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Pulmonary embolism and deep vein thrombosis



Samuel Z Goldhaber, Henri Bounameaux

Pulmonary embolism is the third most common cause of death from cardiovascular disease after heart attack and stroke. Sequelae occurring after venous thromboembolism include chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome. Venous thromboembolism and atherothrombosis share common risk factors and the common pathophysiological characteristics of inflammation, hypercoagulability, and endothelial injury. Clinical probability assessment helps to identify patients with low clinical probability for whom the diagnosis of venous thromboembolism can be excluded solely with a negative result from a plasma D-dimer test. The diagnosis is usually confirmed with compression ultrasound showing deep vein thrombosis or with chest CT showing pulmonary embolism. Most patients with venous thromboembolism will respond to anticoagulation, which is the foundation of treatment. Patients with pulmonary embolism should undergo risk stratification to establish whether they will benefit from the addition of advanced treatment, such as thrombolysis or embolectomy. Several novel oral anticoagulant drugs are in development. These drugs, which could replace vitamin K antagonists and heparins in many patients, are prescribed in fixed doses and do not need any coagulation monitoring in the laboratory. Although rigorous clinical trials have reported the effectiveness and safety of pharmacological prevention with low, fixed doses of anticoagulant drugs, prophylaxis remains underused in patients admitted to hospital at moderate risk and high risk for venous thromboembolism. In this Seminar, we discuss pulmonary embolism and deep vein thrombosis of the legs.

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Introduction

Deep vein thrombosis and pulmonary embolism constitute venous thromboembolism. Deep vein thrombosis occurs most often in the legs, but can form in the veins of the arms,¹ and in the mesenteric and cerebral veins. We focus on deep vein thrombosis of the legs and pulmonary embolism. Although these disorders are part of the same syndrome, important differences in epidemiology, diagnosis, and treatment exist between them.

Epidemiology

In population-based studies, no consensus exists about whether the incidence of venous thromboembolism varies according to sex. In a Norwegian study,² the incidence of all first events of venous thromboembolism was 1.43 per 1000 person-years, and was slightly higher in women than in men. In a Swedish study,³ incidence was equal for both sexes. In a community-based study,⁴ incidence was higher for men than for women (1.14 per 1000 patient-years vs 1.05 per 1000 patient years). In the International Cooperative Pulmonary Embolism Registry,⁵ the primary outcome—all-cause mortality rate at 3 months—associated with acute pulmonary embolism was 17%. This registry, which had no exclusion criteria, enrolled 2454 consecutive patients from 52 hospitals in seven countries in Europe and North America. Pulmonary embolism was considered to be the cause of death in 45% of patients. Important prognostic factors associated with death from pulmonary embolism were age older than 70 years, cancer, congestive heart failure, chronic obstructive pulmonary disease, systolic arterial hypotension, tachypnoea, and right ventricular hypokinesis on echocardiography.

In the Worcester, Massachusetts metropolitan area, patients presenting with pulmonary embolism from the outpatient setting had an all-cause mortality rate of 11.1% at 90 days;⁶ however, some estimates of case fatality rate

are lower. For example, in the Registry of Patients with Venous Thromboembolism (RIETE)⁷ of 6264 patients with pulmonary embolism, the cumulative overall mortality rate was 8.6% at 3 months and the case fatality rate was 1.7%. Mortality rates were low among 1880 patients diagnosed with acute pulmonary embolism in 22 US emergency departments: the all-cause mortality rate was 5.4% at 30 days, and the mortality rate directly attributable to pulmonary embolism was only 1.0%.^{8,9} Although some studies report low rates of short-term mortality, long-term mortality associated with acute pulmonary embolism seems to be high. In an Australian registry⁹ of 1023 patients with confirmed pulmonary embolism followed up for a mean of 4 years, 36% of patients died, but only 3% died in hospital during the index admission for pulmonary embolism. The mortality after discharge of 8.5% per patient-year was 2.5 times higher than that in an age-matched and sex-matched general population. Of the 332 deaths occurring after discharge, 40% were because of cardiovascular causes.

Many individuals who have a first episode of deep vein thrombosis or pulmonary embolism will have a recurrent event. For some, the first event of venous thromboembolism is not diagnosed, whereas for others, venous thromboembolism recurs after anticoagulation treatment is stopped. Two associated illnesses arise after pulmonary embolism or deep vein thrombosis: chronic thromboembolic pulmonary hypertension¹⁰ and post-thrombotic syndrome.¹¹ The term chronic venous insufficiency encompasses post-thrombotic syndrome but can be idiopathic or caused by disorders other than thrombosis. Chronic thromboembolic pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mm Hg that persists 6 months after diagnosis of pulmonary embolism. The disorder occurs in 2–4% of patients after acute pulmonary embolism and results in disabling dyspnoea, both at

rest and with exertion. Life expectancy is often shortened and patients frequently die of sudden cardiac death. Death is usually due to progressive pulmonary hypertension culminating in right ventricular failure. Post-thrombotic syndrome can result in chronic calf swelling, which might lead to brownish skin pigmentation of the lateral medial malleolus and, in extreme circumstances, to venous ulceration of the skin. Only mild to moderate forms of the post-thrombotic syndrome are usually seen; severe forms are rare. In a prospective multicentre cohort study¹² of 387 patients newly diagnosed with symptomatic deep vein thrombosis of the leg who were followed up for 2 years, post-thrombotic syndrome developed in 43% of patients and was mild in 30%, moderate in 10%, and severe in 3%.

The traditional concept of separation of risk factors and pathophysiology for venous thromboembolism and coronary artery disease is being reconsidered. Labelling of venous thromboembolism as a venous disease with red thrombus, by contrast with coronary artery disease as a separate arterial disease with white platelet plaque, might be an oversimplification. For example, 4 years after the onset of acute pulmonary embolism, fewer than half of those who initially survive will remain free of myocardial infarction, stroke, peripheral arterial disease, recurrent venous thromboembolism, cancer, or chronic thromboembolic pulmonary hypertension.¹³

Venous thromboembolism and atherothrombosis have shared risk factors and a common pathophysiology that includes inflammation, hypercoagulability, and endothelial injury.¹⁴ A novel approach reframes venous thromboembolism as a disease that contributes to a pan-vascular syndrome that consists of coronary artery

disease, peripheral arterial disease, and cerebrovascular disease. Risk factors for venous thromboembolism, such as cigarette smoking, hypertension, diabetes, and obesity, are often modifiable and overlap with risk factors for atherosclerosis.¹⁵ Inflammatory disorders, such as inflammatory bowel disease and systemic vasculitis, have been associated with venous thromboembolism. In the Atherosclerosis Risk In Communities (ARIC) study,¹⁶ concentrations of C-reactive protein (a marker of inflammation) above the 90th percentile were associated with a substantial increase in risk of venous thromboembolism compared with lower percentiles.

Venous thromboembolism can be categorised, somewhat arbitrarily, as idiopathic and primary or as provoked and secondary (panel 1). This dichotomy is often unclear and, at times, does not seem to have consistent logic. For example, venous thromboembolism resulting from long-haul travel is usually assigned idiopathic, whereas that caused by oral contraceptives is usually assigned provoked. Patients with idiopathic and primary disease are much more likely to suffer recurrence than are those with the provoked and secondary form if anticoagulation is discontinued. Whether patients with venous thromboembolism should be screened for thrombophilia remains controversial.²⁴ Hypercoagulable states—eg, factor V Leiden or prothrombin gene mutation—can be associated with an initial episode of venous thromboembolism. Factor V Leiden has a much stronger association with deep vein thrombosis than with pulmonary embolism;²⁵ this observation is the Leiden paradox. Neither the factor V Leiden nor the prothrombin gene mutation is a strong predictor of recurrent venous thromboembolism.²⁶

Panel 1: Major risk factors for pulmonary embolism

Idiopathic, primary, and unprovoked

- No apparent cause
- Old age (>65 years)
- Long-haul travel¹⁷
- Associated with thrombophilia (eg, factor V Leiden or prothrombin gene mutation)
- Obesity
- Cigarette smoking¹⁸
- Hypertension
- Metabolic syndrome¹⁹
- Air pollution²⁰

Secondary and provoked

- Immobilisation
- Postoperative
- Trauma
- Oral contraceptives,²¹ pregnancy, postmenopausal hormonal replacement
- Cancer²²
- Acute medical illness (eg, pneumonia, congestive heart failure)²³

Diagnosis

Clinical probability assessment

Diagnosis of deep vein thrombosis and pulmonary embolism is dependent on several, mainly non-invasive, diagnostic techniques that should be used sequentially. Because use of a validated diagnostic work-up is associated with a substantially diminished risk of complications,²⁷ implementation of such standardised approaches is highly recommended. Massive pulmonary embolism should be diagnosed quickly; its clinical features include shock or haemodynamic instability. Clinical probability assessment aims to identify patients with a high or intermediate clinical probability who need anticoagulant treatment while awaiting the results of diagnostic tests. In patients with a low clinical probability, the diagnosis of venous thromboembolism can be ruled out solely with a normal D-dimer test (figure 1). Clinical probability incorporates clinical history (including personal and familial features) and symptoms, signs, and abnormalities of oxygen saturation, chest radiography, and electrocardiography. The probability can be assessed empirically or with prediction rules or scores.

Scoring systems have clinical use and are useful educational methods for clinicians and medical students attempting to diagnose or exclude venous thromboembolism. For suspected pulmonary embolism, two scores are widely used: the Wells score²⁸ and the revised Geneva score²⁹ (table 1). The Wells score can be used to diagnose suspected deep vein thrombosis.³⁰ The Wells score for pulmonary embolism is now mostly used with a cutoff of four points,³¹ which allows a dichotomous classification of likely or unlikely pulmonary embolism. According to a meta-analysis³² of the performance of all available clinical prediction rules for suspected pulmonary embolism, these rules have similar accuracy, but are not totally equivalent. The choice among various prediction rules and classification schemes should be guided by the local prevalence of pulmonary embolism, the type of patients being assessed (outpatients or inpatients), and the type of D-dimer assay used. For example, the revised Geneva score should be used in populations with a prevalence of pulmonary embolism of more than 20%, whereas the Wells score is the only validated score for patients admitted to hospital. The results of arterial blood gas oxygen saturation, electrocardiography (ECG), and chest radiography have low sensitivity and specificity for the diagnosis of pulmonary embolism, and are incorporated in neither the Wells nor the revised Geneva score. Conversely, ECG might be useful to exclude pulmonary embolism (and to suggest acute coronary syndrome, for example), but chest radiography and arterial blood gas saturation should not be used routinely.

Measurement of fibrin D-dimer

Fibrin D-dimer is a degradation product of cross-linked fibrin, and its concentration increases in patients with acute venous thromboembolism. When assayed by a quantitative ELISA or by some automated turbidimetric assays, D-dimer is highly sensitive (more than 95%) in excluding acute deep vein thrombosis or pulmonary embolism, usually below a threshold of 500 µg/L. Hence, a concentration lower than this value rules out acute venous thromboembolism, at least in patients with low or intermediate clinical probability.³³ According to a meta-analysis,³⁴ the VIDAS D-dimer exclusion test (an ELISA assay, bioMérieux) has now been reported in 5060 patients with suspected pulmonary embolism and is associated with a very low (less than 1%) thromboembolic risk at 3 months. The Tinaquant test (an immunoturbidimetric assay, Roche) has been validated in more than 2000 patients,³⁴ and showed a similarly low thromboembolic risk at 3 months. Finally, the SimpliRed assay (a whole blood bedside latex assay, Agen Biomedical) is well validated,³⁴ but interobserver variability might be an issue.³⁵

D-dimer tests have restricted specificity and are less useful than other measures in some groups of patients, including in those with high clinical probability, those admitted to hospital for another reason in whom the

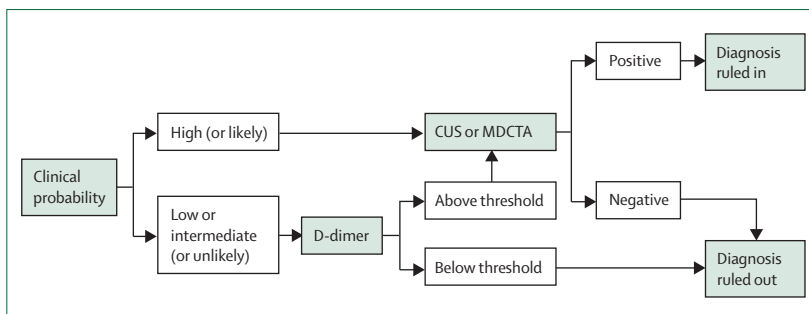


Figure 1: A diagnostic algorithm for clinically suspected deep vein thrombosis or pulmonary embolism
Use of CUS with suspected deep vein thrombosis, and of multidetector CT angiography with pulmonary embolism. CUS=compression ultrasonography. MDCTA=multidetector CT angiography.

	Points
Wells score for DVT*	
Cancer	+1
Paralysis or recent plaster cast	+1
Bed rest >3 days or surgery <4 weeks	+1
Pain on palpation of deep veins	+1
Swelling of entire leg	+1
Diameter difference on affected calf >3 cm	+1
Pitting oedema (affected side only)	+1
Dilated superficial veins (affected side)	+1
Alternative diagnosis at least as probable as DVT	-2
Wells score for PE†	
Previous PE or DVT	+1.5
Heart rate >100 beats per min	+1.5
Recent surgery or immobilisation	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3
Haemoptysis	+1
Cancer	+1
Revised Geneva score for PE‡	
Age >65 years	+1
Previous DVT or PE	+3
Surgery (under general anaesthesia) or fracture (of the lower limbs) within 1 month	+2
Active malignancy (solid or haematological malignancy, currently active or considered as cured since less than 1 year)	+2
Unilateral leg pain	+3
Haemoptysis	+2
Heart rate 75–94 beats per min	+3
Heart rate ≥95 beats per min	+5
Pain on deep vein palpation in leg and unilateral oedema	+4
Scoring systems to assess probability of suspected DVT or PE on the basis of item and assigned points. DVT=deep vein thrombosis. PE=pulmonary embolism. *Patients with a score of 0 are low risk, 1–2 are intermediate risk, and ≥3 are high risk. †For the initial rule, patients with a score of 0–1 are low risk, 2–6 are intermediate risk, and ≥7 are high risk; for the dichotomised rule, patients are unlikely or likely to have PE if they have scores ≥4 and ≤4, respectively. ‡Patients with a score <2 are low risk, 2–6 are intermediate risk, and ≥6 are high risk.	
Table 1: Clinical probability assessment	

suspicion of pulmonary embolism is raised during hospital stay, individuals older than 65 years, and pregnant women.^{33,36} A proposed age-adjusted diagnostic threshold for suspected pulmonary embolism increases the usefulness of D-dimer measurement in elderly patients,³⁷ but clinical implementation should await prospective external validation.

Compression ultrasonography for diagnosing deep vein thrombosis

Compression ultrasonography has largely replaced venography as the main imaging procedure to diagnose deep vein thrombosis (figure 2). Three options are presently used in clinical practice. Some groups look only at proximal (above the calf) veins and, in patients with a negative first exam, repeat the exam 1 week later to detect clinically relevant distal thrombi that might have progressed proximally. This method is resource demanding, cumbersome, and has a very low yield (about 1–2% of results are positive in the second exam). A second approach is to assess proximal and distal veins with complete compression ultrasonography, which is associated with a

low rate of thromboembolism at 3 months.³⁸ However, this approach leads to anticoagulation of many patients with isolated deep vein thrombosis of the distal calf and might increase risk of bleeding in some patients undergoing this procedure.³⁹ A third approach consists of use of a single proximal compression ultrasonography. Deep vein thrombosis can be excluded with this technique if results are negative in patients with a low or intermediate clinical probability, whereas those with a high clinical probability and a negative proximal compression ultrasonography would qualify for additional imaging (distal veins ultrasound imaging or venography) or serial ultrasound surveillance (figure 1). This approach seems to be associated with a 3-month risk of venous thromboembolism that is very similar to that of complete compression ultrasonography, with 30–50% fewer patients prescribed anticoagulant treatment compared with the complete compression ultrasonography strategy.⁴⁰

In 2012, revised American College of Chest Physicians (ACCP) guidelines recommend against routine treatment of asymptomatic isolated calf deep venous thrombosis. Previous guidelines⁴¹ recommended that treatment of distal deep vein thrombosis be similar to that of proximal deep vein thrombosis.

For suspected pulmonary embolism, diagnosis of proximal deep vein thrombosis in a symptomatic patient, or in an asymptomatic patient who has contraindications to CT angiography, is considered sufficient to rule in pulmonary embolism.

Multidetector CT angiography for diagnosing pulmonary embolism

CT angiography (figure 2) has largely replaced ventilation-perfusion (V/Q) lung scintigraphy as the main imaging modality in suspected pulmonary embolism. Single-detector CT angiography has a sensitivity of only about 70%⁴² and needs combination imaging with compression ultrasonography of the proximal veins of the leg if negative.^{43,44} Multidetector CT angiography is more sensitive than single-detector CT angiography.^{31,45,46} This technological advance allows exclusion of pulmonary embolism without additional compression ultrasonography of the leg.⁴⁷ Overall, a meta-analysis⁴⁸ that compiled 23 studies with 4657 patients with a negative CT angiography (mainly single detector) who did not receive anticoagulation showed a 3-month rate of subsequent venous thromboembolism of 1.4% (95% CI 1.1–1.8) and a 3-month rate of fatal pulmonary embolism of 0.51% (0.33–0.76), which compares favourably with the results noted after a normal invasive contrast pulmonary angiogram.⁴⁹

Notably, the increased use of CT angiography might cause an increased incidence of cancer attributable to radiation.⁵⁰ Dangers of radiation mean that protocols for CT angiography should be optimised. For this reason, combined use of CT pulmonary angiography and CT venography should be questioned. In the Prospective

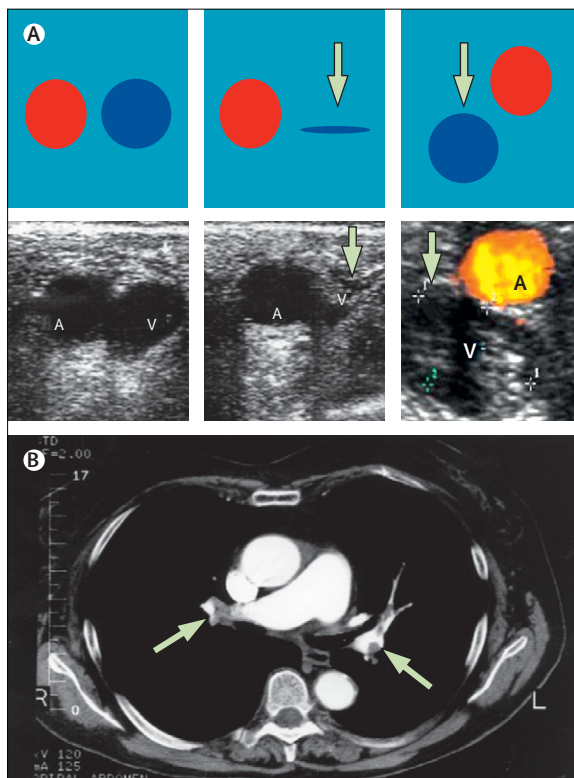


Figure 2: Contemporary imaging of deep vein thrombosis with compression ultrasound or pulmonary embolism with CT angiography

Compression ultrasound (A): upper series, from left to right; representation of vein and artery without and with (arrow) gentle compression with the echocardiographic probe; lower series, corresponding echocardiographic findings. The third image from the left show a thrombus in the vein (vein not compressible by the probe). CT angiography (B): CT angiography showing several emboli (arrows) in the main right pulmonary artery and in left lobar and segmental arteries. A=artery. V=vein.

Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study,⁵¹ no patient with pulmonary embolism or deep vein thrombosis would have been undiagnosed if imaging of the pelvic veins had been omitted. The radiation risk is particularly important in pregnant women in whom the respective advantages of CT angiography versus ventilation-perfusion or perfusion-only lung scintigraphy are still debated.

Other diagnostic imaging modalities for suspected deep vein thrombosis and pulmonary embolism

Gadolinium-enhanced magnetic resonance pulmonary angiography (MRA) could be used to diagnose pulmonary embolism because it is devoid of radiation. The accuracy of this technique combined with magnetic resonance venography (MRV) has been studied in the prospective, multicentre PIOPED III accuracy study.⁵² The proportion of technically inadequate images ranged from 11% to 52% across the seven participating centres. Technically adequate MRA had a sensitivity of 78% and a specificity of 99%, whereas technically adequate MRA and MRV had a sensitivity of 92% and a specificity of 96%. However, 194 (52%) of 370 patients had technically inadequate results, which substantially restricts its clinical use.

Conventional pulmonary angiography and venography remain the gold standards for diagnosis of pulmonary embolism and deep vein thrombosis, respectively. Because these exams are invasive, they should be restricted to patients in whom a clinically likely diagnosis cannot be confirmed by other means, or in whom endovascular treatment of pulmonary embolism is being considered. Table 2 summarises the performance of some diagnostic tests or algorithms to rule in or rule out pulmonary embolism on the basis of a systematic review.⁵³

Treatment

Prognostic stratification of patients with pulmonary embolism

Patients with pulmonary embolism should be stratified according to prognosis.⁵⁴ The Pulmonary Embolism Severity Index⁵⁵ and its simplified version⁵⁶ allow such stratification on a clinical basis (table 3). Several therapeutic implications exist for patients with pulmonary embolism: (1) high-risk patients (who represent about 5% of all symptomatic patients, with about a 15% short-term mortality) should be treated aggressively with thrombolytic drugs or surgical or catheter embolectomy;⁵⁷ (2) low-risk patients (most patients with pulmonary embolism), with a short-term mortality of about 1% might benefit from early discharge or even outpatient treatment;⁵⁸ (3) intermediate-risk patients (who represent about 30% of all symptomatic patients) should probably be admitted to hospital, with potential benefit of thrombolytic treatment, pending results of ongoing clinical trials. Low-risk and intermediate-risk categories are referred to as non-massive pulmonary embolism. Echocardiography or measurement of biomarkers, such as troponin or pro-brain natriuretic peptide,

	Likelihood ratio (95% CI)
To rule in PE	
High-probability ventilation perfusion lung scintigraphy	18.3 (10.3–32.5)
Positive CTA	24.1 (12.4–46.7)
Positive proximal vein CUS of the leg	16.2 (5.6–46.7)
To rule out PE	
Normal or near normal ventilation perfusion lung scintigraphy	0.05 (0.03–0.10)
Negative CTA (mainly single detector)	0.11 (0.06–0.19)
Negative CTA and proximal vein CUS of the leg	0.04 (0.03–0.06)
Negative proximal vein CUS of the leg	0.67 (0.50–0.89)
Quantitative ELISA D-dimer assay less than 500 µg/L	0.08 (0.04–0.18)

Likelihood ratios to rule in PE are positive and to rule out PE are negative. The likelihood ratio is the likelihood that a given test result would be expected in a patient with the target disorder compared with the likelihood that that same result would be expected in a patient without the target disorder—eg, a positive ratio of 20 means that, with the given test result, the patient is 20 times more likely to have PE than not to have PE. Conversely, with a negative ratio of 0.10, with the given test result, the patient is 10 times less likely to have PE than to have PE. PE=pulmonary embolism. CTA=CT angiography. CUS=compression ultrasonography.

Table 2: Performance of some tests or diagnostic algorithms to rule in or rule out PE⁴⁶

	Points
Pulmonary embolism severity index*	
Age >80 years	Age in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Heart rate ≥110 beats per min	+20
Systolic blood pressure <100 mmHg	+30
Respiratory rate ≥30 breaths per min	+20
Temperature <36°C	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20
Simplified pulmonary embolism severity index according to RIETE†	
Age >80 years	+1
History of cancer	+1
History of heart failure or chronic lung disease	+1
Heart rate ≥110 beats per min	+1
Systolic blood pressure <100 mm Hg	+1
Arterial oxygen saturation <90%	+1

In the pulmonary embolism severity index score, classes 1 and 2 are considered low risk, and classes 3–5 high risk. RIETE=Registry of Patients with Venous Thromboembolism. PE=pulmonary embolism. *Class 1=≤65; class 2=66–85; class 3=86–105; class 4=106–125; class 5=>125. †Patients with a score of 0 are low risk; those with scores ≥1 are high risk.

Table 3: Prognostic stratification of PE

might refine prognostic stratification,⁵⁹ but whether their addition to the risk stratification work-up is cost-effective remains to be established.

Standard treatment of deep vein thrombosis and pulmonary embolism

Treatment of non-massive venous thromboembolism has three phases: the initial phase, the early maintenance phase, and the long-term secondary prevention phase (figure 3). Low-molecular-weight heparin and fondaparinux are the cornerstones of initial treatment for patients with deep vein thrombosis and pulmonary embolism.⁴¹ Heparins act by binding to the natural anticoagulant antithrombin, thereby substantially accelerating the inactivation of thrombin by antithrombin and of several other activated coagulation factors (including activated factor X [FXa]). Unfractionated heparin is usually administered as an initial bolus, followed by a continuous intravenous infusion. Because of a large individual difference in the binding of heparins to plasma proteins, the doses should be adjusted to the results of blood tests, such as the activated partial thromboplastin time or the anti-FXa activity.

The main advantage of low-molecular-weight heparins is that they can be administered subcutaneously in fixed weight-adjusted doses without needing monitoring in most cases.⁶² The mechanism of action of these heparins is similar to that of unfractionated heparin, but with a more pronounced effect on FXa compared with thrombin. The clinical equivalence of low-molecular-weight heparin and unfractionated heparin for treating deep vein thrombosis has been confirmed in a meta-analysis.⁶³ One study confirmed this conclusion for

pulmonary embolism.⁶⁴ Fondaparinux, a pentasaccharide, is almost identical to the smallest natural component of heparin that can still bind to antithrombin to specifically inhibit FXa. By contrast with unfractionated heparin and low-molecular-weight heparins, which are derived from the porcine intestinal tract, fondaparinux is a synthetic compound. This drug is non-inferior to low-molecular-weight and unfractionated heparin in patients with deep vein thrombosis^{65,66} and pulmonary embolism,⁶⁶ respectively.

Low-molecular-weight heparin and fondaparinux are mainly cleared by the kidney. Particular caution is advised when the calculated creatinine clearance is less than 30 mL/min. In such cases, anticoagulation options include dose reduction, increase of the interval between injections, monitoring of FXa activity, or use of unfractionated heparin.⁶² Administration of heparins or fondaparinux should overlap during at least 5 days with that of vitamin K antagonists. The parenteral drug can be stopped when the anticoagulant concentration induced by the vitamin K antagonist has reached an international normalised ratio of 2.0. Patients with cancer have been recommended to be treated for at least 3 months with low-molecular-weight heparin rather than with vitamin K antagonists.⁴¹ These antagonists block a late step in the biosynthesis of four plasma coagulation factors (prothrombin or factor II, and factors VII, IX, and X) by the liver. Because of the different half-lives of circulating factors, steady-state anticoagulation cannot be reached before 4–7 days. Vitamin K antagonists include substances with a short (acenocoumarol), intermediate (warfarin, fluindione), or long (phenprocoumon) half-life. For this reason, and because of genetically induced metabolic variability,^{67,68} the variable vitamin K content of food, a narrow therapeutic index, and several interactions with other drugs, treatment with vitamin K antagonists needs close monitoring with the international normalised ratio; the targeted therapeutic level is 2.5 (range 2.0–3.0). Although thrombolysis, regardless of mode of administration, is not better than standard treatment, it could be used in selected patients (especially those with iliac or iliofemoral vein thrombosis and massive pulmonary embolism) if experience and resources are available.

Safety of anticoagulant treatment

All anticoagulant drugs can produce bleeding, especially at the start of treatment (eg, caused by unmasking of lesions). Major bleeding associated with vitamin K antagonists increases with age. Clinical scores—eg, the HEMORR2HAGES score⁶⁹ and the RIETE score⁷⁰ (table 4)—have been prospectively validated (not in venous thromboembolism for the HEMORR2HAGES score), and could guide estimation of the haemorrhagic risk. The safety of treatment with vitamin K antagonists can be improved by encouragement of patients' compliance, avoidance of concurrent drugs with potential

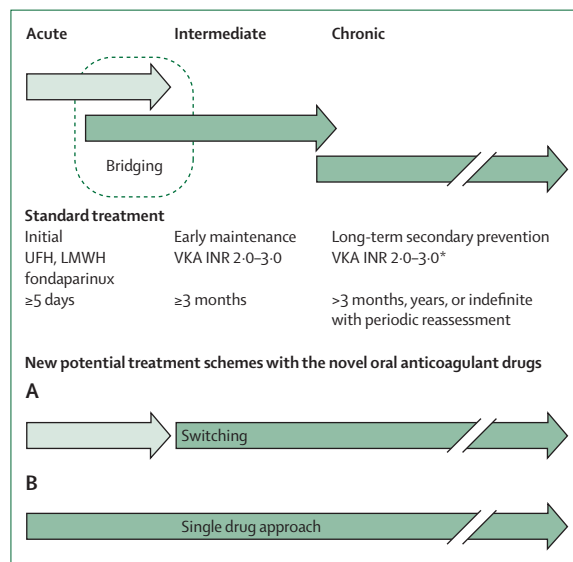


Figure 3: Three phases of the disease with the corresponding standard treatment

A and B depict potentially new treatment schemes that are based on the regimen studied in the RECOVER with dabigatran etexilate (A)⁶⁰ or EINSTEIN DVT with rivaroxaban (B)⁶¹ studies. UFH=unfractionated heparin. LMWH=low-molecular-weight heparin. VKA=vitamin K antagonist. INR=international normalised ratio. *In some patients in whom less frequent INR monitoring is requested, an INR of 1.5–2.0 can also be targeted (American College of Chest Physicians Grade 1A recommendation).⁴¹

interactions, restriction of alcohol ingestion, and, in some patients, with use of self-monitoring or even self-management,⁷¹ which remains debated.^{72,73} Additionally, large loading doses should be avoided to prevent development of a paradoxical prothrombotic state due to the depletion of protein C, a vitamin K-dependent coagulation inhibitor with a very short half-life. Whether rapid turnaround genetic testing will be clinically useful to guide warfarin dosing remains to be established.⁶⁸

Heparin-induced thrombocytopenia is a feared complication of treatment with heparin and low-molecular-weight heparin. Although this complication is rare (extremely rare with fondaparinux), it can provoke devastating venous and arterial thromboembolic consequences.⁷⁴ However, monitoring of platelet counts during treatment with unfractionated and low-molecular-weight heparin has become controversial because of overdiagnosis simply on the basis of a positive heparin-PF4 test. Monitoring of platelet function should not be routinely pursued after 14 days, and should always be combined with clinical risk assessment for heparin-induced thrombocytopenia.

Treatment duration after deep vein thrombosis and pulmonary embolism

The duration of anticoagulation treatment should be dictated by the balance between the risk of recurrent venous thromboembolism with and without treatment, and the risk of treatment-induced haemorrhage. In RIETE,⁷⁵ the rate of recurrent venous thromboembolism while patients were receiving anticoagulant treatment was 7.0%. In the literature review that supports the treatment durations recommended by the 8th ACCP consensus guidelines (table 5), Kearon and colleagues⁴¹ reported that a 3-month course of anticoagulant treatment was as effective as a course of 6–12 months, and that venous thromboembolism related to transient (reversible) risk factors (eg, surgery, trauma) is associated with a reduced risk of recurrence.

The decision about the optimum duration of anticoagulation can be approached on an individual basis that recognises clinical variables,⁷⁶ D-dimer concentration 1 month after stopping of anticoagulant treatment,⁷⁷ or presence of residual thrombi in the leg veins.⁷⁸ These potential methods have not gained widespread attention.⁷⁹ Presently, all patients with deep vein thrombosis or pulmonary embolism should be treated for at least 3 months. In case of a transient or reversible risk factor, especially if this risk factor was the clear precipitant of venous thromboembolism, anticoagulant treatment might then be stopped. In patients with no triggering risk factor (the so-called idiopathic or unprovoked events), anticoagulant treatment should be continued as long as the benefit–risk balance is favourable, whereas patients with venous thromboembolism and cancer should receive anticoagulant treatment until the cancer is considered under control and possibly cured.

	Points
HEMORR2HAGES bleeding risk score*	
Hepatic or renal disease	1
Alcohol abuse	1
Malignancy	1
Age >75 years	1
Uncontrolled hypertension	1
Anaemia	1
Excessive risk of fall	1
Stroke	1
Reduced platelet count or function	1
Previous bleed	2
RIETE bleeding risk score†	
Recent major bleed	2
Creatininaemia >1.2 mg/dL	1.5
Haemoglobin <13 g/dL (male) or 12 g/dL (female)	1.5
Malignancy	1
Clinically overt PE	1
Age >75 years	1

RIETE=Registry of Patients with Venous Thromboembolism. PE=pulmonary embolism. *Patients with a score of 0 have a major bleeding rate (per 1000 patient-years) of 1.9, scores of 1 have a bleeding rate of 2.5, scores of 2 have a bleeding rate of 5.3, scores of 3 have a bleeding rate of 8.4, scores of 4 have a bleeding rate of 10.4, and those with scores >5 have a bleeding rate of 12.3. †Patients with a score of 0 have a major bleeding rate (per 1000 patient-years) of 0.3, scores of 1–3 have a bleeding rate of 2.6, and those with scores ≥4 have a bleeding rate of 7.3.

Table 4: Clinical scores to predict bleeding with anticoagulant treatment

	Recommended treatment duration	Grade of recommendation
First DVT or PE secondary to a transient (reversible) risk factor (provoked event)	3 months	1A
First idiopathic (unprovoked) DVT or PE	At least 3 months	1A
At the end of the initial 3-month period	Assess for long-term Rx	1C
In the absence of contraindication	Long-term Rx	1A
During long-term Rx	Assess risk–benefit balance periodically	1C
Recurrent DVT or PE or strong thrombophilia	Long-term Rx	1A
DVT or PE secondary to cancer	Long-term Rx, preferentially with LMWH during the first 3–6 months, then anticoagulate as long as the cancer is considered active	1A 1C

Recommendation according to the eighth American College of Chest Physicians evidence-based clinical practice guidelines.⁴¹ Grade 1 recommendations pertain to a situation in which the desirable effects clearly outweigh the undesirable effects. A and C qualify the methodological quality of the supporting evidence: A=consistent evidence is available from several randomised controlled trials. C=evidence is available from at least one critical outcome from observational studies, cases series, or randomised controlled trials with flaws. DVT=deep vein thrombosis. PE=pulmonary embolism. Rx=treatment.

Table 5: Recommended duration of anticoagulant treatment for events of venous thromboembolism

Advances in anticoagulant treatment

Several new oral anticoagulant drugs are under development.⁸⁰ These direct (ie, antithrombin-independent) inhibitors of FXa (eg, rivaroxaban, apixaban) or thrombin (eg, dabigatran) avoid most of the drawbacks of heparin and could replace vitamin K antagonists and heparins in

many patients. These drugs are administered in fixed doses, do not need coagulation monitoring in the laboratory, and have very few drug–drug or drug–food interactions. In the randomised, double-blind RECOVER trial,⁶⁰ which involved patients with acute venous thromboembolism who were initially given parenteral anticoagulation treatment for a median of 9 days (IQR 8–11), oral dabigatran etexilate 150 mg twice a day with no monitoring was non-inferior to warfarin (target international normalised ratio of 2·0–3·0) bridged with low-molecular-weight heparin, with a similar safety profile.⁸¹ In the multicentre, randomised, EINSTEIN-DVT and EINSTEIN-EXTENSION studies,⁶¹ rivaroxaban (15 mg twice a day for 3 weeks followed by 20 mg once a day with no monitoring) was non-inferior to a vitamin K antagonist bridged with low-molecular-weight heparin, with a similar safety profile. For long-term secondary prophylaxis, rivaroxaban (20 mg once a day) was better than placebo, with 82% (HR 0·18, 95% CI 0·09–0·39; $p < 0·001$) relative risk reduction of recurrent thromboembolic events and no increase in the risk of major bleeding. However, the rate of clinically relevant non-major bleeding differed significantly between the two groups, increasing from 1·2% in the placebo group to 5·4% in the rivaroxaban group. Figure 3 shows the potential of these new drugs to affect the therapeutic concept of acute venous thromboembolism.

Prevention

Findings from rigorous clinical trials have shown the effectiveness and safety of pharmacological prevention with low, fixed doses of anticoagulant drugs (panel 2). For patients undergoing orthopaedic surgery—eg, total hip or knee replacement—novel oral anticoagulant drugs have been approved for thromboprophylaxis and are available instead of warfarin, heparins, and fondaparinux. Mechanical prophylactic measures, including graduated compression stockings and intermittent pneumatic compression devices, should be considered in

Panel 2: Pharmacological prophylaxis for venous thromboembolism

- Low-dose unfractionated heparin twice or three times a day
- Low-molecular-weight heparins
- Fondaparinux 2·5 mg per day for orthopaedic surgical or general surgical procedures or, in some countries, for acute medical illness (also often used off label when heparin-induced thrombocytopenia is suspected)

Orthopaedics only

- Dabigatran
- Rivaroxaban
- Apixaban
- Warfarin
- Aspirin
- Desirudin

at-risk patients who are not candidates for pharmacological thromboprophylaxis. Inferior vena caval filters can also be used for the primary or secondary prevention of pulmonary embolism, but they will not halt the thrombotic process. In the USA, use of inferior vena caval filters seems to have substantially increased for primary prevention of venous thromboembolism.⁸²

Although prophylaxis for venous thromboembolism is mandated for moderate-risk and high-risk patients at the time of hospital admission,⁸³ the decision to continue prophylaxis after discharge remains difficult. The risk of venous thromboembolism during admission rarely abates by the time a patient is ready for discharge home or to a skilled nursing facility. Rapid transition of patients to skilled nursing or rehabilitation facilities and rapid discharge home with home services have shortened lengths of hospital stay. During admission to hospital, nurses and therapists encourage patients to ambulate and minimise immobilisation. Patients often receive less physical therapy after discharge than during admission, which leads to a paradoxical increase in immobility and a presumed rise in risk of venous thromboembolism. Early hospital discharge minimises the hospital length of stay but blurs the traditional concept of inpatient versus ambulatory care. For example, the risk of venous thromboembolism remains increased in women for the first 12 weeks after surgery.⁸⁴

A contemporary approach to prevention of venous thromboembolism focuses on the continuum of care from hospital to the community. Thus, extended prophylaxis up to 5 weeks is recommended after total hip arthroplasty.⁸³ The MAGELLAN trial⁸⁵ of medical patients admitted to hospital (presented at the 2011 American College of Cardiology Scientific Sessions) reported that in those receiving traditional enoxaparin prophylaxis for 6–14 days for disorders such as heart failure, respiratory failure, or pneumonia, the incidence of death related to venous thromboembolism at 5 weeks was 1·0%, with most deaths occurring after hospital discharge. Findings from a review⁸⁶ of 1897 patients with venous thromboembolism in the Worcester, Massachusetts health-care system showed that 74% of patients suffered deep vein thrombosis or pulmonary embolism in the outpatient setting, not during a hospital admission. 37% of patients with venous thromboembolism had recently been admitted to hospital, and 23% had undergone major surgery in the 3 months before developing acute venous thromboembolism. Of the episodes of venous thromboembolism occurring within 3 months of a previous admission, 67% occurred within the first month after discharge. The median length of admission was 4 days.

In the EXCLAIM Trial,⁸⁷ extended duration prophylaxis for venous thromboembolism was tested after hospital discharge in high-risk medical patients with heart failure, respiratory insufficiency, infection, or reduced mobility. Incidence of venous thromboembolism was reduced in patients receiving extended prophylaxis after

discharge with enoxaparin 40 mg/day. However, a substantial methodological issue with EXCLAIM was the change in enrolment eligibility halfway through the study;⁸⁸ the inclusion criteria were made more restrictive than at the start of the study and required that patients be extremely immobile to participate in the trial. Overall, extended duration enoxaparin reduced the rate of venous thromboembolism at 28 days from 4.0% in the placebo group to 2.5% in the enoxaparin group (absolute risk difference -1.53 , 95% CI -2.54 to -0.52). Major haemorrhage at 30 days was more frequent in patients receiving extended duration enoxaparin than in those receiving placebo. In the IMPROVE registry⁸⁹ of 15 156 medical patients admitted to hospital, 45% of the 184 patients who developed venous thromboembolism had hospital events after discharge rather than in hospital. Independent risk factors for venous thromboembolism were previous venous thromboembolism, known thrombophilia, cancer, age older than 60 years, leg paralysis, immobilisation for at least 1 week, or admission to an intensive-care or coronary-care unit.

The biggest difficulty in the specialty of in-hospital prophylaxis of venous thromboembolism is underuse of available prophylactic anticoagulant drugs. In a review⁹⁰ of almost 200 000 charts of US medical patients at moderate-risk or high-risk of venous thromboembolism who were admitted to hospital, appropriate prophylaxis for venous thromboembolism was ordered in only 34%. In a separate cohort study of patients admitted to hospital with deep vein thrombosis from 183 US institutions, the 2609 medical patients had more concomitant pulmonary embolism than did the 1953 non-medical patients with deep vein thrombosis (22% vs 16%).⁹¹ Paradoxically, patients on the medical service had received prophylaxis for venous thromboembolism far less frequently than had non-medical patients (25% vs 54%). Thus, patients on the medical service are susceptible to so-called double trouble because they more often have prophylaxis omitted, but when they do develop venous thromboembolism, it is often more extensive with more frequent concomitant pulmonary embolism compared with non-medical patients who develop deep vein thrombosis.⁹²

Failure to prevent venous thromboembolism happens worldwide. In ENDORSE, a cross-sectional study, 68 183 patients were enrolled from 358 hospitals in 32 countries across six continents. Of these patients, 52% were at moderate to high risk of developing venous thromboembolism. Although rates of prophylaxis were low, surgical patients more often received guideline recommended prophylaxis than did medical patients (58% vs 40%).⁹³ Of the 9257 US patients from 81 hospitals enrolled in ENDORSE, wide variation was noted in prophylaxis practices for venous thromboembolism. The top quartile of hospitals implemented prophylaxis in 74% of at-risk patients, whereas the bottom quartile implemented prophylaxis in only 40%. Compared with the lowest quartile, more hospitals in the best performing

quartile had residency training programmes (43% vs 5%), a larger number of beds (277 vs 140), and had formulated and implemented individualised hospital-wide prophylaxis protocols for venous thromboembolism (76% vs 40%).⁹⁴ In Switzerland, prophylaxis was not provided to 40% of 257 patients with cancer admitted to hospital before the onset of an acute venous thromboembolic event.⁹⁵

Regardless of the specific prophylaxis strategy selected for venous thromboembolism, institutional and professional culture seems to be changing. Failure to institute venous thromboembolism prophylaxis in at-risk patients will no longer be tolerated. Panel 3 lists catalysts for improved implementation of venous thromboembolism prophylaxis. However, even when pharmacological prophylaxis is ordered for patients admitted to hospital, these orders are not necessarily followed. In one study,⁹⁶ patient refusal was the most common reason for non-adherence to injectable anticoagulant medication for venous thromboembolism.

Diverse approaches are available to improve clinical effectiveness of prophylaxis for venous thromboembolism in patients admitted to hospital. Computerised decision support⁹⁷ with electronic alerts can be a catalyst to the responsible physician to order prophylaxis and, in a randomised controlled trial,⁹⁸ has reduced the rate of symptomatic venous thromboembolism by more than 40%. Multiscreen alerts might be more effective than single-screen alerts.⁹⁹ Such electronic alert systems maintain their effectiveness over time.¹⁰⁰ For hospitals without the resources to establish and maintain computerised systems, hospital staff can screen for at-risk patients not being given prophylaxis and can alert the responsible physician with a telephone call or page.¹⁰¹ Eradication of most hospital-acquired venous thromboembolism is within our reach. By combination of educational efforts with behaviour modifying techniques, implementation of proven prevention strategies can be maximised.¹⁰²

Panel 3: Catalysts for improved implementation of prophylaxis for venous thromboembolism

- Evidence from clinical trials
- Expanded educational outreach to clinicians and the public
- Initiatives for quality improvement, including individualised hospital protocols for prophylaxis
- Electronic reminders to clinicians whose patients admitted to hospital are at high risk, but not given prophylaxis
- Peer pressure
- Oversights in hospital administration
- Government audits and inspection
- Patient and family inquiries
- Advocacy of non-profit organisations
- Financial penalty or withholding of a financial bonus imposed by the government or private insurer
- Malpractice litigation

Contributors

SZG and HB conceptualised and wrote the paper.

Conflicts of interest

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