

Diagnosis and Management of Venous Thromboembolism

Tracy Minichiello, MD^{a,*}, Patrick F. Fogarty, MD^b

^a*Division of Hospital Medicine, Department of Medicine, University of California, 505 Parnassus Avenue, Box 0131, San Francisco, CA 94143, USA*

^b*Division of Hematology/Oncology, Department of Medicine, University of California, 505 Parnassus Avenue, Room M-1286, San Francisco, CA 94143–1270, USA*

Venous thromboembolic disease (VTE), which includes lower-extremity deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major public health concern. In the general population, the annual incidence of VTE has been estimated at approximately 100 per 100,000 persons [1–3], and PE causes up to 200,000 deaths annually in the United States [4].

In hospitalized patients, the prevalence of VTE is approximately 100 times higher than in the general population [1], and varies with indication for admission. Among inpatients not given thromboprophylaxis, the frequency of VTE ranges from 10% to 20% in medical patients up to 80% in high-risk surgical and critical care patients [4]. The frequency of the most devastating consequence of VTE, fatal PE, has been reported to range from 0.01% among low-risk surgical patients to 5% among hospitalized patients who have multiple risk factors [5]. Early, accurate diagnosis and prompt, appropriate treatment of VTE is essential to reducing morbidity and mortality from this disorder.

Diagnosis of venous thromboembolism

In recent years, strategies for assessing pretest probability of VTE have been developed. The original Wells Prediction Rule for DVT [6] comprised a scoring system based on nine clinical characteristics; a score of greater than or equal to 3 (highest pretest probability) was associated with a prevalence of DVT of 17% to 85%, compared with a prevalence of 0% to 13% in

* Corresponding author.

E-mail address: tminichiello@medicine.ucsf.edu (T. Minichiello).

those patients with the lowest pretest probability (Wells score of ≤ 0) [7]. The Rule has since been updated to provide for a “likely” or “unlikely” pretest probability of DVT (Table 1). In the Wells Prediction Rule for PE (Table 2) a score of greater than or equal to 7 (highest pretest probability) correlates with a prevalence of PE of 38% to 78%, compared with a 1% to 3% prevalence among patients with the lowest pretest probability (Wells score of 0–1) [7]. Although the evidence in support of clinical prediction models is strong [7], the value of these methodologies may be highest when combined with D-dimer assessment [8].

D-dimers are generated through degradation of fibrin that has been cross-linked, and indicate recent activity of the coagulation system. The test is sensitive but not very specific for VTE, and a negative D-dimer result (typically reported as < 500 ng/mL) can exclude the diagnosis, particularly in patients with a low pretest probability, averting the need for diagnostic imaging [9]. The highest sensitivity (approximately 95%) exists with ELISA. Agglutination-based assays are less sensitive; indeed, the negative predictive value of non-ELISA-based D-dimer testing may be particularly poor among patient groups with an increased prevalence of VTE, such as elderly or hospitalized individuals [10]. The negative predictive value of D-dimer testing is strengthened when combined with a low pretest probability result from a clinical prediction rule. In this scenario, the incidence of VTE may be as low as 0.5% at 3-months follow-up, whereas patients with a moderate or high pretest probability despite negative D-dimer show a higher frequency of DVT (3.5% and 21.4%, respectively) [8].

Table 1
Pretest probability of DVT: the Wells Prediction Rule

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 d or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2
<i>Interpretation:</i>	
DVT likely	≥ 2
DVT unlikely	< 2

Abbreviation: DVT, deep vein thrombosis.

Adapted from Wells PS, Anderson DR, Rodger M, et al. Evaluation of d-Dimer in the diagnosis of suspected deep vein thrombosis. *N Engl J Med* 2003;349:1227–35; with permission. Copyright © 2003, Massachusetts Medical Society.

Table 2
Pretest probability of PE: the Wells Prediction Rule

Clinical characteristic	Score
Previous PE or deep vein thrombosis	+1.5
Heart rate > 100 beats per minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of deep vein thrombosis	+3
Alternative diagnosis less likely than PE	+3
Hemoptysis	+1
Cancer	+1
<i>Interpretation:</i>	
High probability of PE	≥7
Moderate probability of PE	2–6
Low probability of PE	0–1

Abbreviation: PE, pulmonary embolism.

Data from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED d-dimer. *Thromb Haemost* 2000;83:416–20.

Elevated D-dimer levels are characteristic of recent trauma or bleeding and are also frequently detected in the setting of hospitalization, advanced age, and malignancy, further reducing the positive predictive value of the D-dimer assay in those patient groups [11].

Diagnosis of deep vein thrombosis

Investigation for DVT usually is initiated when a patient is observed to have any of the following: calf or lower-extremity swelling (present in 88% of individuals ultimately diagnosed with DVT); pain or tenderness in the affected extremity (56%); or increased warmth or erythema (30%–40%) [12]. The Homans' sign (posterior calf tenderness on passive dorsiflexion of the foot) is present in fewer than 15% of cases of DVT, and a palpable cord is detectable in only 6% [12]. Alternatively, DVT may be discovered in an asymptomatic patient by radiographic imaging performed for other reasons, or in a patient who has been diagnosed with PE.

Doppler ultrasonography is recommended as the initial test for the radiographic diagnosis of lower-extremity DVT, because of its wide availability; noninvasive nature; low cost; and high sensitivity (89%–100%) and specificity (86%–100%) for symptomatic DVT [13,14]. Sensitivity is highest for proximal DVT, and decreases for distal lesions. Typical findings on Doppler ultrasonography include direct observation of an occlusive intraluminal thrombus, noncompressibility of a vein, or reduced or absent blood flow by color Doppler. Comparison with prior ultrasound studies (if available) may be helpful when assessing for DVT recurrence, because symptoms of the postthrombotic syndrome (PTS) or other conditions in the previously affected extremity may be similar to those of acute thrombosis.

Despite its extensive use in clinical trials and status as the gold standard diagnostic method for identification of DVT, contrast venography is not recommended for routine evaluation of DVT, because of patient discomfort, interobserver variability in interpretation, and high cost, among other factors [15]. Impedance plethysmography [16] and MRI [17] are generally not as accessible as Doppler ultrasonography in most institutions, but may have a role for evaluation of recurrent DVT.

Thrombi that are detected in the veins of the calf are generally accepted to have a lower potential for proximal propagation, leading to a reduced clinical concern for evolution to PE [18]. Although withholding anticoagulation may be acceptable in asymptomatic patients with distal lower-extremity DVT, serial imaging over a period of 1 to 2 weeks is recommended to ensure absence of clot extension [19]. In contrast, if a patient has symptoms (eg, pain, swelling) in the affected extremity, treatment should be administered as for proximal DVT (see later).

Diagnosis of pulmonary embolism

Typically, evaluation for PE is pursued when a patient complains of sudden shortness of breath; chest pain; hemoptysis; or when clinical findings, such as tachypnea (70% of patients with PE), tachycardia (43%), hypoxia (18%), or hypotension (10%), are present [12]. Alternatively, PE may be incidentally detected when performing imaging of the thorax for other reasons. Three main categories of overall clinical presentation exist: (1) massive PE marked by persistent hemodynamic instability; (2) submassive PE marked by evidence of right ventricular (RV) strain on echo, ECG, or right heart catheterization, without hemodynamic compromise; and (3) non-massive PE marked by lack of RV compromise and normal hemodynamics.

The gold standard for diagnosis of PE is the pulmonary angiogram. This procedure is associated with a mortality rate of less than 0.5% and a slightly higher rate of other complications, including contrast nephropathy, cardiac arrhythmias, and cardiac perforation [20]. Ventilation perfusion scanning is noninvasive, but results are frequently nondiagnostic. Helical CT scanning is noninvasive, typically readily available, and has sensitivity for PE of up to 90% and a specificity of 95% [21]. Although sensitivity declines for detection of distal thrombi, negative CT results are associated with a low frequency (approximately 1%) of subsequent detection of clinically significant VTE, especially in the setting of a low clinical probability of VTE [22,23]. A diagnostic algorithm involving a low-probability clinical prediction rule, negative D-dimer assessment, and negative CT has been evaluated, showing a low frequency (<1.5%) of subsequent fatal and non-fatal VTE [24]. MRA has better sensitivity for lobar thromboses than for segmental or subsegmental lesions [25]; high cost and limited availability, among other issues, have hindered widespread use of this diagnostic modality.

Abnormalities of the transthoracic echocardiogram in patients with PE include RV hypokinesis, RV hypertrophy, and tricuspid regurgitation, and may be prognostic. For instance, RV dysfunction is associated with a doubling of PE-related mortality, although the effect may be most pronounced in hypotensive patients [26]. In one retrospective analysis of normotensive patients who presented with PE, however, RV hypokinesis remained an independent predictor of early death (hazard ratio, 1.94) [27]. Further data are required to clarify the role of echocardiogram in the initial assessment of patients with PE. Two tests, brain natriuretic peptide and serum troponin level, lack sufficient specificity to be useful in the diagnosis of PE, but may be helpful in determining prognosis. Elevated brain natriuretic peptide levels (>90 pg/mL) in patients who present with acute PE are associated with adverse clinical outcomes, including need for thrombolysis, requirement for cardiopulmonary resuscitation, and death [28]. Elevations in troponin levels indicate cardiac injury and are associated with an increased incidence of 30-day mortality [29]. In one study, a concomitant troponin level of greater than 0.07 $\mu\text{g/L}$ and brain natriuretic peptide level of 600 ng/L were associated with a 33% mortality at 40 days, compared with no deaths among patients with normal levels [30]. Insufficient data exist, however, to lead to a recommendation that these adjunctive laboratory tests be performed at presentation in all patients.

Treatment of venous thromboembolism

The mainstay of treatment for VTE is anticoagulation. Anticoagulants do not dismantle thrombi directly; rather, they prevent propagation of the thrombus while the endogenous fibrinolytic system works to decrease the clot burden. In most cases, treatment of VTE should be based on confirmatory diagnostic studies, but if the pretest probability is high enough, anticoagulation may be started empirically pending definitive testing. Before initiation of anticoagulation, baseline laboratory studies should be obtained including urinalysis, Hemocult, hemoglobin, hematocrit, platelet count, prothrombin time, International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), blood urea nitrogen, and creatinine. Suggested anticoagulation regimens according to presentation are listed in Table 3.

Parenteral agents for the acute treatment of VTE include weight-based unfractionated heparin (either intravenously [31,32] or subcutaneously dosed [33]); weight-based low-molecular-weight heparin (LMWH) [34,35]; and the synthetic anti-Xa agent, fondaparinux (see Table 3) [36,37].

Intravenous unfractionated heparin typically is administered by an initial bolus (loading) dose followed by a continuous infusion; ensuing dose adjustments should be made using a standard nomogram [38,39]. Weight-based, subcutaneous unfractionated heparin also may be used with aPTT monitoring and dose adjustment to maintain the aPTT in therapeutic range

Table 3
Suggested anticoagulation regimens for the initial treatment of VTE

Event	Treatment (choose one)
DVT, lower extremity	<p>LMWH</p> <p>Enoxaparin, 1 mg/kg subcutaneously twice daily Enoxaparin, 1.5 mg/kg subcutaneously daily Tinzaparin, 175 units/kg subcutaneously daily Dalteparin, 200 units/kg subcutaneously daily</p> <p>Subcutaneous UFH: aPTT monitoring 15,000 units or 17,500 units every 12 h (initial dose for patients weighing 50–70 kg and > 70 kg, respectively) with aPTT monitoring</p> <p>Subcutaneous UFH: no aPTT monitoring 330 units/kg × 1 then 250 units/kg every 12 h</p> <p>Fondaparinux 7.5–10 mg subcutaneously daily, depending on weight</p> <p>IV UFH 80 units/kg bolus (minimum, 5000 units; maximum, 10,000 units) followed by a continuous infusion of 18 units/kg/h.</p> <p>Note: begin warfarin concurrent with initial dose of parenteral anticoagulant as selected above</p>
DVT, upper extremity	<p>See DVT, lower extremity</p> <p>Consider thrombolysis in appropriate candidates</p>
Nonmassive PE	<p>See DVT, lower extremity</p> <p>Risk stratification suggested to guide additional therapy and triage</p>
Submassive PE	<p>See DVT, lower extremity</p> <p>Risk stratification suggested to guide additional therapy</p> <p>Thrombolysis in selected patients</p>
Massive PE	<p>IV UFH</p> <p>Thrombolytic therapy (choose one)</p> <p>Alteplase, 100-mg infusion over 2 h, followed by IV UFH Alteplase, 100-mg bolus (if cardiac arrest) Urokinase, 4400 IU/kg loading dose over 10 min followed 4400 IU/kg/h for 12 h</p> <p>Note: for urokinase, heparin infusion should be administered concurrently</p>
VTE and CrCl < 30 mL/min	<p>UFH (see DVT, lower extremity)</p>
VTE and cancer	<p>Dalteparin (see DVT, lower extremity)</p> <p>Tinzaparin (see DVT, lower extremity)</p> <p>Use LMWH as initial treatment and for at least 3–6 mo</p>

Abbreviations: aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

[40,41]. More recently, it has been shown that weight-based, subcutaneous unfractionated heparin without aPTT-based dose adjustment was as safe and effective as LMWH in the acute treatment of VTE. Interestingly, no association between a low aPTT and recurrent VTE or between a high aPTT and bleeding complications was observed [42].

LMWH and unfractionated heparin are equally efficacious for the acute treatment of DVT and nonmassive PE, both reducing the risk of early recurrence to approximately 3% [43,44]. Given the ease of dosing, lack of need for laboratory monitoring, trend toward superiority in prevention of recurrence and lower bleeding rates in systematic reviews, and ease of transition to the outpatient arena, LMWH is the recommended agent [40]. Some LMWHs can be dosed once or twice daily, without a significant difference in major bleeding or VTE recurrence [45,46]. Once-daily dosing with some LMWH preparations, however, may not be appropriate for patients with renal insufficiency, obesity, pregnancy, or active malignancy.

Fondaparinux, administered subcutaneously once daily, has been compared with LMWH for acute treatment of DVT [35] and unfractionated heparin for acute treatment of PE [37]. A weight-based regimen has been shown to be equally effective as LMWH or unfractionated heparin in preventing recurrent VTE with no difference in bleeding or mortality. Fondaparinux has a very long half-life (17 hours) and currently there is no antidote for easy reversal of the anticoagulant effect.

Warfarin is generally started at daily doses ranging from 2.5 to 10 mg and can be initiated along with a parenteral anticoagulant for the acute treatment of VTE. Selection of the starting dose of warfarin should include consideration of ethnicity, weight, age, nutritional status, and thyroid function (Box 1); concomitant medications should also be considered (Box 2). In

Box 1. Initiation of warfarin therapy in the hospitalized patient

- Usual initiation dose = 5 mg
- Consider higher initial dose (eg, 7.5 mg) in the following populations
 1. Weight >85 kg
 2. African American patients
 3. Clinical hypothyroidism
 4. Concomitant medications that decrease warfarin effect^a
- Consider lower initial dose (eg, 2.5 mg) in the following populations
 1. Frail or advanced age (>75 years)
 2. Asian patients
 3. Hepatic insufficiency
 4. Malnutrition or poor oral intake
 5. Clinical hyperthyroidism
 6. High bleeding risk
 7. Concomitant medications that increase warfarin effect^a

^a See Box 2.

Box 2. Effect of selected agents on the INR in warfarin-anticoagulated patients↑ *INR*

Erythromycin
Metronidazole
Fluconazole
Itraconazol
Ketoconazole
SMX-TMP
Amiodarone
Cimetidine
Phenytoin
Statins
Alcohol

↓ *INR*

Phenobarbital
Rifampin, rifabutin
Carbamazepine
Vitamin K
Phenytoin (chronic use)
Sucralfate
Ginseng
Alcohol

hospitalized patients, a starting daily dose of 5 mg usually results in timely achievement of a therapeutic INR without excessive bleeding [47,48]. Various polymorphisms for the CYP2C9 gene in the cytochrome P-450 system correlate with impaired warfarin metabolism [49,50], whereas polymorphisms in the VKORC1 gene in the vitamin K epoxide reductase complex correlate with warfarin sensitivity or resistance [51,52]. Recently, algorithms have been developed to predict the starting dose of warfarin based on genetic variables, clinical data, and initial INR values [53]. Outcomes studies evaluating the clinical impact of genetic testing to guide warfarin therapy have not been completed and recommendations to test patients before initiation are premature.

In hospitalized patients, the INR should be monitored daily during warfarin initiation. As a vitamin K antagonist, warfarin depletes vitamin K–dependent coagulation factors with the shortest half-life first. Activities of factor VII (accounting for the initial rise in INR), and protein C (a natural anticoagulant, resulting in a transient hypercoagulable state) are reduced initially, followed by factor IX, factor X, and prothrombin. The

half-lives of these factors are 12 hours, 45 hours, and 60 hours, respectively; an average of 5 days is required to achieve a steady-state reduction. For this reason, the parenteral anticoagulant should be continued for a minimum of 5 days, and at least and until the INR is greater than 2.0 on 2 consecutive days.

Both LMWH and fondaparinux are cleared by the kidneys, leading to accumulation in patients with renal insufficiency, and fondaparinux is contraindicated in patients with a creatinine clearance less than 30 mL/min. Treatment with unfractionated heparin is preferred. If the creatinine clearance is between 30 and 50 mL/min, LMWH may be used, but anti-Xa levels (drawn after ≥ 24 hours on therapy, 4–6 hours after a given dose) should be monitored. LMWH also has less predictable pharmacokinetics in this group of patients, and should be used with caution in patients weighing less than 50 kg. Anti-Xa monitoring is advised in these patients.

Thrombolysis

Thrombolytic agents activate the fibrinolytic system, resulting in more rapid resolution of a thrombus than with use of anticoagulation alone. Because the risk of bleeding is increased with use of these agents, patients who may benefit from thrombolysis should be selected carefully.

The pharmacologic approach to therapy in patients with nonmassive PE and most DVT involves only anticoagulation. Although there are no prospective randomized studies evaluating the efficacy of thrombolysis in patients with massive PE, the extremely high in-hospital mortality rate (approaching 30%) and potentially improved outcomes on subgroup analysis [44] have led to recommendations for use of thrombolysis in this setting [40]. In contrast, administration of thrombolytic agents for submassive PE remains controversial. Mortality from submassive PE, despite initial hemodynamic stability, is significant and ranges from 4% to 13% [54]. A single randomized, controlled trial of systemic thrombolysis for submassive PE compared with usual care with anticoagulation alone [55] showed a significant difference in the primary outcome (combined end point of treatment escalation and mortality) between the treatment groups, favoring thrombolysis. The difference, however, was related entirely to escalation of treatment, and the groups were similar in terms of mortality and recurrent VTE. A large European trial is underway to define better the risks and benefits of thrombolysis in patients with submassive PE.

Large proximal iliofemoral DVT has been associated with an increased risk of PTS. Manifestations of PTS can range from mild swelling of the affected leg on exertion or assumption of dependent positioning to constant pain, swelling, and inability to bear weight for any length of time. Because PTS is thought to be related to valvular incompetence, which is related to rates of recanalization, it has been postulated that more rapid and complete clearing of a significant intraluminal thrombus may lead to reduced risk for

PTS. Indeed, registry data show that patients with acute thrombosis (symptoms <10 days) who are treated with catheter-directed thrombolysis and achieve complete resolution of the thrombus have higher 1-year patency rates than those who do not achieve complete lysis [56]. A single, small randomized trial evaluating thrombolytic therapy versus conventional anticoagulation for acute proximal DVT [57] showed a 6-month patency rate of 72% in patients who received catheter-directed thrombolysis, compared with 12% in patients treated with anticoagulation alone. Given the increased bleeding risk associated with thrombolysis, the decision to pursue this therapy must be considered carefully. Ideally, only patients with significant proximal disease who are at low risk of bleeding, and find themselves in a center experienced with this approach, should be regarded as eligible. Although there are currently no randomized controlled trials of the use of thrombolytic agents in the management of upper-extremity DVT, reports of improved outcomes in selected cases has led the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy to propose that thrombolytics be considered in patients who have a low risk of bleeding and recent onset of symptoms [40]. Otherwise, the initial therapy in patients with acute upper-extremity DVT should mirror that of DVT of the lower extremity.

Cancer-related venous thromboembolism

None of the components of Virchow's triad (underlined in the bulleted points next) can be underestimated in their potential to promote and maintain a prothrombotic state in the cancer patient:

- Chemotherapy, cytokines induced by tumor cells, and malignant cells themselves can all lead to endothelial damage.
- Tumors may produce a circulating procoagulant or stimulate disseminated intravascular anticoagulation resulting in a hypercoagulability.
- Venous compression by metastatic disease or bulky lymphadenopathy can result in stasis.

Patients with cancer-related thrombosis have a threefold higher rate of recurrence while on oral anticoagulation compared with patients with non-cancer-related thrombosis. There may also be an increased risk of bleeding associated with warfarin therapy in cancer patients [58].

Some LMWHs seem to be more effective than warfarin in preventing recurrent thrombosis in patients with cancer and VTE, as evidenced in a recent trial that evaluated the efficacy of extended-duration treatment (6 months) with the LMWH dalteparin versus standard long-term treatment with warfarin. In this study, the frequency of VTE recurrence was 17% in the warfarin group, compared with 9% in the dalteparin group. There was no significant difference in bleeding events between the two groups. American College of Chest Physicians in their 2004 recommendations suggest at least

3 to 6 months of LMWH, with once-daily tinzaparin or once-daily dalteparin, for acute treatment of cancer-related VTE because of this significant reduction in symptomatic recurrences [40].

Outpatient management of venous thromboembolism

Most DVT is now treated in the outpatient arena, a practice that is strongly supported by the evidence [59]. One recent study highlighted a number of factors that may be associated with higher risk of earlier complications, and identify patients who might benefit from inpatient treatment. Cancer, bilateral DVT, renal insufficiency, congestive heart failure, weight less than 70 kg, and immobility predicted a higher risk of recurrence or bleeding complications [60].

Scant evidence is available regarding outpatient treatment of PE. The FIDO trial, based in Canada, compared unmonitored weight-based subcutaneously dosed unfractionated heparin with LMWH for the acute treatment of DVT or PE; over one third of patients with symptomatic PE were able to be treated entirely as outpatients [42]. One small prospective cohort study found outpatient treatment of PE to be safe and effective for selected patients, but required admission for those patients with hemodynamic instability, hypoxia requiring oxygen therapy, severe pain, high risk of major bleeding, or a concomitant condition requiring hospitalization [61]. In the United States, however, most patients with suspected acute PE are treated in the hospital, at least initially.

Adjunctive therapy for venous thromboembolism

All patients diagnosed with DVT should be prescribed a graduated compression stocking for the affected lower extremity; ideally, these should exert 30 to 40 mm Hg pressure at the ankle. The stocking should be worn for 1 to 2 years on the affected leg. When combined with long-term anticoagulation, graduated compression stocking may reduce the incidence and severity of PTS, in some cases by up to 50% [62,63].

Although historically it was thought that bed rest was safest for preventing PE in patients with acute proximal DVT, this has not been supported in the literature [64]. Early ambulation with compression may decrease both propagation of the thrombus and development of PTS [65,66].

Inferior vena cava filters

The use of inferior vena cava (IVC) filters is becoming increasingly common. The only generally agreed on indication for placement of an IVC filter is prevention of PE in a patient with an acute DVT in the setting of absolute contraindication to anticoagulation. The following additional uses of caval filters have also been described: to prevent PE in patients with free-floating iliofemoral thrombus, in chronic thromboembolic pulmonary hypertension,

in acute PE and significant underlying cardiopulmonary disease, in cases of recurrent PE despite adequate anticoagulant therapy, and in patients undergoing thrombolysis. In other settings, placement of IVC filters should be avoided if at all possible. Complications associated with filter placement include migration, insertion site infections, and vessel penetration. IVC thrombosis following placement of IVC filters occurs commonly; rates are reported to be between 2% and 10%, although one study that provided long-term follow-up found rates to be as high as 20% to 30% [67].

The only randomized trial evaluating the use of IVC filters to prevent PE in patients with proximal iliofemoral DVT showed that, compared with patients who received anticoagulation alone, those who received IVC filter placement in addition to anticoagulant therapy had lower rates of symptomatic PE at 14 days (1.1% versus 4.8%; 95% confidence interval [CI], 0.05–1.05) and 2 years (3.4% versus 6.3%; 95% CI, 0.21–1.41) but higher rates of DVT at 2 years (20.8% versus 11.6%; 95% CI, 1.09–2.94) [68]. An 8-year follow-up study of this trial was recently published, which again found decreased rates of symptomatic PE in patients with IVC filter but increased rates of DVT [69]. There was no difference in the rates of PTS. No randomized controlled data on the performance of these devices in patients in the acute phase who are not concurrently anticoagulated are available.

If an IVC filter must be placed in a patient with a temporary contraindication to anticoagulation, it is recommended to start a full course of anticoagulation as soon as deemed safe. Guidelines created by the Thrombosis Interest Group of Canada are available on-line and have been recently reviewed (www.tigc.org).

Within the past several years, certain types of IVC filters have been approved for temporary use and retrieval; these are most useful for individuals with venous thrombosis who have a time-limited barrier to use of anticoagulants (eg, impending surgery). A retrospective review found retrievals, performed between days 1 and 139 postplacement, successful in 85% of patients [70]; anticoagulation was not interrupted for filter retrieval. Retrieval failures were attributed to thrombus within the filter (50%) and technical difficulties, including tilting of the filter, and embedding in the vessel wall (50%) [70]. The rate of success of retrieval probably declines as time progresses, so to avoid inadvertent conversion of a temporary filter to a permanent one, it is critical to arrange close follow-up for patients postplacement so that removal actually occurs.

Etiology of venous thromboembolism

Understanding the risk factors for thrombosis helps providers estimate the risk of recurrence and make appropriate recommendations regarding duration of treatment. The most important predictor of recurrence is the presence or absence of removable (eg, transient) risk factors at the time of the event (Table 4) [71]. Assessment for a transient risk factor is best

Table 4
Risk of recurrent VTE after stopping anticoagulant therapy

Variable	Relative risk of recurrence
Transient risk factor	0.5
Persistent risk factor	≥ 2
Cancer	< 3
Discontinuation of estrogen	< 1
Unprovoked VTE	≥ 2
Distal DVT versus proximal DVT or PE	0.5
Venal caval filter	< 1.8
Protein C, S, antithrombin deficiencies	1–3
Heterozygous factor V Leiden	1–2
Homozygous factor V Leiden	4.1
Heterozygous prothrombin gene mutation G20210A	1–2
Heterozygous for both factor V Leiden and G20210A prothrombin gene	2–5
Factor VIII level > 200 IU/dL	< 6
Antiphospholipid antibodies	2–4
Hyperhomocysteinemia	2.7
Second versus first episode of VTE	< 1.5

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

Adapted from Kearon C. Long-term management of patients after venous thromboembolism. *Circulation* 2004;110(Suppl I):I-10–I-18; with permission.

performed at the time of presentation, when patient recall is highest for such factors as trauma; medications (oral contraceptives, hormone-replacement therapy, exposure to heparin); prolonged air travel; immobilization; or recent surgery. Additionally, VTE is associated with a number of systemic diseases (Table 5). It is the duty of the treating clinician to search for associated diseases that may change management and uncover a previously undiagnosed disorder.

Cancer

Approximately 10% of patients who present with unprovoked events are diagnosed with cancer within a few years of presentation with VTE [72]. This risk is highest in the first 1 to 6 months after presentation and declines over the subsequent 2 years.

In addition to a thorough history and physical examination, current practice for cancer screening includes performing a complete blood count, liver function tests, calcium level, urinalysis, chest radiograph, and age-appropriate malignancy screening. A recent trial of screening for occult malignancy in patients with idiopathic VTE randomized patients to the current practice versus extensive screening, including abdominal ultrasound, CT scan, barium swallow, sigmoidoscopy and colonoscopy, Hemoccult assessment, sputum cytology and tumor markers, mammography, Pap smear, and prostate-specific antigen. The authors found malignancy in 13% of the

Table 5
Systemic diseases associated with thrombosis

Systemic disease	Clinical features	Diagnostic data
Inflammatory bowel disease	Bloody diarrhea, aphthous ulcers, arthritis, rash	Histologic analysis of intestinal biopsy specimens
Nephrotic syndrome	Periorbital edema, peripheral edema	Urine protein analysis
Behçet's disease	Oral ulcers, genital ulcers, ophthalmologic issues	—
Myeloproliferative disorders (P. Vera, essential thrombocytosis)	Pruritis, plethora	CBC, JAK-2 mutation
Sickle cell disease	Anemia, sickle crises	Evaluation of the blood smear, hemoglobin electrophoresis
Antiphospholipid antibody syndrome	Livedo, arthritis, rash	Lupus anticoagulant, ELISA for anticardiolipin antibody IgG and IgM (assess ≥ 3 mo after acute event)
Cancer	Weight loss, night sweats	CBC, LFTS, PSA, pap smear, routine cancer screening
Paroxysmal nocturnal hemoglobinuria	Hemolytic anemia	CBC, flow cytometry for CD55, CD59
Pregnancy	Amenorrhea	Urine pregnancy test (all women of childbearing age)

Abbreviations: CBC, complete blood count; LFTs, liver function tests; PSA, prostate-specific antigen.

intervention group with only a single case of malignancy subsequently identified, whereas 10% of the control group was found to have a malignancy at 2-year follow-up. Those malignancies identified by extensive screening were earlier stage; however, there was no difference in cancer-related mortality at 2 years [73]. Given the lack of a survival advantage and the significant cost, extensive cancer screening currently cannot be recommended; a cost-effectiveness analysis is underway.

Thrombophilia

About 50% of patients presenting with unprovoked VTE have laboratory evidence of an inherited thrombophilic disorder. Deficiencies in protein C, S, and antithrombin tend to present a higher risk for first and recurrent VTE and present at a younger age, whereas heterozygosity for the factor V Leiden or prothrombin gene mutations are weaker risk factors (see Table 4). Sending a thrombophilia work-up at the time of acute thrombosis is associated with high rate of false positivity, because acute thrombosis may result in decreased levels of protein C, protein S, and antithrombin, and increased anticardiolipin antibodies, appearance of lupus anticoagulants, and elevated factor VIII levels. Moreover, heparin can decrease antithrombin levels,

warfarin decreases proteins C and S, and both warfarin and heparin can interfere with lupus anticoagulant assessment. For these reasons, it is best to delay testing in most patients until 3 months after the event. If a clear transient risk factor for thrombosis is present and there is no family history, however, testing is not likely to change management and should be deferred.

Duration of anticoagulation

Decisions regarding the duration of anticoagulation beyond the usual treatment of VTE must take into consideration both the risk of clinically significant recurrent thrombosis were anticoagulation to be discontinued [71] and the risk of bleeding caused by anticoagulation. This assessment must be performed on a case-by-case basis and should be repeated annually in patients who are being managed with indefinite anticoagulation. Patient preferences must also be considered.

The major determinant of risk of recurrence is the clinical scenario surrounding the initial event. The risk of recurrence after anticoagulation is stopped is much lower if the event was provoked by a removable risk factor [74,75]: the more significant the removable risk factor, the lower the risk of recurrence. The following may also influence decisions regarding duration of anticoagulation or extension of anticoagulation beyond the usual treatment period:

- Location of the thrombosis: For instance, patients who present with isolated calf vein thrombosis have a lower risk of recurrence (RR, 0.5) compared with those with proximal vein thrombosis. Concern over recurrence may be enhanced, however, if the initial event occurred in a particularly problematic site, such as dural sinus, mesenteric vessel, and so forth.
- Type of thrombosis: In patients who initially present with PE, the risk that a recurrent event also will be PE is higher than in patients who initially present with DVT [76].
- Cancer: Patients with active malignancy and VTE have a recurrence risk that is two to three times that of patients with non-cancer-related thrombosis.

Importantly, results from the laboratory work-up of thrombophilia typically have little impact on decisions regarding duration of anticoagulation, with the exception of detection of the antiphospholipid antibody syndrome (which usually mandates indefinite anticoagulation) and perhaps discovery of (rarer) serious, familial disorders (eg, antithrombin deficiency).

Duration of anticoagulation: current clinical practice

Studies have shown that anticoagulation with a vitamin K antagonist for less than 3 months after detection of VTE is associated with higher risk of

recurrence, whereas extended duration therapy is associated with the lowest risk of recurrence [59]. Current recommendations for duration of therapy according to presentation and other clinical risk factors are outlined in Table 6 [40].

The goal INR for initial treatment of VTE with warfarin is 2.5 (range INR, 2.0–3.0); patients whose thrombosis occurred in the setting of a transient, reversible risk factor may receive 3 months of treatment, whereas patients with an idiopathic event usually receive a minimum of 6 to 12 months of treatment, although recurrent rates rise once anticoagulation is discontinued regardless of the duration.

Intensity of anticoagulation

After a minimum of 3 months of full-intensity warfarin, treatment with lower-intensity warfarin (goal INR, 1.5–2.0) was tested in the extended treatment of unprovoked VTE in the PREVENT trial [77]. At 1-year follow-up, low-intensity warfarin was associated with an incidence of recurrence of 2.6% per patient-year versus 7.2% per patient-year in the placebo arm. In the ELATE trial, however, full-intensity therapy was superior to

Table 6
Recommendations for duration of therapy from the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy: evidence-based guidelines

Scenario	Duration of therapy	Additional comments
Transient risk factor ^a	3 mo	Give VTE prophylaxis in any subsequent high-risk setting
Isolated calf vein thrombosis	3 mo	—
Unprovoked thrombosis	6–12 mo	Consider indefinite anticoagulation
Cancer-related VTE	Continue while cancer active, metastatic, or undergoing therapy	Treatment with LMWH (dalteparin or tinzaparin) recommended for first 3–6 mo
Recurrent VTE	Indefinite	—
Significant underlying thrombophilia ^b	12 mo	Consider indefinite anticoagulation

Abbreviations: LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

^a Major transient risk factors include major surgery, major trauma, major hospitalization, plaster cast immobilization. Minor transient risk factors include pregnancy; hormonal therapy; prolonged airline travel (>8 h).

^b Significant thrombophilia includes documented antiphospholipid antibody syndrome; two or more thrombophilic conditions (combined factor V Leiden and prothrombin 20210 gene mutation); antithrombin deficiency; protein C deficiency; protein S deficiency; hyperhomocysteinemia; persistently elevated factor VIII levels.

Data from Buller HR, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3 Suppl):401S–428S.

low-intensity therapy (0.6% recurrent VTE per patient-year versus 1.9% recurrence per patient year, respectively); there was no difference in major bleeding between the groups [78]. Full-intensity warfarin is preferred for extended-duration treatment, because it is more effective than low-intensity treatment, and is not associated with an increase in major bleeding rates over a low-intensity program. Patients may prefer the convenience of low-intensity anticoagulation, however, because INR monitoring may be performed less frequently.

Further risk stratification

Committing a patient to lifelong anticoagulation is clearly not without risk. Because up to 70% of patients with unprovoked thrombosis do not experience recurrence, reserving indefinite therapy for only those who are at highest risk seems to be the best approach. There are increasing data available to help individualize this assessment of risk.

Prandoni and colleagues [79] examined patients with unprovoked thrombosis for evidence of residual vein obstruction by ultrasound at 3 months postdiagnosis (and serially thereafter, if residual vein obstruction was present). Evidence of residual vein obstruction was associated with a higher risk of VTE recurrence once anticoagulation was stopped, compared with those without residual vein obstruction (23% versus 4%, respectively, over 2 years).

A number of cohort studies have now shown that patients with elevation in D-dimers measured approximately 30 days after cessation of an adequate course of anticoagulation are at increased risk of recurrence compared with those patients with normal or low D-dimers [80–82]. Palareti and colleagues [83] performed D-dimer testing (measured by qualitative assay 1 month after cessation of anticoagulation) in patients with a first occurrence of unprovoked VTE who had received a minimum of 3 months of anticoagulation. Patients with a negative D-dimer remained off anticoagulation, whereas patients with positive D-dimer were randomized to either restart anticoagulation or remain off therapy. At an average follow-up time of 18 months, patients with an elevated D-dimer level who did not receive anticoagulation had a recurrence rate of 15%, compared with 3% among patients in whom anticoagulation had been resumed because of an elevated D-dimer and 6% among patients who remained off anticoagulation in response to a normal D-dimer. Given concerns about the persistent risk of VTE recurrence rate after discontinuation of anticoagulation despite a negative D-dimer and uncertainties regarding interpretation of clinical trials results that are based on qualitative versus quantitative D-dimer assays, the role of routine D-dimer testing to determine duration of anticoagulation for idiopathic VTE is still debated. Another large management trial is underway that may help to clarify these issues.

In patients with PE, RV dilation on presentation is a predictor of short-term adverse outcome. Further, more recent data suggest that persistent RV

dilation at the time of discharge also predicts for a higher risk of recurrent VTE over the subsequent 2 to 3 years (30%, compared with 3% and 11%, respectively, in those with regression of RV dilation or no RV dilation on admission) [84].

Improving safety of anticoagulation

Anticoagulants are among the most common drugs associated with medication errors [85]. The Institute for Healthcare Improvement has included the prevention of harm from anticoagulants in its recently launched 5 Million Lives Campaign (<http://www.ihl.org/IHI/Programs/Campaign/>). Additionally, as a 2008 National Patient Safety Goal, the Joint Commission has proposed the addition of a requirement to “reduce the likelihood of patient harm associated with the use of anticoagulation therapy.”

Inpatient anticoagulation services, staffed and managed by pharmacists, can be indispensable in advancing safe in-hospital practices surrounding the use of anticoagulation. Such services have been associated with a reduction in supratherapeutic INRs, fewer bleeding incidents, decreased length of stay, and decreased readmission for bleeding complications [86,87].

One specific focus of the proposed patient safety provisions concerns the discharge process for patients who have received therapeutic-dose anticoagulation during the hospital admission and who have been directed to continue anticoagulation as an outpatient. Communication between inpatient and outpatient providers at the time of discharge is critical. Inpatient providers should furnish those who will see the patient in follow-up for management of their anticoagulation with detailed information including discharge medications, recent INR trend, recent warfarin daily doses, and the recommended timing of the initial postdischarge INR measurement. Before discharge, patients and family members should also receive intensive education about anticoagulation therapy, highlighting (for patients discharged on warfarin) the importance of diet issues (including alcohol use), prescription and over-the-counter medications, and herbal preparations. Patients should be familiar with the signs and symptoms of bleeding or recurrent thrombosis and should be explicitly instructed to seek medical attention if they are concerned about either of these complications. Providers must emphasize the potential risks of anticoagulant therapy, the narrow therapeutic window, and the need for meticulous follow-up.

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