Strategies to reduce the burden of venous thromboembolism

Venous thromboembolism (VTE) is a serious and potentially fatal illness. It affects not only hospitalized patients and those undergoing major surgery, but also patients not admitted to hospital and otherwise healthy ambulatory individuals.[1-4] VTE produces few specific symptoms and its diagnosis remains a challenge;[5] the first clinical presentation may be fatal pulmonary embolism (PE). Furthermore, undetected deep-vein thrombosis (DVT) may lead to long-term morbidity from post-thrombotic syndrome, and places patients at risk of recurrent DVT.[6]

Deep-vein thrombosis and PE are viewed in the medical literature as different clinical manifestations of the same disease – VTE. In this review we discuss methods for diagnosing VTE, and outline current recommendations for prophylaxis and treatment. However, current management of patients with VTE is suboptimal since, despite the existence of a wide range of therapies for the prevention or treatment of this disease, a significant proportion of patients still suffer thrombotic complications. This may be due to underutilization of prophylaxis in patients at risk and the generally silent nature of the disease, but also to inadequate antithrombotic therapies. There is a need for new anticoagulant agents with better efficacy and safety profiles to reduce the morbidity and mortality associated with this common yet preventable disease.

Epidemiology

Venous thromboembolism (VTE) can be viewed as a spectrum of disorders ranging from a localized clot in a peripheral vein to a massive pulmonary embolism (PE).[7] In the same way that myocardial infarction, stroke and limb gangrene can represent the serious and often fatal consequences of underlying atherosclerotic peripheral arterial disease, the major complications of venous thrombosis are PE and post-thrombotic syndrome.[8]

VTE is the third most common cardiovascular disease after acute ischemic syndromes and stroke.[9] Each year, venous thrombosis occurs in about 1 in 1000 people in developed countries,[10-12] but the incidence is likely to be much higher because many patients with VTE remain asymptomatic.[13] For example, approximately 80% of cases of deep-vein thrombosis (DVT) are clinically silent,[14] and fewer than half of all fatal PE cases are detected before death.[15] The fact that such a high proportion of cases remains undiagnosed highlights the need for better methods of detection.

A study from the United States provided retrospective 25-year (1966 to 1990) population-based data on the incidence of first lifetime episodes of VTE in the Caucasian population of Olmsted County (Minnesota, USA). The average incidences of DVT alone, according to sex and type of VTE disease, were 48/100,000 per year in women of all ages and 51/100,000 per year in men of all ages. For PE with or without DVT, the average incidence was 40/100,000 per year in women of all ages and 56/100,000 per year in men of all ages. In addition, it was shown that the incidence of VTE rose markedly with increasing age in both sexes, with PE accounting for most of the increase. The incidence of VTE in the age range 65 to 69 years reached 300/100,000 per year and was more than 800/100,000 per year among people aged 80 years and older.[16]

A Swedish study on the incidence of a first venous thromboembolic event in men aged 50 to 80 years reported an incidence of 138/100,000 per year for DVT, 67/100,000 per year for non-fatal PE, and 105/100,000 per year for fatal PE.[17] In the population-based EPI-GETBO study, which was carried out in western France between April 1998 and March 1999, all VTE events were registered. The total occurrence of VTE disease was 183/100,000 per year, with a recurrence rate of 27% for DVT and 23% for PE.[18]

Thrombus formation and progression

It was over 150 years ago that Rudolf Virchow described the now classic triad of causative factors for venous thrombosis: vascular damage, stasis of blood flow and activation of blood coagulation.[19] The complex and multifactorial etiology of VTE arises from a disturbance of normal hemostasis. The fine balance between thrombus formation and hemorrhage is controlled by a complex interaction between blood flow, components of the blood vessel wall, platelets, plasma proteins, procoagulants and anticoagulants.[20,21] Disturbance of this balance can trigger the development of a thrombus.

Most venous thrombi occur in regions of slow or disturbed blood flow. Thrombosis in the lower limb can involve the superficial leg veins, the deep veins of the calf, proximal veins and iliac veins.[22] Most thrombi in the superficial veins resolve spontaneously but occasionally they extend into the deep

veins. Here, complete lysis rarely occurs. Venous thrombi may obstruct blood flow within the vein causing inflammation of the vessel wall and symptoms. Continued flow of blood past a DVT can also cause part of it to break away, forming an embolus that moves freely within the venous circulation, finally lodging in the lungs and causing PE.[22]

The outcome of a PE is dependent on the size of the embolus, the number and size of vessels occluded, the patient's age, and cardiorespiratory comorbidity. While in some cases PE is asymptomatic or causes only mild chest pain and dyspnea, a massive PE, due to a very large clot, can cause respiratory arrest, cardiovascular collapse and sometimes sudden death. The lodged embolus can also continue to grow so that death occurs a few hours to several days after the occurrence of the initial PE.[21]

Long-term clinical course

While PE represents the most clinically important short-term complication of DVT, causing significant morbidity and mortality, DVT is further complicated by the risk of recurrent VTE and post-thrombotic syndrome. The leg pain and edema that characterize symptomatic DVT often occur without any pulmonary symptoms,[7] but carry a high risk of recurrent VTE that can persist for years.[23] Within the first year of an initial episode of DVT around one-third of patients have symptoms suggesting a recurrence. One-third of these patients actually have a recurrence while the others are diagnosed with post-thrombotic syndrome or non-thrombotic disorders.[24,25]

Post-thrombotic syndrome is thought to be caused by a combination of venous hypertension, due to persistent venous obstruction and valve damage, and an abnormal microcirculation.[24] This underlying pathology can give rise to symptoms ranging from mild edema and discomfort to incapacitating limb swelling with pain and ulceration.[26] Recent studies have shown that post-thrombotic syndrome takes around 2 years to manifest clinically,[26,27] which challenges the commonly held view that it takes 5 to 10 years to develop.[26,28] Estimates of the incidence of post-thrombotic syndrome vary greatly, and may reflect differences in populations of patients and the lack of an established definition for post-thrombotic syndrome.[26] Recent studies have reported rates between 23% and 47%,[26,27] whereas others in which patients received between anticoagulation have reported rates ranging from 4.7[29] to 24%.[30] Data from clinical trials are sparse with respect to the management of post-thrombotic syndrome, but the medical costs of treatment and the socioeconomic burden of this late complication of VTE are enormous.[31,32] Bergqvist *et al.*, for example, estimated that the additional long-term health-care cost of post-thrombotic complications adds a further 75% to the costs of treating primary DVT.[32]

PE and DVT: a single pathophysiology, in which PE is the consequence of DVT

Current medical opinion views DVT and PE as manifestations of the same disease.[33] Compelling evidence is available from prospective studies of autopsied patients and from clinical studies to indicate that DVT and PE are part of a spectrum of disorders with the same etiological basis.[7,16,34-38] These studies demonstrate that, in an individual patient, abnormal imaging tests are often found in both the deep veins and the lungs. The strong overlap in the incidences of PE and DVT is not surprising when the pathophysiology of these conditions is examined – a thrombus underlies both manifestations of VTE. When a thrombus develops in the deep veins of the lower or upper extremities, it has the potential to embolize to the pulmonary arteries and may result in PE. The composition of the thrombus is identical for both PE and DVT, it is only the location that varies. Although a venous thrombus can occur within several different vessels, it usually originates in the deep proximal or calf muscle veins of the leg.[39] Consequently, the deep veins of the legs also represent the most common site of origin of thrombi embolizing to the lungs[40] – more than 90% of pulmonary emboli originate from a DVT.[41]

PE and DVT: an overlapping risk factor profile

Venous thromboembolic disorders develop as a result of a combination of specific risk factors, each of which exerts its effect through one or more of the three main causes of thrombosis originally described by Virchow (Table 1). Acquired factors tend to increase the risk of thrombosis through vascular injury and stasis of blood flow, while hypercoagulability may be induced by either acquired or inherited factors.

VTE risk factors are not all of equal value. A number of factors are sufficient by themselves to warrant VTE prophylaxis: these include major general surgery, hip or knee replacement, spinal cord injury, major trauma, and hip or leg fracture.[42] While others are not sufficient alone to justify prophylaxis, the presence of multiple risk factors in an individual patient is common and the effects are cumulative, further increasing the risk of a venous thromboembolic event.[4,39,43,44]

As DVT and PE are caused by the same underlying pathology, the risk factors for both are identical. Any factor that increases the risk of one manifestation of VTE also increases the risk of the other. In a family study of various inherited hypercoagulable disorders, 19% of individuals with a genetic coagulation disorder had experienced a VTE compared with less than 1% of their relatives without such a defect.[45] Of those with a diagnosis of DVT, approximately 10% within each deficiency group also had had PE, while PE had occurred in only 0.3% of those without a genetic defect.[45]

Table 1. Risk factors for venous thromboembolism according to Virchow's triad.[6,153]

Acquired risk factors
• Advanced age
• Prolonged immobility
• Major surgery (particularly operations involving the abdomen, pelvis and lower extremities
• Trauma (especially fracture of the pelvis, hip or leg)
• Malignant disease and its treatment
• History of thromboembolism
• Pregnancy and puerperium
• Oral contraceptives
• Indwelling venous catheters
• Acute medical conditions (e.g. myocardial infarction, acute heart failure infectious diseases, acute respiratory failure)
• Chronic medical conditions (e.g. stroke, chronic heart failure, hypertension, chronic obstructive pulmonary disease, obesity, varicose veins, irritable bowel disease, nephrotic syndrome)
Inherited risk factors
• Deficiency of antithrombin III, protein C or S, heparin co-factor II
• Activated protein C resistance (factor V Leiden)
• Elevated plasminogen activator inhibitor
• Hyperhomocysteinemia
• High plasma concentrations of factor VIII
• Prothrombin gene mutation (20210A)
• Antiphospholipid antibodies
• Decreased levels of plasminogen or plasminogen activators
• Heparin-induced thrombocytopenia

Table 2. Risk classification for venous thromboembolism. Adapted from Geerts *et al*.[6]

Risk category	*Calf DVT (%)*	*Proximal DVT (%)*	*Clinical PE (%)*	*Fatal pulmonary embolism (%)*
Primary prophylaxis recommended				
Low risk	2	<0.4	0.2	<0.002
• Minor surgery • Age <40 years • No additional risk factors				
Moderate risk	10–20	2–4	1-2	0.1–0.4
• Minor surgery + additional risk factors • Non-major surgery + age 40–60 years + no additional risk factors • Major surgery + age <40 years + no additional risk factors				
High risk	20–40	4–8	2-4	0.4-1.0
• Non-major surgery + age >60 years or additional risk factors • Major surgery + age >40 years or additional risk factors				
Highest risk	40–80	10–20	4-10	0.2-5.0
• Major surgery + age >40 years + prior VTE, cancer, or molecular hypercoagulable state • Hip or knee arthroplasty, hip fracture surgery • Major trauma • Spinal cord injury				

DVT: deep-vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.

Although VTE can occur spontaneously in individuals with inherited thrombophilia, approximately half of all VTE events that occur in patients with genetic abnormalities are provoked by an acquired risk factor[46] such as pregnancy, surgery or trauma. It is therefore vital that clinicians are aware of the high risk of DVT and PE in individuals with multiple risk factors, and take appropriate action to prevent a thrombotic event from occurring.

Prevention of DVT and PE

Patients are classified as being at low, moderate or high risk of developing VTE according to a number of well-defined criteria (Table 2). Primary thromboprophylaxis is recommended in patients at moderate to high risk of VTE to reduce the rate of fatal PE and the morbidity associated with post-thrombotic syndrome.[6] Without prophylaxis, for example, asymptomatic VTE occurs in 50% to 60% of patients following major orthopedic surgery.[6] Patients who have undergone elective hip surgery constitute a high risk group, with between 4% and 7% suffering a fatal PE.[47]

Thromboprophylaxis can be achieved by preventing venous stasis and/or by modulating blood coagulation.[22] The currently available prophylactic regimens are outlined in Table 3. The choice of prophylactic therapy for an individual patient is made on the basis of that patient's specific risk factors.

Mechanical prophylaxis

Mechanical prophylaxis employs compression methods such as intermittent pneumatic compression (IPC) boots or sleeves and graduated compression stockings to increase blood flow in the deep veins.[48] In total hip replacement, IPC reduces the risk of asymptomatic DVT but has little impact on the risk of proximal (e.g. femoral or popliteal) DVT.[49-55] IPC has been shown to be effective in elective knee replacement surgery, especially when applied during or immediately after surgery and worn until the patient is fully mobile.[53,56-61] Mechanical prophylaxis is recommended alone in patients who have a greater than usual risk of bleeding, and as an adjuvant to pharmacologic therapy for patients who are at substantial risk of thromboembolic complications.[6]

Very limited data are available, and the findings are conflicting, regarding the efficacy of graduated compression stockings in preventing VTE in orthopedic patients.[60,62-64] Further studies are needed to evaluate the role of this form of mechanical prophylaxis in these individuals.

Pharmacologic prophylaxis

Heparin and low-molecular-weight heparin (LMWH) form a heterogeneous group of compounds that are derived from animal tissue. Prophylaxis with low-dose unfractionated heparin is often used

Table 3. Prophylactic regimens for venous thromboembolism.

Agent	*Regimen*
Low-dose unfractionated heparin	Heparin 5000 U SC given q8–12 h starting before operation
Adjusted-dose heparin	Heparin SC given q8h, starting at approximately 3500 U and adjusted by ±500 U per dose to maintain a mid-interval aPTT at high normal values
Low-molecular-weight heparin and heparinoids (orthopedic surgery)	Dalteparin 5000 U 8-12 h pre-op and once daily starting 12-24 h post-op Dalteparin 2500 U 6-8 h post-op; then 5000 U once daily Danaparoid 750 U 1-4 h pre-op and q12h post-op Enoxaparin 30 mg q12h starting 12-24 h post-op Enoxaparin 40 mg once daily starting 10-12 h pre-op Nadroparin 38 U/kg 12 h preop, 12 h post-op, and once daily on post-op days 1, 2, and 3; then increase to 57 U/kg once daily Tinzaparin 75 U/kg once daily starting 12-24 h post-op Tinzaparin 4,500 U 12 h pre-op and once daily post-op
Fondaparinux (major orthopedic surgery)	Fondaparinux 2,5 mg once daily starting ≥6 h post-op
Perioperative warfarin	Start daily dose with approximately 5-10 mg the day of or the day after surgery; adjust dose for a target INR 2.5 (range 2–3)
Intermittent pneumatic compression/elastic stockings	Start immediately before operation and continue until fully ambulatory

in patients undergoing elective general surgery who are at moderate risk of VTE,[4] but it is less effective than other forms of prophylaxis in high-risk patients undergoing major orthopedic surgery.[6] In patients undergoing general surgery, low-dose subcutaneous heparin results in a 50 to 70% risk reduction in VTE.[65] However, this still means that a significant proportion of patients remain at risk of DVT and PE. Adjusted-dose heparin is more effective, particularly in orthopedic and other high-risk patients,[66] but it requires frequent monitoring of the activated partial thromboplastin time.[22] Heparin-induced thrombocytopenia (HIT) is a potentially very serious side effect of unfractionated heparin that warrants immediate discontinuation of therapy.[48]

LMWHs provide a number of advantages over unfractionated heparin, which make them more convenient for outpatient administration. They have a better safety profile, although bleeding rates are the same as for unfractionated heparin in orthopedic patients, higher bioavailability, longer half-life (allowing once-daily subcutaneous administration) than unfractionated heparin and may require less rigid laboratory monitoring of platelets for the development of HIT.[48] However, even though the incidence of HIT may be reduced, they are still contraindicated in patients with a history of this adverse event. LMWHs are effective across a number of high-risk patient groups, including those undergoing general surgery, elective hip surgery and major knee surgery, and patients with hip fracture, spinal injury and stroke. Despite the improved efficacy of LMWH compared with unfractionated heparin, the risk of DVT and PE remains significant in treated patients.[67] For example, DVT detected on venography is apparent in 15% of patients who undergo total hip replacement and in 30% of those who undergo total knee replacement. In addition, a further 20 to 40% develop new asymptomatic thrombi within 3 weeks of discharge from hospital.[68] The rate of symptomatic VTE in patients who have undergone lower extremity arthroplasty and who have received the LMWH enoxaparin is around 2%.[68] White *et al.*[69] reported that 3% of patients who had undergone total hip replacement and 2% of those who had undergone total knee replacement developed symptomatic VTE within 3 months of surgery despite receiving thromboprophylaxis. Moreover, there is a persisting high mortality rate due to fatal PE among major orthopedic surgery patients despite heparin prophylaxis: in hip fracture the incidence of fatal PE has been shown to be up to 2.2%.[70]

Warfarin, a vitamin K antagonist, is prescribed in the prevention of VTE in all risk categories,[47] including high-risk patients who have undergone hip surgery and major gynecologic surgery.[71] Careful laboratory monitoring of warfarin is required because its anticoagulant response can be influenced by a number of genetic, environmental and dietary factors, as well as by various disease states and drugs.[71] Warfarin may also be associated with rebound hypercoagulation on treatment withdrawal.[72] The most important side effects of treatment include hemorrhage, which is related to the intensity of therapy as well as to concomitant treatment with commonly used agents such as aspirin,[73] and skin necrosis.[74] Furthermore, as with heparins, warfarin leaves the patient significantly at risk of DVT and PE.[75] Several studies[75-77] and meta-analyses[78,79] have also demonstrated that warfarin is significantly less effective than LMWH in preventing asymptomatic and symptomatic in-hospital VTE.

Aspirin prophylaxis has been extensively studied in orthopedic surgery. Although a meta-analysis[80] demonstrated that perioperative aspirin is more effective than placebo, it is less effective than other currently available thromboprophylactic agents,

and leads to an increase in the incidence of wound-related and gastrointestinal bleeding.[81] Aspirin is not, therefore, recommended in patients undergoing orthopedic surgery.[6]

VTE prevention in the medical patient

VTE prophylaxis is well established in surgical patients, but its use in medical patients is subject to controversy. Research into VTE in medical patients is more limited and tends to focus on those with acute myocardial infarction or stroke, in whom the incidence of VTE is approximately 24% and 55%, respectively.[6] The incidence of VTE (defined as DVT detected by venography or documented PE) in acutely ill medical patients, with illnesses such as congestive heart failure, acute respiratory failure, acute infection, rheumatic disorders, acute arthritis, or inflammatory bowel disease, is reported to be about 15%.[82] In a meta-analysis of 17 randomized clinical trials involving unfractionated heparin or LMWH, and excluding studies that involved patients with acute myocardial infarction or stroke, Mismetti *et al.* reported that heparin prophylaxis halves the risk of VTE when compared with placebo.[83]

The Sixth American College of Chest Physicians (ACCP) Consensus Guidelines, which represent an unbiased overview of all of the available data for antithrombotic therapies and which take into account the strength of the evidence, recommend the use of prophylaxtic low-dose unfractionated heparin and high-dose LMWH in general medical patients with acute medical illnesses, including heart failure, chronic respiratory disease or severe chest infection, and in critically ill patients with disease- or patient-related risk factors for VTE.[6]

Duration of antithrombotic prophylaxis

Pharmacologic thromboprophylaxis is often given for 5 to 7 days, or during the period of hospitalization.[24] However, the thromboembolic risk persists beyond this period, leaving patients unprotected against an event. For example, after total hip replacement the risk of DVT persists for up to 2 months,[84-87] and symptomatic VTE at 90 days has been reported in individuals who have undergone total hip or knee replacement.[68,88,89] Several studies have demonstrated the requirement for prolonged out-of-hospital prophylaxis in individuals who have undergone hip arthroplasty.[90-95] In all of these studies, extended out-of-hospital prophylaxis for a total of 5 weeks with LMWH reduced the rate of total and proximal DVT by at least 50%. As a result, the Sixth ACCP Consensus Guidelines recommend continuation of prophylaxis for 7 to 10 days following major orthopedic surgery, and suggest extended prophylaxis for patients with a history of VTE or ongoing risk factors such as obesity or immobilization.[6]

Diagnosis of VTE

Deep-vein thrombosis. An accurate diagnosis of DVT cannot be made on the basis of the patient's history and clinical examination alone. In symptomatic patients, a clinical pre-test model – only one of which has been formally tested in a clinical setting[96] – can be used to determine the probability of DVT. This model includes the following clinical features: active cancer, paralysis or recent plaster cast, recent immobilization or surgery, swelling of leg, pitting edema, collateral superficial veins and alternative diagnosis.[96] Once the presence of DVT is suspected in an individual patient, a variety of algorithms can be used to reach a diagnosis.[97,98]

D-dimer blood testing has recently been introduced in the diagnosis of VTE. Elevated levels of D-dimer occur in patients with thromboembolism, but are also associated with increasing age and the presence of cancer or inflammation. Furthermore, the sensitivity and specificity of D-dimer assays vary. Very highly sensitive tests are useful as stand-alone tests for excluding the presence of DVT and PE, but they tend to yield high numbers of false positives.[99]

Compression ultrasound is a non-invasive technique that is used to diagnose DVT. Its accuracy is very high in symptomatic patients,[100] with a sensitivity rate higher than 95%. Compression ultrasound is not as accurate in post-surgical asymptomatic patients, its sensitivity being no higher than 65%. It is highly sensitive for detecting proximal DVT but is less accurate for identifying isolated calf vein DVT.[101] Impedance plethysmography (IPG) has been extensively investigated in clinical trials. This technique is able to detect only proximal DVT and has a higher rate of false positives than compression ultrasonography. Ascending contrast venography remains the gold standard diagnostic test for symptomatic DVT, but it is uncommon now due to the availability of other non-invasive tests such as compression ultrasonography. Venography is used primarily in clinical studies to assess outcomes, or when non-invasive test results are conflicting or inconclusive and a diagnosis of calf-vein thrombosis needs to be excluded.[98]

Pulmonary embolism

Acute PE can be difficult to diagnose and, if left untreated, can be fatal[102] or lead to disabling morbidity from pulmonary hypertension.[103] However, in patients with suspected PE, a careful risk-benefit decision must be made before administering anticoagulant therapy because this treatment can result in intracranial hemorrhage and death in 2% and 0.5% of patients, respectively.[104]

Symptoms of PE tend to be non-specific, but in the majority of patients, suspicion is raised by the presence of dyspnea, chest pain or syncope, which

Table 4. Signs and symptoms in patients with suspected pulmonary embolism.

Symptoms	*Signs*
Dyspnea	Tachypnea (≥ 20/min)
Chest pain (pleuritic)	Tachycardia (>100/min)
Chest pain (substernal)	Signs of DVT
Cough	Fever (>38.5° C)
Hemoptysis	Cyanosis
Syncope	

may occur alone or in combination. A wide variety of other signs and symptom are also associated with PE (Table 4).[105] The presence or one or more risk factors for VTE is a good indication of the likelihood of PE, but PE can also occur in individuals with no risk factors.[106]

Clinical assessment of patients with suspected PE — using either non-standardized (empirical)[107-110] or standardized models or prediction rules[111-113] — can stratify patients' probability of having PE. In patients with a low clinical probability, the prevalence is expected to be ≤ 10%, in those with intermediate probability it is around 25%, and in those with a high probability it is 60% or over.[114] Clinical assessment, combined with the patient's characteristics, helps to guide the choice of initial diagnostic test thereby minimizing the number of steps necessary to diagnose or exclude PE.[114] A number of diagnostic algorithms have been developed.[97,98] Alternative algorithms utilize a very highly sensitive D-dimer test first to rule out the presence of PE.[98]

Ventilation-perfusion scanning is the pivotal non-invasive diagnostic test in acute PE, and has been extensively evaluated in clinical trials. However, it is diagnostic in a minority of cases: one-quarter of patients with suspected PE will have a high probability lung scan and require treatment, and another quarter will have a normal perfusion scan. The remaining 50% of patients will have a non-diagnostic result and require further evaluation.[105] Pulmonary angiography is the gold standard diagnostic technique for PE, with a failure rate of only 2%.[115] However, it is invasive, and can lead to complications in a minority of patients.[98]

Spiral volumetric computed tomography (spiral CT) has been introduced recently as a rapid, non-invasive diagnostic test for PE. This technique has a high sensitivity and specificity for central pulmonary arteries but tends to miss smaller, more peripheral subsegmental emboli, the clinical significance of which is unknown.[116] Much additional research is needed into the use of spiral CT in the diagnosis of PE. Another widely available, non-invasive test is echocardiography. This test is useful in patients with suspected massive PE, but further studies are needed to determine whether it can be used to identify patients who could benefit from thrombolytic therapy in the absence of hemodynamic instability or cardiogenic shock.[105]

Treatment of DVT and PE

The Sixth ACCP Consensus Guidelines view DVT and PE as clinically important outcomes of a single underlying condition.[6] Clinical trials involving patients with DVT alone have validated treatment regimens that are similar to those used in patients with coexisting DVT and PE and in patients with PE alone. As a consequence, treatments for DVT and PE are similar, with the exception of mechanical methods of prophylaxis in patients with DVT who are at risk of post-thrombotic syndrome.[33]

Antithrombotic treatment

Unfractionated intravenous heparin, LMWH and adjusted-dose subcutaneous heparin are used for the treatment of acute DVT and PE (Table 5).[33] LMWHs are gradually replacing unfractionated heparin as the treatment of choice because they require less frequent laboratory monitoring and can be safely used for out-of-hospital treatment.[117] A meta-analysis of 14 studies comparing fixed-dose subcutaneous LMWH with adjusted-dose unfractionated heparin has revealed that LMWH is at least as efficacious as unfractionated heparin in preventing symptomatic recurrent VTE, and significantly reduces the occurrence of major hemorrhage and the overall mortality rate.[118] In a subanalysis of the data from five studies involving patients with proximal DVT, the risk of recurrence, major hemorrhage and overall mortality was significantly lower with LMWH than with unfractionated heparin.[118]

Initial treatment with one of these agents is usually given for at least 5 days followed by an oral anticoagulant (usually warfarin) for a minimum of 3 months and for 12 months or longer in patients with recurrent idiopathic VTE or another continuing risk factor (*see below*).[33] An overlap of 4–5 days between the two treatments is required because of the delay in onset of action of warfarin.[119]

Thrombolytic therapy

Thrombolytics, such as streptokinase, urokinase and alteplase, are first-line agents in an emergency situation in which the standard agents do not work sufficiently quickly to save the patient's life. However, these agents carry a significant risk of serious bleeding and may lead to intracranial hemorrhage.[104,119] Thrombolytic agents are an established treatment for patients with acute massive PE and hemodynamic instability or cardiogenic shock,

Table 5. Treatment regimens for venous thromboembolism.

Agent	*Application*
Heparin	Prevention and treatment of VTE
LMWH, and heparinoids	Prevention and treatment of VTE
Fondaparinux	Prevention of VTE
Hirudin and direct thrombin inhibitors	Prevention and treatment of VTE; treatment of heparin-induced thrombocytopenia
Warfarin	Long-term treatment of VTE; prevention of VTE
Streptokinase	Treatment of severe or life-threatening PE or DVT
Urokinase	Treatment of severe or life-threatening PE or DVT
Alteplase	Treatment of severe or life-threatening PE or DVT
Reteplase	Treatment of severe or life-threatening PE or DVT

whereas their use in individuals with submassive PE remains the subject of intense debate.[120,121] The recently published American College of Emergency Physicians guidelines state that fibrinolytic therapy should be considered in hemodynamically unstable patients with confirmed PE (level B recommendation).[122] They also suggest that it should be considered in hemodynamically unstable patients with confirmed PE and right ventricular dysfunction on echocardiography, and in unstable patients with a high clinical index of suspicion, particularly in those with right-ventricular dysfunction (level C recommendation).[122]

The use of thrombolytic treatment in stable hemodynamic patients with PE remains controversial. In a registry study of 719 patients with major PE, Konstantinides *et al.* reported that early thrombolytic treatment improves clinical outcomes.[123] Despite describing these patients as being hemodynamically stable, they had evidence of pulmonary hypertension and/or failure of the right side of the heart. In a randomized, placebo-controlled study involving 256 patients with acute submassive PE and pulmonary hypertension or right ventricular dysfunction, Konstantinides *et al.* reported that alteplase plus heparin improved the clinical course when compared with that in patients who received heparin plus placebo.[124] By contrast, in a retrospective cohort study of 153 patients, Hamel *et al.* found no reduction in PE recurrences in hemodynamically stable patients with massive PE and right ventricular dysfunction who were treated with thrombolysis rather than with heparin.[125] Furthermore, Ribeiro *et al.* reported similar hospital mortality rates in patients with severe PE and stable hemodynamics treated with either heparin or thrombolysis.[126] Clearly, further studies are needed to clarify the role, if any, of thrombolysis in these groups of patients.

Pulmonary embolectomy, the first definitive therapy for PE, is still used in emergency situations in patients with a massive PE who are hemodynamically unstable and who have failed to benefit from thrombolytic therapy or have contraindications to its use.[33]

Ambulatory therapy

Recent studies have demonstrated that outpatient treatment of proximal DVT with LMWH is as safe and effective as treatment given during hospitalization.[127-129] Partsch *et al.* conducted a randomized controlled trial into the benefits of compression stockings and walking exercises in comparison with bed rest in 45 patients with acute proximal DVT. They found that the rate of resolution of pain (assessed by visual analog scores) and swelling was significantly quicker in mobile patients treated with elastic compression stockings and LMWH than in patients treated with LMWH who underwent bed rest and no compression. Furthermore, they reported that ambulatory therapy did not increase the risk of PE.[130] Further studies are needed to evaluate the role of ambulatory therapy in patients with VTE and to identify which individuals could benefit most from this management approach.

Optimal duration of oral anticoagulant treatment (secondary VTE prevention)

Following initial treatment for DVT over 5 to 10 days with heparin or LMWH, patients typically receive between 3 and 12 months of oral anticoagulation with full-dose warfarin (with dose adjustment to achieve an INR between 2.0 and 3.0). However, after discontinuation of this treatment, between 6% and 9% of patients each year develop recurrent VTE.[27,131] Extended use of full-dose warfarin is associated with a reduction in the risk of recurrent VTE but leads to a risk of major hemorrhage.[132-134]

To date, from a number of prospective cohort studies, population-based studies, and randomized clinical trials, it is possible to derive some sufficiently clear statements.[135-137] Five to ten percent of patients with secondary DVT from transient risk factors (such as surgery, trauma, immobilization) have a recurrence after 3 months of oral anticoagulant therapy; in contrast, 15% to 30% of patients with idiopathic DVT have a recurrent VTE after 3 months. Prolongation of anticoagulant treatment to 6 months, 1 year, or even 2 years does not modify

this picture. The annual incidence of major bleeding from oral anticoagulant therapy is 1.5% to 2.0%. The case-fatality rate of an episode of major bleeding is four times as high as that observed in patients with recurrent VTE.

To optimize the long-term treatment of VTE, new strategies and new drugs are currently under investigation.[138] The former include evaluation of the benefit-to-risk ratio of reducing the intensity of oral anticoagulants,[139] and that of tailoring the duration of anticoagulants according to residual vein thrombosis, as shown by repeat leg vein ultrasonography,[140,141] and/or the behavior of the D-dimer test.[142,143] The latter include the evaluation of new categories of drugs. A recently published randomized, double-blind, placebo-controlled study by Ridker *et al.*[139] involving 508 patients with idiopathic VTE who were followed for up to 4.3 years, reported that extended treatment with low-dose warfarin (target INR, 1.5 to 2.0) reduced the risk of recurrent VTE by between 76 and 81% when compared with placebo. The composite endpoint of recurrent VTE, major hemorrhage or death was reduced by 48%. In addition, there was little evidence of any increase in the risk of major hemorrhage or stroke in patients treated with warfarin. They concluded that long-term, low-intensity treatment with warfarin is a highly effective method of preventing recurrent VTE.

Need for new therapies

Existing therapies for the prevention or treatment of VTE have significant limitations, including an increased risk of hemorrhage and heparin-induced thrombocytopenia, an unpredictable dose-response, the need for monitoring, and rebound hypercoagulation. Furthermore, even with the best available therapies, patients still suffer debilitating or event fatal thrombotic complications. This has led to the development of several new classes of anticoagulants. When compared with currently available treatments, these agents aim to provide enhanced safety and efficacy while producing predictable clinical responses.

A number of agents are currently in development: these include selective factor Xa inhibitors, selective thrombin inhibitors, and selective factor VII/tissue factor inhibitors. The most extensively studied of these is the synthetic pentasaccharide fondaparinux, a highly selective factor Xa inhibitor. In a dose-finding study, fondaparinux, relative to the LMWH enoxaparin, showed the potential to improve significantly the risk–benefit ratio for the prevention of VTE in patients undergoing total hip replacement.[144] Furthermore, four phase III clinical trials comparing enoxaparin with fondaparinux for the prevention of VTE in over 7000 patients undergoing major orthopedic surgery (i.e., total hip replacement, knee surgery and hip fracture), demonstrated that fondaparinux is more effective than enoxaparin in preventing venous thromboembolism and is equally safe.[145-148] A meta-analysis[149] of the combined results of these trials demonstrated a highly significant risk reduction of 55.2% in favor of fondaparinux, with a similar safety profile regarding clinically relevant bleeding events. Based on these favorable results, fondaparinux is being investigated in the prevention of VTE in general abdominal surgery and in acutely ill medical patients. In addition, an extensive clinical development program is now ongoing, investigating the efficacy and safety of fondaparinux in the treatment of DVT and PE. In a phase II study involving 456 patients with symptomatic proximal DVT who were treated with either fondaparinux or a LMWH, fondaparinux appeared to be a safe and effective treatment.[150] The results from two large phase III studies, MATISSE PE and MATISSE DVT, which involved nearly 4,500 patients with VTE, were presented recently.[151] The findings from both studies were consistent, showing that fondaparinux, administered subcutaneously in a fixed dose for at least 5 days, was at least as effective and as safe as dose-adjusted intravenous unfractionated heparin (MATISSE PE) or body-weight adjusted subcutaneous LMWH (MATISSE DVT), both of which were also given for at least 5 days. In addition, 30% of patients with DVT and 15% with PE were treated on a partially outpatient basis. Another synthetic pentasaccharide – idraparinux – is currently under investigation in phase II clinical trials for the secondary prevention of proximal DVT.[152]

The direct thrombin inhibitors, melagatran and oral ximelagatran, have been evaluated in phase II and III randomized trials involving patients undergoing major orthopedic surgery. The results of the METHRO II dose-finding study involving patients undergoing total hip or knee replacement revealed that sequential therapy, comprising subcutaneous melagatran starting immediately before surgery followed by oral ximelagatran starting the day after surgery, is a safe and effective treatment.[153] In addition, the frequency of VTE was significantly lower with the highest dose of melagatran/ximelagatran than with dalteparin. In METHRO III, treatment comparing subcutaneous melagatran started shortly after total hip or knee replacement followed by oral ximelagatran was compared with that of subcutaneous enoxaparin started shortly after surgery. While treatment with the direct thrombin inhibitors was found to have similar safety and tolerability profiles to those of enoxaparin, it was less effective.[154] By contrast, preliminary results from the EXPRESS study, which also compared treatment with ximelagatran/melagatran with that of enoxaparin, demonstrated a relative risk reduction in VTE of 24% in favor of the direct thrombin inhibitors.[155] The initial results of two further phase III studies

involving patients undergoing total knee replacement – EXULT (EXanta Used to Lessen Thrombosis) and THRIVE III (Oral Direct THRombin Inhibitor ximelagatran for Venous thromboEmbolism) – were presented recently.[156] In the EXULT study, treatment with ximelagatran was associated with a 26% reduction in the risk of thrombosis when compared with warfarin. The THRIVE III study demonstrated the safety and tolerability of extended secondary prevention of VTE following 6 months of standard anticoagulant therapy.

Conclusions

The immediate challenge in the management of DVT and PE is to improve the rates of prevention and detection of this potentially fatal yet preventable disease. Randomized clinical trials and hence consensus guidelines for the prevention and treatment of VTE are based on the evidence that DVT and PE are different symptoms of the same disease. Therefore, careful assessment of risk factors in individual patients will allow prophylactic therapy to be administered to prevent a first VTE event. Equally, diagnosing DVT earlier will allow treatment to be implemented. There is now an important need to change our management of DVT-improved rates of prevention and detection, combined with more effective drug therapies, have the potential to substantially reduce the morbidity and mortality caused by this disease.

Franco Piovella, Marisa Barone
Servizio Malattie Tromboemboliche
I.R.C.C.S. Policlinico San Matteo,
27100 Pavia, Italy
E-mail: f.piovella@smatteo.pv.it

Disclosure

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The burden of venous thromboembolism

As discussed by Piovella and Barone in the previous editorial, venous thromboembolism is a common, serious illness. In the last few years this journal has published supplements on this topic that can be downloaded for free at URLs *http://www.haematologica.org/free/platelets2003.pdf*, and *http://www.haematologica.org/free/heparins.pdf*). Additional papers may be found in the regular journal.[1-20]

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