Deep vein thrombosis

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Lancet 2005; 365: 1163–74

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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.

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 β2 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 β2 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 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 thrombolembolism.[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]

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

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 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]

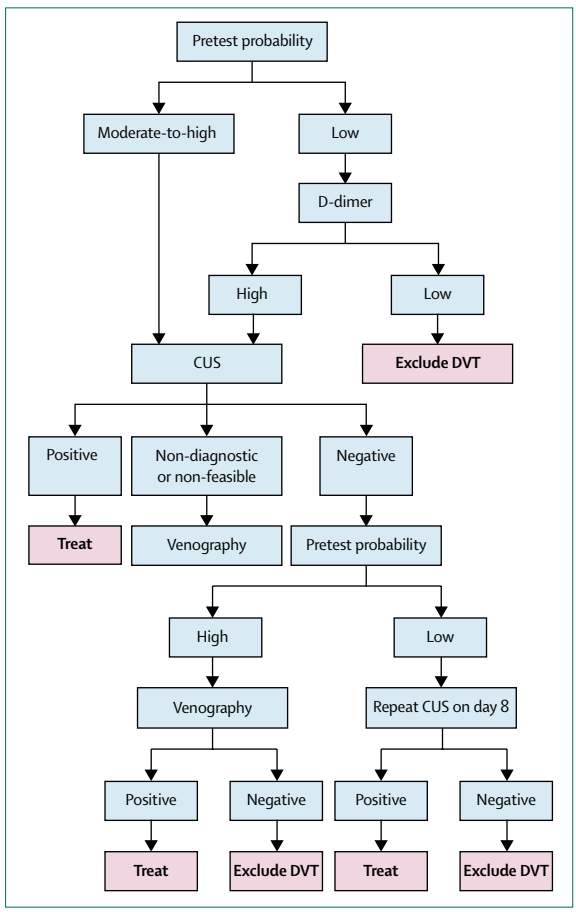

Figure 1: **Procedure to safely exclude deep vein thrombosis**[66,67]
CUS=compression ultrasonography. DVT=deep vein thrombosis.

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, extension of the thrombus can be detected in about 2% of patients.[67,77,78]

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**

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 thrombocytopenia[83] or osteoporosis.[84] Once-daily low-molecular-

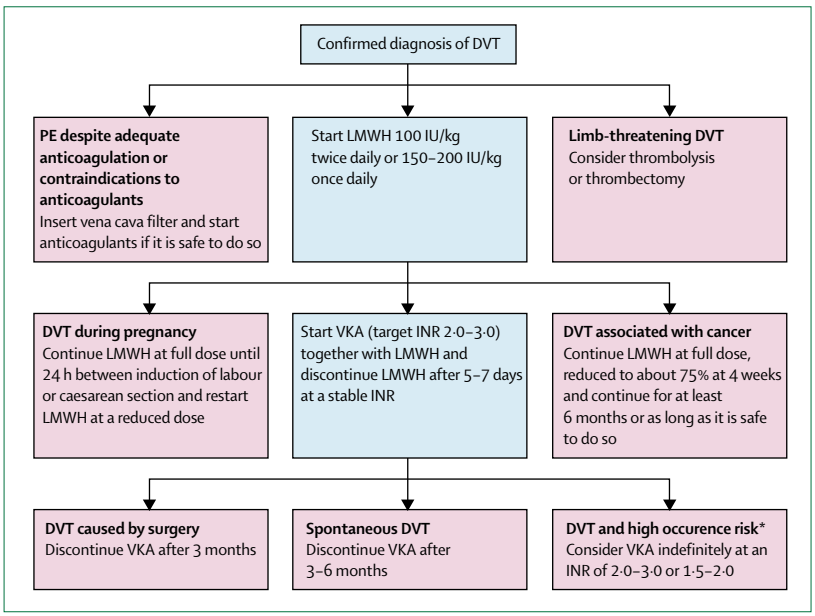

Figure 2: **Suggested treatment protocol for deep vein thrombosis**
DVT=deep vein thrombosis. PE=pulmonary embolism. LMWH=low-molecular-weight heparin. VKA=vitamin K antagonist. INR=international normalised ratio. *Includes antithrombin deficiency, presence of the lupus anticoagulant, homozygous or combined 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 investigators[104] 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 investigators[105] 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 Leiden[113] and a 16-fold enhanced risk in women with the prothrombin mutation[114] 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/m^2, 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, antifactor 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 [xi]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.

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