergoing major orthopaedic surgery, fondaparinux (an indirect factor Xa inhibitor) 2.5 mg daily, started 6 h after surgery, is an effective alternative to low-molecular-weight heparin.⁵⁶ In orthopaedic patients, beginning low-molecular-weight heparin 6–8 h after surgery is as effective and at least as safe as a preoperative start.^{57,58} After total hip replacement, continuing low-molecular-weight heparin prophylaxis for up to 35 days is recommended since it greatly reduces occurrence of symptomatic venous thromboembolism without increasing the bleeding rate.⁵⁹ In a randomised study,⁶⁰ fondaparinux for 28 days, compared with fondaparinux for 7 days followed by placebo, safely reduced the rate of symptomatic venous thromboembolism in patients after hip fracture surgery.

Melagatran, a direct thrombin inhibitor, has been licensed in some European countries. This drug, given subcutaneously before and after surgery followed by oral ximelagatran, was more effective but less safe than preoperative enoxaparin.^{61,62} Conversely, melagatran started postoperatively was as safe as preoperative enoxaparin but less effective.⁶³ In knee arthroplasty, ximelagatran is at least as effective as warfarin, with a comparable bleeding risk.^{64,65}

Diagnosis

In patients with suspected deep vein thrombosis, accurate diagnosis is mandatory: an untreated thrombus can result

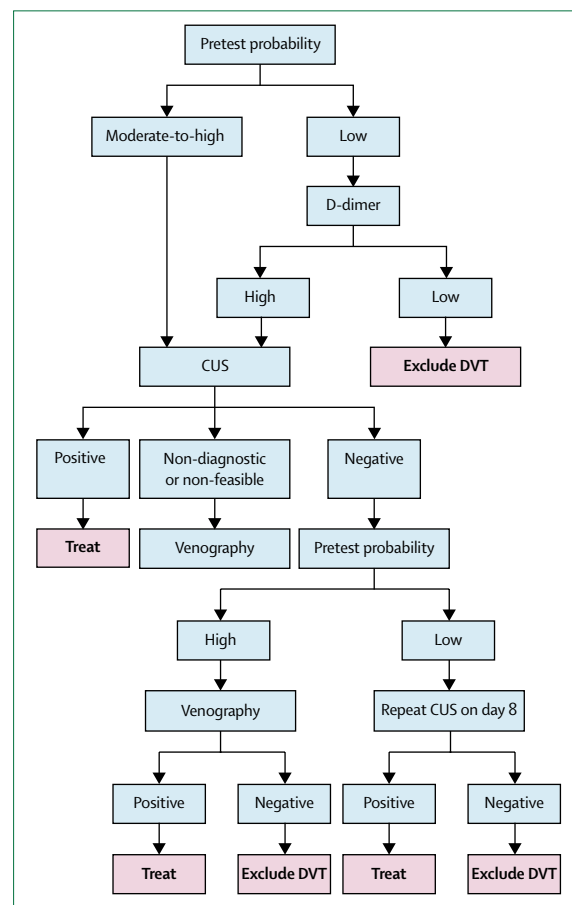


Figure 1: Procedure to safely exclude deep vein thrombosis^{66,67}
CUS=compression ultrasonography. DVT=deep vein thrombosis.

in fatal pulmonary embolism, whereas anticoagulation in the absence of thrombosis is irresponsible. Little consensus exists in published work about the best diagnostic strategy. Since only a quarter of patients with suspected deep vein thrombosis actually have the disease, our diagnostic strategy is to safely rule out thrombosis by non-invasive, rapid, and cost-effective methods. To achieve this goal, we combine clinical assessment, laboratory studies, and imaging techniques (figure 1).^{66,67}

Clinical assessment

Assessment of the pretest probability, based on physical examination and medical history, is the first step when deep vein thrombosis is suspected. Patients can be stratified into categories of low, intermediate, or high probability either by standardised prediction rules or by empirical methods (table 2).⁶⁸ Assessment of the pretest probability is affected by many alternative diagnoses, which raises concern about the reliability of the assessment when undertaken by less experienced medical staff. An extensive overview shows that the clinical prediction rules can be accurately applied in inpatients and outpatients by medical staff of various

degree of training,⁶⁹ and simplified models have been successfully validated in emergency departments.⁷⁰

Laboratory studies

Because of its high sensitivity, measurement of D-dimer (a fibrin split product) has gained a prominent role as a rapid, simple, and inexpensive test for ruling out acute deep vein thrombosis.⁷¹ Published work does not support the use of D-dimer as a stand-alone test.⁷² The predictive value of negative D-dimer is, however, greatly improved if the results are used as part of a diagnostic algorithm.⁷³ A negative D-dimer together with a low clinical probability safely rules out acute deep vein thrombosis. In a randomised study,⁶⁶ 0.4% of patients with a low pretest probability and a negative D-dimer had confirmed venous thromboembolism during 3-month follow-up. The diagnostic strategy for assessment of patients with suspected deep vein thrombosis based on pretest probability and D-dimer is safe and feasible in emergency departments.⁷⁴ However, D-dimer concentrations can be raised in various situations, such as inflammation, surgery, or cancer, which limits its usefulness in inpatients.

Imaging techniques

Contrast venography is the most sensitive and accurate test for diagnosis of deep vein thrombosis and is regarded as the gold standard. Because venography is invasive and has potential contraindications, it should be reserved either for patients with negative non-invasive tests and high clinical probability or for those in whom non-invasive tests are equivocal or non-feasible.

Compression ultrasonography is the most useful initial imaging test. Full compressibility of either of the femoral and popliteal veins excludes proximal deep vein thrombosis. Compared with venography, ultrasonography has a sensitivity of 97–100% and a specificity of 98–99% for detection of proximal thrombosis.^{75,76} The rate of venous thromboembolism in patients with a negative ultrasonography result was 0.7% during 6-month follow-up, indicating that few thromboses were missed and that anticoagulation can be safely withheld.⁷⁷

Ultrasonography is less accurate in diagnosis of distal (calf vein) thrombosis. The lower sensitivity (about 70%) carries a risk for false-negative results, whereas the low specificity (about 60%) can result in over-treatment. Non-extending distal deep vein thrombosis is rarely complicated by pulmonary embolism, and extension to the proximal veins after 1 week is unusual. Hence, non-invasive diagnostic strategies combining clinical assessment, D-dimer testing, and serial ultrasonography can safely be applied in patients with distal thrombosis. A low pretest probability together with a negative D-dimer excludes deep vein thrombosis. If results are conflicting then ultrasonography is done. If the result is negative, anticoagulation can be withheld and ultrasonography is repeated after 1 week. At that time,

Clinical feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the legs and feet	1
Recently bedridden >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 3 cm greater than asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (confined to the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	-2

For patients with symptoms in both legs, the most symptomatic leg is used. Modified from reference 68 with permission of Schattauer Publishers.

Table 2: Standardised prediction rule for assessing pretest probability of acute deep vein thrombosis

extension of the thrombus can be detected in about 2% of patients.^{67,77,78}

Recurrent deep vein thrombosis

Clinical assessment of recurrent ipsilateral deep vein thrombosis is hampered by the similarity between symptoms of post-thrombotic syndrome and acute deep vein thrombosis. Negative D-dimer might be helpful to rule out recurrent thrombosis, although this strategy has been assessed in only one study.⁷⁹ Use of ultrasonography is limited because abnormalities in the proximal veins are reported in about 50% of patients 1 year after first deep vein thrombosis and because comparison with previous ultrasonography results is needed.⁸⁰

Diagnosis of recurrent deep vein thrombosis requires the detection of a new non-compressible segment by ultrasonography. If the result of this test is non-diagnostic, or if there is high clinical probability and a negative finding on ultrasonography, venography should be done. Unequivocal diagnosis of recurrent thrombosis is not possible in many patients. Results of studies assessing alternative diagnostic methods such as magnetic resonance venography or CT are awaited.

Treatment

Figure 2 outlines a suggested protocol for treatment of deep vein thrombosis.

Initial treatment

Firm evidence is available that fixed-dose, weight-adjusted, subcutaneous low-molecular-weight heparin is at least as effective and safe as unfractionated heparin given as an intravenous bolus followed by continuous infusion at a dose that prolongs the activated partial thromboplastin time at least 1.5 times the control value.^{81,82} Compared with unfractionated heparin, low-molecular-weight heparin has a more predictable dose-response relationship (which obviates the need for laboratory monitoring), has a longer half-life (which allows once-daily or twice-daily administration), and confers a lower risk for immune-mediated thrombocytopenia⁸³ or osteoporosis.⁸⁴ Once-daily low-molecular-

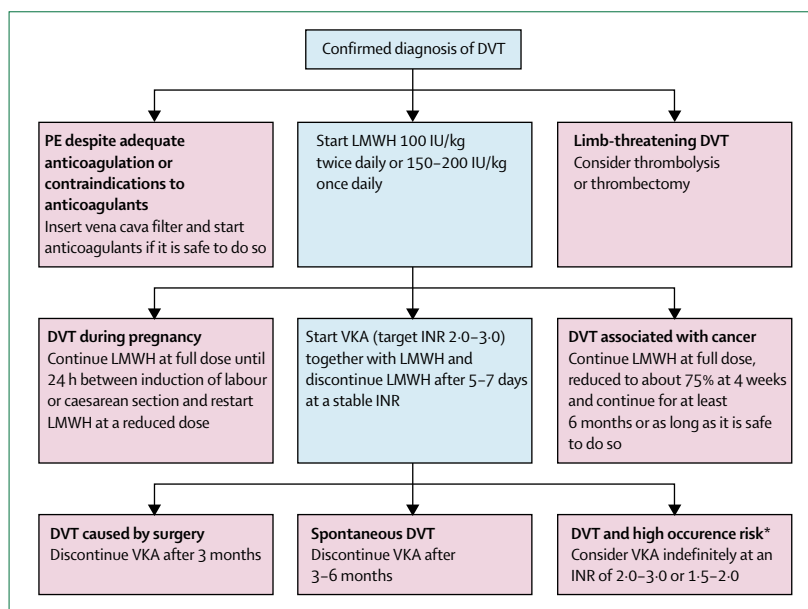


Figure 2: Suggested treatment protocol for deep vein thrombosis

DVT=deep vein thrombosis. PE=pulmonary embolism. LMWH=low-molecular-weight heparin. VKA=vitamin K antagonist. INR=international normalised ratio. *Includes antithrombin deficiency, presence of the lupus anticoagulant, homozygous or combined defects, more than one episode of spontaneous deep vein thrombosis.

weight heparin at a dose of 150–200 U/kg antifactor Xa is as effective and safe as twice-daily 100 U/kg antifactor Xa.⁸⁵ Monitoring antifactor Xa activity 4 h after injection can be useful in patients with impaired renal function and in severely obese individuals.⁸⁶ Low-molecular-weight heparin is also safe and effective in the outpatient setting, even for patients with proximal deep vein thrombosis.^{87,88} Treatment with this drug is cost effective because it reduces the length of admission and eliminates need for laboratory monitoring.^{81,89,90} Because of its shorter half-life, unfractionated heparin might be useful in surgical patients with deep vein thrombosis in whom rapid reversal of anticoagulation is necessary.

Venous thrombi can be dissolved by thrombolytic drugs given either systemically or directly onto the thrombus via local catheter-directed infusion. Thrombolytic therapy diminishes pain and swelling and prevents destruction of the venous valves. Whether it can lower the incidence or severity of post-thrombotic syndrome is uncertain. Compared with standard anticoagulation, thrombolytic therapy confers an increased bleeding risk.⁹¹ It should, therefore, be reserved for patients with limb-threatening thrombosis and possibly for young patients with major iliofemoral deep vein thrombosis.

In patients with proximal deep vein thrombosis, vena cava filters are effective in preventing the short-term incidence of pulmonary embolism but they do not affect mortality.^{92,93} Vena cava filters are thrombogenic and double the recurrence risk. They should be used selectively in patients with contraindications to anticoagulants, recurrent pulmonary embolism despite

adequate anticoagulation, or chronic thromboembolic pulmonary hypertension. Concurrent anticoagulation should be given if safe to do so. Temporary filters can be useful to cover a surgical procedure when anticoagulation has to be withdrawn.

Long-term prevention

Long-term protection from thrombus progression and recurrence can be accomplished by vitamin K antagonists started simultaneously with heparin as soon as the diagnosis of deep vein thrombosis has been confirmed.^{94,95} Anticoagulation is monitored by the prothrombin time, expressed in terms of the international normalised ratio (INR). The dose is titrated to achieve a ratio between 2.0 and 3.0, a range thought to provide the lowest combined incidence of thromboembolism and bleeding. Heparin can be discontinued after 5–7 days, as long as the ratio is stable and is 2.0 or greater. Low-molecular-weight heparin followed by a 3-month course of vitamin K antagonists prevents recurrence in about 95% of patients and confers a risk for severe bleeding of about 1%.⁹⁶

The optimal duration of anticoagulation is ascertained with the risks for recurrence and for major bleeding, both of which vary individually. Patients with deep vein thrombosis caused by surgery have a low recurrence risk and should receive vitamin K antagonists for 3 months.⁹⁷ Many people with spontaneous thrombosis do not benefit from anticoagulation for longer than 3–6 months.^{98–102} Patients in whom the risk for severe bleeding seems to be outweighed by the likelihood of recurrence might benefit from extended anticoagulation, but studies showing an advantage of long-term therapy in terms of reduction of mortality or morbidity are lacking. Even so, indefinite anticoagulation might be justified in patients with a high risk for recurrence, including those with the lupus anticoagulant, antithrombin deficiency, combined or homozygous defects, or in people with more than one spontaneous episode. The decision about duration of anticoagulant therapy is also affected by patient's preference and risk for bleeding.

In patients with mild hyperhomocysteinaemia, supplementation of vitamin B6, vitamin B12, and folic acid reduces homocysteine concentrations but does not affect recurrence risk.¹⁰³

New treatment strategies

To reduce the recurrence risk without increasing risk for bleeding, new strategies of long-term secondary thromboprophylaxis have been developed. The PREVENT investigators¹⁰⁴ compared low-intensity warfarin (INR 1.5–2.0) with placebo in patients with spontaneous venous thromboembolism who had received conventional-intensity anticoagulation for at least 3 months. After 4 years, symptomatic thrombosis recurred in 15% of patients assigned placebo and in

5.5% of those allocated low-intensity warfarin. Major haemorrhage was rare in both groups. The ELATE investigators¹⁰⁵ compared low-intensity warfarin (INR 1.5–2.0) with conventional-intensity warfarin (INR 2.0–3.0). Recurrence was seen in 4.3% of the low-intensity group and in 1.6% of the conventional-intensity group. The rate of major bleeding was about 2% in both groups. Thus, conventional-intensity warfarin seems to be more effective than low-intensity warfarin. However, the surprisingly low rate of major bleeding recorded in the conventional-intensity warfarin arm might not be accomplished in day-to-day clinical practice. Low-intensity warfarin substantially reduces risk for recurrent deep vein thrombosis, confers a low risk for bleeding, and might, thus, be an attractive option for indefinite anticoagulation.

Several new anticoagulants have been evaluated in phase III trials. In the THRIVE study,¹⁰⁶ ximelagatran was non-inferior to enoxaparin followed by warfarin in preventing recurrence in patients with acute venous thromboembolism (2.0% vs 1.5% at 6 months) and was associated with a favourable outcome with respect to major bleeding (1.3% vs 2.2%) and mortality (2.3% vs 3.4%). In another study,¹⁰⁷ patients with deep vein thrombosis who had completed a 6-month course of anticoagulation were assigned placebo or ximelagatran. At 18 months, the likelihood of recurrence was 12.6% in the placebo group and 2.8% in patients allocated ximelagatran. Major bleeding was very rare in both groups.¹⁰⁷ Ximelagatran can be given orally without laboratory monitoring. In 5–10% of patients, this drug is associated with increased concentrations of liver enzymes. The relevance of this occurrence is unclear.

In a randomised trial,¹⁰⁸ fondaparinux was compared with enoxaparin followed by warfarin in patients with acute deep vein thrombosis. At 3 months, symptomatic venous thromboembolism had recurred in 3.9% of patients assigned fondaparinux and in 4.9% allocated enoxaparin and warfarin. Major bleeding was recorded in about 1% of people in both groups.

Women and thrombosis

Oral contraceptives, pregnancy, and menopause represent special challenges in assessing risk for thrombosis and in diagnosing and treating deep vein thrombosis. Overall risk for thrombosis in oral contraceptive users is about threefold higher than for non-users and is highest during the first year of use.^{109,110} Lowering the oestrogen dose reduces risk for thrombosis.¹¹¹ Preparations containing third-generation progestogens are associated with an increased risk for thrombosis compared with levonorgestrel.¹¹¹ Oral contraceptives enhance thrombosis risk in families with a natural inhibitor deficiency.^{41,112} The identification of factor V Leiden and factor II G20210A led to discussions about the use of oral contraceptives in carriers of these mutations. Although a 20–30-fold

increased risk for thrombosis in heterozygous women with factor V Leiden¹¹³ and a 16-fold enhanced risk in women with the prothrombin mutation¹¹⁴ have been reported during oral contraceptive intake, these numbers have to be set into perspective with the very low absolute risk for deep vein thrombosis in young women.^{1,2,6} Thus, oral contraceptives are not contraindicated a priori in heterozygous women with factor V Leiden without a history of venous thromboembolism.

Hormone replacement therapy during menopause is associated with a two to fourfold increased risk for deep vein thrombosis, and it confers an enhanced recurrence risk.^{110,115}

Pregnancy and the puerperium are associated with a twofold and 14-fold increased risk for first deep vein thrombosis, respectively.¹¹⁶ The frequency of thrombosis is similar during the three trimesters,¹¹⁷ the left leg is more likely to be affected than the right,¹¹⁷ and thrombotic risk is highest after caesarean section.¹¹⁸ In women with thrombophilia, risk for deep vein thrombosis is higher than usual during pregnancy.¹¹⁹

The diagnostic repertoire for deep vein thrombosis is less well studied in pregnant women. Clinical assessment is affected by common symptoms of pregnancy such as leg swelling and pain. The role of D-dimer is limited since—even during uncomplicated pregnancy—its concentrations rise with gestational age.¹²⁰

On suspicion of deep vein thrombosis, we advise clinical assessment with emphasis on the patient's thrombosis and family history. A normal D-dimer in a healthy pregnant woman with a low clinical probability might exclude thrombosis, although this approach is not validated.

Ultrasonography is the diagnostic method of choice. In case of a high clinical probability and non-feasibility of ultrasonography, or equivocal non-invasive tests, venography should be done. After appropriate precautions, the amount of radiation delivered to the fetus is low.¹²¹ Limited ability to diagnose thrombosis in the iliac veins by ultrasonography, insensitivity in the diagnosis of iliofemoral thrombosis by venography in case of lead shielding, and reluctance to use radiation or contrast might be overcome by use of MRI.

For treatment of acute deep vein thrombosis in pregnant women, fixed-dose, weight-adjusted subcutaneous low-molecular-weight heparin is to be preferred over unfractionated heparin. Studies on the duration and intensity of anticoagulation are lacking. We recommend low-molecular-weight heparin at a therapeutic dose throughout pregnancy. It should be discontinued 24 h before induction of labour or caesarean section, restarted at a reduced dose when safe to do so, and continued for a further 6–8 weeks. In women with a very high risk for recurrence, a temporal cava filter might be needed.

The overall risk for recurrence in pregnant women with a history of deep vein thrombosis is fairly low.^{122,123} Recurrence risk is lowest in those without thrombophilia and deep vein thrombosis caused by clinical conditions such as surgery. Women with thrombophilia and venous thromboembolism are at high risk for recurrence.¹²⁴ Prophylaxis with low-molecular-weight heparin during pregnancy is safe.¹²⁵ Therefore, this drug at a high dose is recommended for these women throughout pregnancy. Whether all women with a history of deep vein thrombosis should receive thromboprophylaxis during pregnancy, particularly those with a thrombus caused by another clinical event, is uncertain.

Cancer and thrombosis

The association between cancer and thrombosis is twofold. First, deep vein thrombosis is sometimes the presenting symptom of cancer and, second, thrombosis can arise during the course of malignant disease. In two population-based case series,^{126,127} the standardised incidence—ie, the ratio of the observed number of incident cancers to those expected—at the time of venous thromboembolism or in the first 6–12 months afterwards were 4·4 and 3·0. The risks were especially high for cancers of the liver, pancreas, ovary, and brain. In subsequent years, a persistent increase in risk for cancer remained. The incidence of cancer is higher in patients with spontaneous deep vein thrombosis than in those with thrombosis caused by surgery or trauma.¹²⁸

Although extensive screening for a hidden cancer results in a high diagnostic yield,¹²⁹ studies showing that this approach translates into an improved clinical outcome are lacking. Hence, a simple clinical assessment, consisting of medical history, physical examination, routine laboratory tests, and chest radiography, seem to be sufficient.

Cancer patients have an enhanced risk for deep vein thrombosis, particularly during risk conditions including immobilisation, infection, treatment with antineoplastic drugs, surgery, or insertion of a central venous catheter. Those admitted with an acute medical illness benefit from low-molecular-weight heparin at a high prophylactic dose.¹⁶ In surgical cancer patients, this drug, at a high prophylactic dose, is as effective and safe as unfractionated heparin (5000 U three times daily).¹³⁰ Risk for thrombosis in surgical cancer patients is persistent. In one study,¹³¹ extended thromboprophylaxis reduced the incidence of deep vein thrombosis by two-thirds but most events were asymptomatic or involved the distal veins, and a benefit in terms of mortality was not seen. Further studies are needed before extended prophylaxis can be recommended.

Deep vein thrombosis of the arms arises in up to 30% of cancer patients in whom a central venous catheter has been inserted. The rate of catheter-associated thrombosis was substantially reduced by low-intensity

warfarin or low-dose low-molecular-weight heparin.^{132,133} Two larger studies than these were unable to confirm these results^{134,135} and reported much lower overall rates of deep vein thrombosis. Currently, cancer patients with central venous catheters should not receive routine thromboprophylaxis.

Treatment of acute deep vein thrombosis in cancer patients consists of low-molecular-weight heparin at a therapeutic dose. Secondary thromboprophylaxis with vitamin K antagonists is associated with a high risk for both bleeding and recurrence.¹³⁶ Findings of one study show that extended anticoagulation with low-molecular-weight heparin at a therapeutic dose is more effective and as safe as vitamin K antagonists at conventional intensity.¹³⁷ The optimal duration of secondary thromboprophylaxis is less well defined. Since cancer patients have a high recurrence risk, we treat them with low-molecular-weight heparin for at least 6 months. Those who do not achieve remission could benefit from prolonged anticoagulation.

Post-thrombotic syndrome of the leg

Post-thrombotic syndrome of the leg arises in a third of patients with first proximal deep vein thrombosis who received standard treatment with anticoagulants.^{138,139} Typical symptoms include pain, swelling, and skin changes. Risk factors are recurrence in the ipsilateral leg and possibly proximal thrombosis.¹⁴⁰ The incidence of post-thrombotic syndrome seems to be lower in patients treated with thrombolytic drugs.⁹¹ In most people, the disorder arises within 2 years.²⁴ The incidence is not affected by duration of anticoagulation. Severe post-thrombotic syndrome is infrequent. In a prospective cohort study,²⁴ the cumulative incidence of severe disorder was 8% after 5 years. Results of two prospective trials^{138,139} show that the incidence of post-thrombotic syndrome in patients with first proximal deep vein thrombosis can be reduced by a below-knee graduated elastic compression stocking (30–40 mm Hg at the ankle). Since patients at risk for post-thrombotic syndrome cannot be identified in advance, all patients with deep vein thrombosis should be advised to wear such a stocking during the first 2 years.

Deep vein thrombosis of the arms

Deep vein thrombosis of the arms arises as a complication of central venous catheters due to compression at the thoracic outlet between the first rib and the clavicle, after unusual effort or without an obvious reason (Paget-Schroetter syndrome). Although idiopathic disorder is rare (0·02 per 1000 people per year), the growing use of intravenous access devices increases the incidence of local thrombotic complications.¹⁴¹ Risk is higher than usual in patients with thrombophilia.¹⁴² In a prospective registry, age younger than 67 years, a body-mass index of less than 25 kg/m², and admission were independent predictors of

non-catheter associated deep vein thrombosis of the arms.¹⁴³ This disorder is complicated by symptomatic pulmonary embolism in about 8% of patients and by asymptomatic embolism in about 35%.^{141,144} Within 2 years, a quarter of patients develops post-thrombotic syndrome.¹⁴⁵

Symptoms of deep vein thrombosis of the arms include pain, oedema, and cyanosis in this area of the body. On clinical suspicion, compression ultrasonography is the preferred diagnostic method.¹⁴⁶ The diagnosis is established by visualisation of a thrombus; non-compressibility in a segment of vein in the upper arm (eg, axillary vein, distal subclavian vein) or neck (jugular vein); or both. In case of a suspected thrombus in any other venous segment of the arms, or if ultrasonography is inconclusive or negative despite a high clinical probability, venography should be done.

Although controlled trials are lacking, low-molecular-weight heparin at therapeutic doses (ie, antithrombotic Xa 150–200 U/kg once daily or 100 U/kg twice daily) is the preferred treatment. Catheters should be removed. Other treatment options, such as thrombolysis or thrombectomy, are less well studied and should be restricted to selected patients who might be severely compromised by post-thrombotic syndrome. In patients with underlying venous compression, first rib resection or physical therapy might be considered. In those with idiopathic deep vein thrombosis of the arms, the recurrence risk is about 10% at 5 years.^{142,145} The optimal duration of anticoagulation has not been evaluated. We discontinue vitamin K antagonists after 3 months.

Conflict of interest statement

PAK is an investigator in a study supported by Bayer, is a consultant for AstraZeneca (manufacturer of [x]melagatran), and has received speaker's fees from Aventis (manufacturer of enoxaparin) and Pfizer (manufacturer of dalteparin). SE received speaker's fees from SanofiSynthelabo (former manufacturer of fondaparinux).

Acknowledgments

We thank Michaela Bronhagl for editing of the manuscript. We did not receive funding for writing this Seminar.

References

- Fowkes FJL, Price JF, Fowkes FGR. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. *Eur J Vasc Endovasc Surg* 2003; **25**: 1–5.
- Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb Haemost* 2001; **86**: 452–63.
- Stein PD, Patel KC, Kalra NK, et al. Deep venous thrombosis in a general hospital. *Chest* 2002; **122**: 960–62.
- Kniffin WD, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med* 1994; **154**: 861–66.
- Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med* 2002; **162**: 1245–48.
- Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med* 2004; **117**: 19–25.
- Patel RK, Lambie J, Bonner L, Arya R. Venous thromboembolism in the black population. *Arch Intern Med* 2004; **164**: 1348–49.
- Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. *Am J Cardiol* 2000; **85**: 1334–37.
- Anderson FA, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT Study. *Arch Intern Med* 1991; **151**: 933–38.
- Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med* 2004; **350**: 2558–63.
- Nicolaides AN, Kakkar VV, Field ES, Renney JT. The origin of deep vein thrombosis: a venographic study. *Br J Radiol* 1971; **44**: 653–63.
- Killewich LA, Bedford GR, Beach KW, Strandness DE Jr. Spontaneous lysis of deep venous thrombi: rate and outcome. *J Vasc Surg* 1989; **9**: 89–97.
- White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 2003; **90**: 446–55.
- Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000; **160**: 761–68.
- White RH, Gettner S, Newman JM, Trauner KB, Romano P. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. *N Engl J Med* 2000; **343**: 1758–64.
- Geerts WH, Pineo G, Heit J, et al. Prevention of venous thromboembolism: the 7th ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; **126**: 338S–400S.
- Douketis JD, Eikelboom JW, Quinlan DJ, Willan AR, Crowther MA. Short-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. *Arch Intern Med* 2002; **162**: 1465–71.
- Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994; **331**: 1601–06.
- Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002; **347**: 726–30.
- Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999; **341**: 793–800.
- Leizorovicz A, Cohen AT, Turpie AGG, Olsson CG, Vaitkus PT, Goldhaber SZ, for the PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004; **110**: 874–79.
- Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch Intern Med* 2000; **160**: 3415–20.
- Alikhan R, Cohen AT, Combe S, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. *Arch Intern Med* 2004; **164**: 963–68.
- Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; **125**: 1–7.
- Mateo J, Oliver A, Borrell M, Sala N, Fontcuberta J. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism: results of the Spanish Multicentric Study of Thrombophilia (EMET-Study). *Thromb Haemost* 1997; **77**: 444–51.
- Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood* 2003; **101**: 1827–32.
- Wahl DG, Guillemin F, de Maistre E, Perret-Guillaume C, Lecomte T, Thibaut G. Meta-analysis of the risk of venous thrombosis in individuals with antiphospholipid antibodies without underlying autoimmune disease or previous thrombosis. *Lupus* 1998; **7**: 15–22.
- Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995; **332**: 993–97.

- 29 Galli M, Luciani D, Bertolini G, Barbui T. Anti- β_2 -glycoprotein I, antithrombin antibodies, and the risk of thrombosis in the antiphospholipid syndrome. *Blood* 2003; **102**: 2717–23.
- 30 Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994; **369**: 64–67.
- 31 Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. *Lancet* 1995; **346**: 1133–34.
- 32 Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med* 1995; **332**: 912–17.
- 33 Eichinger S, Weltermann A, Mannhalter C, et al. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. *Arch Intern Med* 2002; **162**: 2357–60.
- 34 Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. *Lancet* 1993; **342**: 1503–06.
- 35 Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma P. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). *Blood* 1995; **85**: 1504–08.
- 36 Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996; **88**: 3698–703.
- 37 Rosendaal FR, Doggen CJ, Zivelin A, et al. Geographic distribution of the 20210 G to A prothrombin variant. *Thromb Haemost* 1998; **79**: 706–08.
- 38 Hillarp A, Zoller B, Svensson PJ, Dahlback B. The 20210 A allele of the prothrombin gene is a common risk factor among Swedish outpatients with verified deep venous thrombosis. *Thromb Haemost* 1997; **78**: 990–92.
- 39 Simioni P, Prandoni P, Lensing AW, et al. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. *Blood* 2000; **96**: 3329–33.
- 40 Tait RC, Walker ID, Perry DJ, et al. Prevalence of antithrombin deficiency in the healthy population. *Br J Haematol* 1994; **87**: 106–12.
- 41 Martinelli I, Mannucci PM, De Stefano V, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. *Blood* 1998; **92**: 2353–58.
- 42 Thaler E, Lechner K. Antithrombin III deficiency and thromboembolism. *Clin Haematol* 1981; **10**: 369–90.
- 43 Tait RC, Walker ID, Reitsma PH, et al. Prevalence of protein C deficiency in the healthy population. *Thromb Haemost* 1995; **73**: 87–93.
- 44 Koster T, Rosendaal FR, Briet E, et al. Protein C deficiency in a controlled series of unselected outpatients: an infrequent but clear risk factor for venous thrombosis (Leiden Thrombophilia Study). *Blood* 1995; **85**: 2756–61.
- 45 Dykes AC, Walker ID, McMahon AD, Islam SI, Tait RC. A study of protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. *Br J Haematol* 2001; **113**: 636–41.
- 46 Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* 1995; **345**: 152–55.
- 47 van Hylckama Vlieg A, van der Linden IK, Bertina RM, Rosendaal FR. High levels of factor IX increase the risk of venous thrombosis. *Blood* 2000; **95**: 3678–82.
- 48 Meijers JC, Tekelenburg WL, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med* 2000; **342**: 696–701.
- 49 Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med* 2000; **343**: 457–62.
- 50 Weltermann A, Eichinger S, Bialonczyk C, et al. The risk of recurrent venous thromboembolism among patients with high factor IX levels. *J Thromb Haemost* 2003; **1**: 28–32.
- 51 Eichinger S, Schönauer V, Weltermann A, et al. Thrombin activatable fibrinolysis inhibitor and the risk of recurrent venous thromboembolism. *Blood* 2004; **103**: 3773–76.
- 52 Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. *Lancet* 1999; **354**: 407–13.
- 53 Eichinger S, Stümpflen A, Hirschl M, et al. Hyperhomocysteinemia is a risk factor of recurrent venous thromboembolism. *Thromb Haemost* 1998; **80**: 566–69.
- 54 den Heijer M, Rosendaal FR, Blom HJ, Gerrits WB, Bos GM. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. *Thromb Haemost* 1998; **80**: 874–77.
- 55 Collins R, Scrimgeour A, Yusuf S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin: overview of results of randomised trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988; **318**: 1162–73.
- 56 Turpie AG, Eriksson BI, Bauer KA, Lassen MR. New pentasaccharides for the prophylaxis of venous thromboembolism: clinical studies. *Chest* 2003; **124**: 371S–78S.
- 57 Strebel N, Prins M, Agnelli G, Buller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med* 2002; **162**: 1451–56.
- 58 Hull RD, Pineo GF, Stein PD, et al. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2001; **161**: 1952–60.
- 59 Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trial. *Lancet* 2001; **358**: 9–15.
- 60 Eriksson BI, Lassen MR, PENTasaccharide in Hip-Fracture Surgery Plus Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2003; **163**: 1337–42.
- 61 Eriksson BI, Agnelli G, Cohen AT, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. *J Thromb Haemost* 2003; **1**: 2490–96.
- 62 Eriksson BI, Bergqvist D, Kalebo P, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet* 2002; **360**: 1441–47.
- 63 Eriksson BI, Agnelli G, Cohen AT, et al. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. *Thromb Haemost* 2003; **89**: 288–96.
- 64 Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind trial. *Ann Intern Med* 2002; **137**: 648–55.
- 65 Francis CW, Berkowitz SD, Comp PC, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 2003; **349**: 1703–12.
- 66 Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003; **349**: 1227–35.
- 67 Tick LW, Ton E, van Voorthuizen T, et al. Practical diagnostic management of patients with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography, and D-dimer test. *Am J Med* 2002; **113**: 630–35.
- 68 Wells PS, Anderson DR, Bormanis J, et al. Application of a diagnostic clinical model for the management of hospitalized patients with suspected deep-vein thrombosis. *Thromb Haemost* 1999; **81**: 493–97.
- 69 Kelly J, Hunt BJ. The utility of pretest probability assessment in patients with clinically suspected venous thromboembolism. *J Thromb Haemost* 2003; **1**: 1888–96.

- 70 Dryjski M, O'Brien-Irr MS, Harris LM, Hassett J, Janicke D. Evaluation of a screening protocol to exclude the diagnosis of deep venous thrombosis among emergency department patients. *J Vasc Surg* 2001; **34**: 1010–15.
- 71 Kelly J, Hunt BJ. A clinical probability assessment and D-dimer measurement should be the initial step in the investigation of suspected venous thromboembolism. *Chest* 2003; **124**: 1116–19.
- 72 Heim SW, Schectman JM, Siadat MS, Philbrick JT. D-dimer testing for deep venous thrombosis: a meta-analysis. *Clin Chem* 2004; **50**: 1136–47.
- 73 Stein PD, Hull RD, Patel KC, et al. D-Dimer for the exclusion of acute venous thrombosis and pulmonary embolism. *Ann Intern Med* 2004; **140**: 589–602.
- 74 Anderson DR, Kovacs MJ, Kovacs G, et al. Combined use of clinical assessment and D-dimer to improve the management of patients presenting to the emergency department with suspected deep vein thrombosis (the EDITED Study). *J Thromb Haemost* 2003; **1**: 645–51.
- 75 Lensing AW, Prandoni P, Brandjes D, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989; **320**: 342–45.
- 76 Quintavalla R, Larini P, Miselli A, et al. Duplex ultrasound diagnosis of symptomatic proximal deep vein thrombosis of lower limbs. *Eur J Radiol* 1992; **15**: 32–36.
- 77 Cogo A, Lensing AW, Koopman MM, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ* 1998; **316**: 17–20.
- 78 Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med* 1998; **129**: 1044–49.
- 79 Rathbun SW, Whitsett TL, Raskob GE. Negative D-Dimer result to exclude recurrent deep venous thrombosis: a management trial. *Ann Intern Med* 2004; **141**: 839–45.
- 80 Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation* 1993; **88**: 1730–35.
- 81 Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. *Ann Intern Med* 1999; **130**: 800–09.
- 82 Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism. *Arch Intern Med* 2000; **160**: 181–88.
- 83 Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention. *Chest* 2004; **126**: 311S–37S.
- 84 Monreal M, Lazo E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. *Thromb Haemost* 1994; **71**: 7–11.
- 85 Van Dongen CJ, Mac Gillavry MR, Prins MH. Once versus twice daily LMWH for the initial treatment of venous thromboembolism (Cochrane Review). *Cochrane Database Syst Rev* 2003; **1**: CD003074.
- 86 Bounameaux H, de Moerloose P. Is laboratory monitoring of low molecular weight heparin therapy necessary? No. *J Thromb Haemost* 2004; **2**: 551–54.
- 87 Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996; **334**: 677–81.
- 88 Koopman MMW, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996; **334**: 682–87.
- 89 Boccalon H, Elias A, Chalé JJ, Cadène A, Gabriel S, for the Vascular Midi-Pyrenees Network Group. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin. *Arch Intern Med* 2000; **160**: 1769–73.
- 90 Segal JB, Bolger DT, Jenckes MW, et al. Outpatient therapy with low molecular weight heparin for the treatment of venous thromboembolism: a review of efficacy, safety, and costs. *Am J Med* 2003; **115**: 298–308.
- 91 Watson LI, Armon MP. Thrombolysis for acute deep vein thrombosis (Cochrane Review). *Cochrane Database Syst Rev* 2004; **3**: CD002783.
- 92 Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med* 1998; **338**: 409–15.
- 93 White RH, Zhou H, Kim J, Romano PS. Population-based study of the effectiveness of inferior vena cava filter use among patients with venous thromboembolism. *Arch Intern Med* 2000; **160**: 2033–41.
- 94 Gallus A, Jackaman J, Tillett J, Mills W, Wycherley A. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. *Lancet* 1986; **2**: 1293–96.
- 95 Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med* 1990; **322**: 1260–64.
- 96 Van den Belt AGM, Prins MH, Lensing AWA, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism (Cochrane Review). *Cochrane Database Syst Rev* 2004; **3**: CD001100.
- 97 Kearon C, Ginsberg JS, Anderson DR, et al. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. *J Thromb Haemost* 2004; **2**: 743–49.
- 98 Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995; **332**: 1661–65.
- 99 Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999; **340**: 901–07.
- 100 Pinede L, Ninet J, Duhaut P, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; **103**: 2453–60.
- 101 Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med* 2001; **345**: 165–69.
- 102 van Dongen CJ, Vink R, Hutten BA, Buller HR, Prins MH. The incidence of recurrent venous thromboembolism after treatment with vitamin K antagonists in relation to time since first event: a meta-analysis. *Arch Intern Med* 2003; **163**: 1285–93.
- 103 Den Heijer M, Willems HPJ, Blom HJ, et al. Homocysteine lowering by B vitamins and the prevention of secondary deep-vein thrombosis and pulmonary embolism: a randomized, placebo-controlled, double-blind trial. *J Thromb Haemost* 2003; **1** (suppl 1): OC 161.
- 104 Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; **348**: 1425–34.
- 105 Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; **349**: 631–39.
- 106 Francis CW, Ginsberg JS, Berkowitz SD, et al. Efficacy and safety of the oral direct thrombin inhibitor ximelagatran compared with current standard therapy for acute symptomatic deep vein thrombosis, with or without pulmonary embolism: the THRIVE treatment study. *Blood* 2003; **102**: 7 (abstr).
- 107 Schulman S, Wahlander K, Lundstrom T, Clason SB, Eriksson H, for the THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003; **349**: 1713–21.
- 108 Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; **140**: 867–73.

- 109 Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. *Arch Intern Med* 2000; **160**: 49–52.
- 110 Rosendaal FR, van Hylckama Vlieg A, Tanis BC, Helmerhorst FM. Estrogens, progestogens and thrombosis. *J Thromb Haemost* 2003; **1**: 1371–80.
- 111 Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ* 2001; **323**: 131–34.
- 112 Simioni P, Sanson BJ, Prandoni P, et al. Incidence of venous thromboembolism in families with inherited thrombophilia. *Thromb Haemost* 1999; **81**: 198–202.
- 113 Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet* 1994; **344**: 1453–57.
- 114 Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. *Arterioscler Thromb Vasc Biol* 1999; **19**: 700–03.
- 115 Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy: results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost* 2000; **84**: 961–67.
- 116 Rosendaal FR. Risk factors for venous thrombosis disease. *Thromb Haemost* 1999; **82**: 610–19.
- 117 Ginsberg JS, Brill-Edwards P, Burrows RF, et al. Venous thrombosis during pregnancy: leg and trimester of presentation. *Thromb Haemost* 1992; **67**: 519–20.
- 118 Greer IA. Prevention of venous thromboembolism in pregnancy. *Best Pract Res Clin Haematol* 2003; **16**: 261–78.
- 119 Friederich PW, Sanson BJ, Simioni P, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. *Ann Intern Med* 1996; **125**: 955–60.
- 120 Eichinger S, Weltermann A, Philipp K, et al. Prospective evaluation of hemostatic system activation and thrombin potential in healthy pregnant women with and without factor V Leiden. *Thromb Haemost* 1999; **82**: 1232–6.
- 121 Ginsberg JS, Hirsh J, Rainbow AJ, Coates G. Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. *Thromb Haemost* 1989; **61**: 189–96.
- 122 Brill-Edwards P, Ginsberg JS, Gent M, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *N Engl J Med* 2000; **343**: 1439–44.
- 123 Pabinger I, Grafenhofer H, Kyrle PA, et al. Temporary increase in the risk for recurrence during pregnancy in women with a history of venous thromboembolism. *Blood* 2002; **100**: 1060–62.
- 124 Simioni P, Tormene D, Prandoni P, Girolami A. Pregnancy-related recurrent events in thrombophilic women with previous venous thromboembolism. *Thromb Haemost* 2001; **86**: 929.
- 125 McColl MD, Greer IA. Low-molecular-weight heparin for the prevention and treatment of venous thromboembolism in pregnancy. *Curr Opin Pulm Med* 2004; **10**: 371–75.
- 126 Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. *Lancet* 1998; **351**: 1077–80.
- 127 Sorensen HT, Mellekjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998; **338**: 1169–73.
- 128 Prandoni P, Lensing AW, Buller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 1992; **327**: 1128–33.
- 129 Monreal M, Fernandez-Llamazares J, Perandreu J, Urrutia A, Sahuguillo JC, Contel E. Occult cancer in patients with venous thromboembolism: which patients, which cancers. *Thromb Haemost* 1997; **78**: 1316–18.
- 130 Mismetti P, Laporte S, Darmon JY, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg* 2001; **88**: 913–30.
- 131 Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002; **346**: 975–80.
- 132 Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters; a randomized prospective trial. *Ann Intern Med* 1990; **112**: 423–28.
- 133 Monreal M, Alastrue A, Ruli M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices—prophylaxis with low molecular weight heparin (Fragmin). *Thromb Haemost* 1996; **75**: 251–53.
- 134 Couban S, Goodyear M, Burnell M, et al. A randomized double-blind placebo-controlled study of low dose warfarin for the prevention of symptomatic central venous catheter-associated thrombosis in patients with cancer. *Blood* 2002; **100**: 2769.
- 135 Reichart P, Kretzschmar A, Biakhov M, et al. A phase III double blind placebo-controlled study evaluating the efficacy and safety of daily low-molecular weight heparin (dalteparin sodium, Fragmin) in preventing catheter-related complications in cancer patients with central venous catheters. *Proc Am Soc Clin Oncol* 2002; **21**: 1474.
- 136 Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; **100**: 3484–88.
- 137 Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **349**: 146–53.
- 138 Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; **349**: 759–62.
- 139 Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004; **141**: 249–56.
- 140 Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med* 2004; **164**: 17–26.
- 141 Bernardi E, Piccioli A, Marchiori A, Girolami B, Prandoni P. Upper extremity deep vein thrombosis: risk factors, diagnosis, and management. *Semin Vasc Med* 2001; **1**: 105–10.
- 142 Martinelli I, Battaglioli T, Bucciarelli P, Passamonti SM, Mannucci PM. Risk factors and recurrence rate of primary deep vein thrombosis of the upper extremities. *Circulation* 2004; **110**: 566–70.
- 143 Joffe HV, Kucher N, Tapson VF, Goldhaber SZ, for the Deep Vein Thrombosis (DVT) FREE Steering Committee. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. *Circulation* 2004; **110**: 1605–11.
- 144 Monreal M, Lafoz E, Ruiz J, Valls R, Alastrue A. Upper-extremity deep venous thrombosis and pulmonary embolism: a prospective study. *Chest* 1991; **99**: 280–83.
- 145 Prandoni P, Bernardi E, Marchiori A, et al. The long term clinical course of acute deep vein thrombosis of the arm: prospective cohort study. *BMJ* 2004; **329**: 484–85.
- 146 Baarslag HJ, Koopman MMW, Reekers JA, van Beek EJR. Diagnosis and management of deep vein thrombosis of the upper extremity: a review. *Eur Radiol* 2004; **14**: 1263–74.