Current and emerging options in the management of venous thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is a common disease whose diagnosis is challenging. The best diagnostic approaches combine the patient's pretest clinical probability of disease with D-dimer testing and/or diagnostic imaging. In light of several advantages, low-molecular-weight heparins are now recommended over unfractionated heparin for most patients with acute VTE. Newer anticoagulants such as the factor Xa inhibitor fondaparinux also show promise for acute VTE. For chronic management, the duration and intensity of warfarin therapy should be tailored to the individual patient.

New drug classes and diagnostic tests for the management of venous thromboembolism (VTE) have proliferated in the 45 years since parenteral heparin was first shown to have a life-saving role in the treatment of pulmonary embolism. At the same time, clinical trials with older anticoagulants such as warfarin have helped to define and refine the optimal duration of therapy in patients with idiopathic VTE. In this article we review the latest evidence on the diagnosis and treatment of this common disease and provide practical recommendations on key aspects of its management.

EPIDEMIOLOGY OF VTE: WIDESPREAD, OFTEN DEADLY

VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease in the United States, with an average annual incidence of more than 100 cases per 100,000 population.[1] Autopsy studies demonstrate large numbers of silent events,[2,3] leading to the widely reported estimates of 2 million DVT cases and up to 200,000 deaths from PE annually.[4] The aging of the US population will only cause these numbers to grow.

VTE accounts for about 10% of all in-hospital deaths, with a long-term case-fatality rate of about 19% to 30% at 1 to 3 years,[5] presuming the patient survives the initial thrombotic event. However, it is estimated that up to one quarter of all PE cases present as sudden death.[6] Even after 6 months or more of anticoagulation following a first VTE event, there is a persistently elevated risk (5% to 12% annually) for subsequent VTE.[7]

Age and the presence of identifiable VTE risk factors both influence the incidence of first-time VTE. The annual incidence of first-time VTE rises exponentially from fewer than 5 cases per 100,000 population in persons younger than 20 years of age to nearly 500 cases per 100,000 for those 80 years of age or older.[5] Most first-time VTE events occur in patients with an identifiable risk factor. Nursing home residents or persons recently discharged from the hospital accounted for almost 60% of first-time VTE events in the community in a recent population-based study.[8] That same study found the incidence of VTE to be 135-fold higher in hospitalized patients than in community residents.[8]

RISK FACTORS FOR VTE: VARYING MAGNITUDES, UNCERTAIN INTERACTION

Virchow's triad describes three etiologic factors for thrombosis: stasis of blood flow, endothelial injury, and hypercoagulability. Established VTE risk factors reflect these underlying pathophysiologic processes. Important risk factors for VTE include increased age (especially beyond age 40), prolonged immobility, malignancy, major surgery, multiple traumas, prior VTE, and chronic heart failure.[9] However, the magnitude of risk conferred by these and other factors varies **(Table 1)**. It is not yet known how these factors interact to determine a given patient's individual risk, but there is evidence that VTE risk increases in proportion to the number of predisposing factors present.[10]

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DIAGNOSIS: COMBINE PRETEST PROBABILITY WITH DIAGNOSTIC TESTING

Accurate diagnosis of VTE remains challenging since symptoms of VTE may be atypical or absent and because noninvasive diagnostic tests have imperfect accuracy. Furthermore, since VTE can be fatal, and since effective treatments are available, it is an important diagnosis not to miss.

For these reasons, serial noninvasive diagnostic testing is often used, which may include D-dimer testing, compression ultrasonography, helical computed tomography (CT) of the chest, and nuclear lung scans. However, the cornerstone of VTE diagnosis remains assessment of pretest clinical probability.

Without standardized diagnostic algorithms (simply using clinical impression), the PIOPED investigators[11] classified patients as having low, intermediate, or high pretest probabilities of PE with remarkable accuracy. Of those patients deemed to be at high risk, 68% had PE, in contrast to 9% of those deemed to be at low risk. Formal algorithms have since been created and validated to help even novice clinicians estimate the pretest probability for VTE.[12–17]

Bayes' theorem dictates that the posttest odds of disease is equal to the pretest odds of disease multiplied by the likelihood ratio of the diagnostic test used.[17,18] Likelihood ratios of various diagnostic tests used in the evaluation of VTE are shown in **Table 2**.[11,18–24]

A key concept is that a diagnosis of VTE can generally be secured or excluded when the pretest clinical probability is concordant with an appropriate diagnostic test.[18] For example, a high pretest clinical suspicion of PE in conjunction with a high-probability lung scan is adequate to confirm the diagnosis of PE (> 95% certainty), while a low pretest clinical suspicion of DVT in conjunction with a negative D-dimer test can exclude the diagnosis. When the clinical impression is discordant with the diagnostic test result (eg, a high pretest clinical suspicion of PE in the setting of a negative helical CT scan), further diagnostic testing is often warranted. This applies even to noninvasive tests that are often thought to "rule in" the diagnosis when positive: a positive helical CT or high-probability lung scan in the context of a low pretest suspicion for PE does not rule in the diagnosis of PE.[11,25] In such cases, it is reasonable to order a pulmonary arteriogram.

Whether pulmonary CT angiography is accurate enough to render conventional angiography obsolete is being addressed in an ongoing prospective, multicenter trial (PIOPED II). Until its results are available, we may still need to pursue pulmonary angiography in patients with high clinical suspicion for PE but negative helical CT findings, and most current diagnostic algorithms still rely on angiography as a gold standard fall-back test when the diagnosis remains ambiguous after multiple noninvasive tests.[26–28]

TABLE 1
Risk factors for venous thromboembolism

Strong risk factors (odds ratio ≥ 10)

- Fracture (hip or leg)
- Hip or knee replacement
- Major general surgery
- Major trauma
- Spinal cord injury

Moderate risk factors (odds ratio 2 to 9)

- Arthroscopic knee surgery
- Central venous lines
- Chemotherapy
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Pregnancy/postpartum
- Previous venous thromboembolism
- Thrombophilia

Weak risk factors (odds ratio < 2)

- Bed rest > 3 days
- Immobility due to sitting (eg, prolonged car or air travel)
- Increased age
- Laparoscopic surgery (eg, cholecystectomy)
- Obesity
- Pregnancy/antepartum
- Varicose veins

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INITIAL THERAPY: OPTIONS ARE EXPANDING

Prompt initiation of anticoagulant therapy is essential in the management of acute VTE, except in patients who are actively bleeding or in whom the risk of bleeding outweighs the benefits of anticoagulation.

Several groups of drugs are commercially available to treat acute DVT and PE: unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs) and factor Xa inhibitors (pentasaccharides). Parenteral direct thrombin inhibitors are approved for use in patients with acute VTE in the setting of heparin-induced thrombocytopenia (HIT). The oral direct thrombin inhibitor ximelagatran was recently denied FDA approval due to concerns over liver toxicity. The pharmacologic profiles of these drug classes are discussed in detail by Nutescu et al in the first article in this supplement. We have summarized the

TABLE 2
Approximate likelihood ratios of commonly used diagnostic tests for venous thromboembolism

Diagnostic test	Likelihood ratio*	Clinical setting	Comments
D-dimer[19]		Evaluation of suspected acute DVT or PE in symptomatic nonanticoagulated outpatients	Questionable reliability in patients on anticoagulant drugs, those with nonacute symptom onset, and hospitalized patients[20]
• Quantitative ELISA			
—Negative test	0.07–0.12		
—Positive test	1.5–3.0		
• Other assays			
—Negative test	0.11–0.36		
—Positive test	1.6–5.0		
Helical chest CT[21]		Suspected PE	Accuracy is user-dependent.[22] Best for ruling in or ruling out large (central) emboli. Likelihood ratio for a positive study may greatly exceed 7.1 if multiple unambiguous large filling defects are seen. However, confirmatory pulmonary angiography may be indicated in a patient with low pretest suspicion of PE and only 1 or 2 small filling defects on CT.[22,23] May reveal alternate source of dyspnea, hypoxia, or chest pain.
—Negative study	0.29		
—Positive study	7.1		
Nuclear lung scan[11]		Suspected PE	Patients with known pulmonary disease (eg, chronic obstructive pulmonary disease) may be unlikely to have normal or near-normal scans
High probability	23		
Intermediate	0.87		
Low probability	0.26		
Normal/near-normal	0.17		
Duplex ultrasonography[24]		Suspected symptomatic proximal lower extremity DVT	Accuracy may be lower for distal DVT, asymptomatic DVT (eg, postoperative surveillance), and upper extremity thrombosis. Since most PEs arise from thrombi in the legs, duplex ultrasonography can also be used in the evaluation of suspected PE.
—Negative	0.05		
—Positive	24		

* When likelihood ratios were not specifically reported, they were calculated using standard formulas.[18] Likelihood ratios are interpreted as follows using Bayes' theorem: *(pretest odds of disease) × (likelihood ratio for given finding) = posttest odds of disease*. Odds and probabilities can be interconverted using the following formulas: *odds = probability/(1 – probability)* or *probability = odds/(1 + odds)*.

Example: In a patient with an estimated pretest probability of 80% for PE (very high pretest suspicion), the probability of PE after a negative helical CT of the chest is calculated as follows: Pretest probability of 80% is converted to pretest odds of 80/20 (= 4). Likelihood ratio of disease with a negative helical CT of the chest is approximately 0.29. Posttest odds of PE is 4 × 0.29 = 1.16. Posttest probability of PE is 1.16 /(1 + 1.16) = 54%. Further testing is clearly indicated, since this patient still has a greater than 50% chance of having a PE despite the negative helical CT.

CT = computed tomography; DVT = deep vein thrombosis; ELISA = enzyme-linked immunosorbent assay; PE = pulmonary embolism

available options for initial VTE therapy in **Table 3**.

Unfractionated heparin

Until 1996, when LMWHs were approved by the US Food and Drug Administration (FDA) for the outpatient treatment of DVT, patients with DVT were generally treated in the hospital with UFH.

Studies demonstrate that 5 to 7 days of intravenous (IV) UFH is as effective as longer treatment durations.[29] Moreover, use of a weight-based nomogram helps to achieve a therapeutic activated partial thromboplastin time (aPTT) within the first 24 hours more quickly than fixed dosing does. Compared with fixed dosing (5,000-U bolus followed by IV infusion of 1,000 U/hr), weight-based nomogram dosing (bolus of 80 U per kilogram of ideal body weight followed by IV infusion of 18 U/kg/hr) decreases the rate of recurrent thromboembolism in patients with underlying VTE, arterial thromboembolism, or unstable angina.[30] Each laboratory should determine its own therapeutic aPTT range, corresponding to a heparin level of 0.3 to 0.7 U/mL of anti-Xa activity.

Problems associated with UFH use include its higher incidence of HIT (≈3%) relative to other anticoagulants, its variable bioavailability, bone demineralization, and the need for inpatient treatment (for IV dosing and frequent laboratory monitoring).[31]

Low-molecular-weight heparins

These shortcomings of UFH spurred the development of LMWHs, whose advantages relative to UFH include once- or twice-daily subcutaneous (SC) dosing; more predictable pharmacokinetics and bioavailability; a lower incidence of HIT (≈1%); and freedom from laboratory

monitoring requirements in most clinical situations.[31]

Outpatient DVT therapy. Two landmark studies established the safety and efficacy of LMWHs for the outpatient treatment of DVT.[32,33] One study compared SC weight-based enoxaparin to IV UFH.[32] There were no differences between the groups in the incidence of recurrent VTE, major bleeding, or death. However, length of stay was approximately 1 day in the enoxaparin group compared with 6.5 days in the UFH group. In the other study,[33] 500 patients were randomized to SC nadroparin (a LMWH not available in the United States) or IV UFH. Again, there was no difference between the groups in rates of recurrent VTE, bleeding, or mortality.

Gould et al[34] conducted a meta-analysis comparing a variety of LMWHs with UFH for the treatment of acute DVT across 11 trials comprising 3,566 patients. The results indicated that LMWH therapy was superior to UFH, reducing mortality by approximately 30% (absolute risk reduction, 1.65%; number needed to treat to prevent a death, 61; $P = .02$). Rates of recurrent thromboembolism and major bleeding were similar between the LMWH and UFH groups, although there was a trend toward reduction in both of these outcomes in the LMWH group.

VTE therapy in cancer patients. Rates of warfarin-resistant thrombosis and warfarin-associated bleeding are elevated in patients with cancer,[35] and results from meta-analyses[36,37] have suggested that cancer patients may achieve a particular mortality benefit from LMWH therapy. This has prompted recent investigations of LMWHs specifically in cancer patients.

The CLOT investigators[38] randomized cancer patients with acute VTE to either the LMWH dalteparin (200 IU/kg/day for 1 month, followed by 150 IU/kg/day for 5 months) or traditional therapy, consisting of dalteparin for 5 to 7 days followed by oral anticoagulation for 6 months. During the 6-month study period, recurrent VTE occurred in 27 of 336 patients (8.0%) in the LMWH group compared with 53 of 336 (15.8%) in the oral anticoagulation group (hazard ratio, 0.48; $P = .002$). Most recurrences occurred while patients were on anticoagulation. Rates of major and minor bleeding were similar between the groups. A smaller study comparing enoxaparin 1.5 mg/kg/day with warfarin in cancer patients demonstrated a similar risk reduction with LMWH therapy, though it failed to reach statistical significance.[35] However, any increased efficacy of LMWHs over oral anticoagulation in the treatment of cancer-associated VTE must be weighed against the cost of LMWHs and the willingness of the patient or caregiver to administer daily injections.

TABLE 3
Options for initial therapy for venous thromboembolism

Unfractionated heparin

Use nomogram—bolus of 80 U/kg ideal body weight followed by continuous IV drip of 18 U/kg/hr

Goal activated partial thromboplastin time*: 60–80 sec

Low-molecular-weight heparins

Enoxaparin: 1 mg/kg SC twice daily or 1.5 mg/kg SC once daily

Dalteparin: 200 IU/kg SC once daily†

Tinzaparin: 175 IU/kg SC once daily

Factor Xa inhibitor

Fondaparinux: 5 mg SC once daily (if body weight < 50 kg), 7.5 mg SC once daily (if body weight 50–100 kg), or 10 mg SC once daily (if body weight > 100 kg)

* May vary from institution to institution. Maintain in therapeutic range, which must correspond to heparin levels of 0.3–0.7 U/mL.
† Not FDA-approved for treatment of venous thromboembolism.

Acute PE therapy. The safety of LMWHs for treating acute PE has been established in two large clinical trials[39,40] and confirmed in a recent meta-analysis.[41] The Columbus Investigators[39] randomized more than 1,000 patients to the LMWH reviparin (not available in the United States) or IV UFH. Rates of recurrent VTE, bleeding, and death were similar between the two groups. The authors concluded that reviparin and UFH are equally effective and safe. Similarly, Simonneau et al[40] compared the LMWH tinzaparin with IV UFH for the treatment of acute symptomatic PE in 612 patients. The two groups had similar rates of VTE recurrence, major bleeding, and death. The meta-analysis[41] concluded that fixed-dose LMWH therapy appears to be as effective and safe as IV UFH for the initial treatment of nonmassive PE, and showed a nonsignificant trend toward improved outcomes in LMWH recipients.

Although the outpatient use of LMWHs is not yet approved for treating acute PE, we believe that off-label outpatient treatment is reasonable in selected patients at low risk for clinical deterioration (see below).

Fondaparinux, a factor Xa inhibitor

Fondaparinux is the first synthetic selective inhibitor of factor Xa available for patients. It inhibits both free and platelet-bound factor Xa. It binds antithrombin with high affinity, has close to 100% bioavailability, and is given by once-daily SC administration. It does not bind platelet factor 4 and therefore should not cause HIT. There is currently no antidote for fondaparinux, although factor VIIa infusion might be effective.[42]

Fondaparinux was recently approved by the FDA for treatment of acute DVT and PE on the basis of two randomized noninferiority trials.[43,44]

In the Mattise-DVT trial,[43] 2,205 patients with acute DVT were treated with once-daily SC fondaparinux (dosed as outlined in **Table 3**) or enoxaparin 1 mg/kg SC twice daily for 5 days, followed in each group by a 3-month course of an oral vitamin K antagonist. Recurrent thromboembolic events occurred in 43 (3.9%) of 1,098 fondaparinux recipients compared with 45 (4.1%) of 1,107 enoxaparin recipients, for an absolute difference of –0.15% in favor of fondaparinux (95% confidence interval [CI], –1.8% to 1.5%). Major bleeding occurred in 1.1% of fondaparinux recipients and in 1.2% of enoxaparin recipients. Mortality rates were 3.8% and 3.0%, respectively. The authors concluded that once-daily fondaparinux was at least as effective and safe as twice-daily, weight-adjusted enoxaparin in the initial treatment of patients with symptomatic DVT.

In another study by the Matisse investigators,[44] 2,213 patients with acute symptomatic PE were randomized in an open-label fashion to continuous IV infusion of UFH or once-daily SC fondaparinux (dosed as in **Table 3**), each given for at least 5 days and until vitamin K antagonist therapy resulted in an international normalized ratio (INR) above 2.0. At 3 months, recurrent thromboembolism occurred in 42 of 1,103 fondaparinux recipients (3.8%) and in 56 of 1,110 UFH recipients (5.0%), for an absolute difference of –1.2% in favor of fondaparinux (95% CI, –3.0% to 0.5%). Major bleeding occurred in 1.3% of fondaparinux recipients and in 1.1% of UFH recipients. Mortality at 3 months was similar in the two groups. This study suggests that once-daily SC administration of fondaparinux without monitoring is at least as effective and safe as adjusted-dose IV UFH in the initial treatment of hemodynamically stable patients with PE.

Direct thrombin inhibitors

The direct thrombin inhibitors are another class of anticoagulants that can be used to treat VTE. All four FDA-approved direct thrombin inhibitors (argatroban, lepirudin, bivalirudin, and desirudin) are administered parenterally, and all are indicated for conditions other than initial VTE therapy, although some are approved to treat thrombosis in patients with HIT. Other articles in this supplement detail the pharmacology of the direct thrombin inhibitors (see Nutescu et al) and their use in HIT (see Bartholomew et al).

The oral direct thrombin inhibitor ximelagatran has been studied in phase 3 trials in patients without HIT, and appears to be effective for VTE prevention after orthopedic surgery, for stroke prevention in patients with atrial fibrillation, and for treatment of acute VTE.[45] Unlike other oral anticoagulants, ximelagatran can be given in fixed daily doses without laboratory monitoring. Although approved for use in several European countries for VTE prevention following major orthopedic surgery, ximelagatran was rejected by the FDA last fall because of concerns about liver enzyme elevations in up to 9% of patients receiving long-term therapy.

The THRIVE Treatment Study[46] was a double-dummy, randomized noninferiority study of 2,489 patients with acute VTE that compared oral ximelagatran (36 mg twice daily) with enoxaparin (1 mg/kg twice daily for a minimum of 5 days) followed by warfarin (to a target INR of 2.0 to 3.0). Treatment was for 6 months and patients were followed for an additional 40 days. Recurrent VTE occurred in 2.1% of ximelagatran recipients and in 2.0% of enoxaparin/warfarin recipients. All-cause mortality rates were 2.3% with ximelagatran and 3.4% with enoxaparin/warfarin; major bleeding rates were 1.3% and 2.2%, respectively. These results suggest that ximelagatran is an effective and safe alternative to LMWH for the acute treatment of VTE. However, the rate of elevated transaminase levels was as high as 9.6% in this study.

WHAT'S THE ROLE OF THROMBOLYSIS?

Over the last 30 years, clinical observations and randomized trials have consistently shown favorable effects of thrombolysis on angiographic, hemodynamic, and scintigraphic measures in patients with acute PE. Tissue-type plasminogen activator (tPA), streptokinase, and urokinase are thrombolytic agents that have been approved by the FDA for the treatment of PE. tPA is comparable to urokinase and streptokinase in thrombolytic capacity but can be administered over a shorter time period.[31]

A recent meta-analysis[47] of nine small randomized trials compared rates of death, recurrent PE, or major bleeding between patients with acute PE treated with thrombolytic agents plus heparin or with heparin alone. At least one of these events occurred in 56 (23.2%) of 241 patients in the thrombolysis group compared with 57 (25.9%) of 220 patients in the heparin group (relative risk [RR], 0.9; 95% CI, 0.57 to 1.32). Eleven thrombolytic recipients died (4.6%), compared with 17 heparin recipients (7.7%) (RR, 0.59; 95% CI, 0.27 to 1.25). However, the incidence of major bleeding was 12.9% in the thrombolysis group (31/241) compared with 8.6% in the heparin group (19/220) (RR, 1.49; 95% CI, 0.85 to 2.81). Five fatal

bleeding episodes occurred in the thrombolysis group (2.1% incidence), compared with none in the heparin group (P = .06). Six studies provided data on recurrent PE. Recurrence occurred in 14 (6.6%) of 214 thrombolytic recipients and in 22 (10.9%) of 201 heparin recipients (RR, 0.60; 95% CI, 0.29 to 1.15). The composite end point of recurrence or death occurred in 10.4% of the thrombolysis group (25/241) compared with 17.3% of the heparin group (38/220) (RR, 0.55; 95% CI, 0.33 to 0.96; P = .03).

The authors concluded that, in patients with PE, thrombolysis was associated with a lower risk of the composite of death or PE recurrence compared with heparin therapy alone.[47] However, excessive bleeding is the trade-off for this improved efficacy, which is a major concern for patients with risk factors for bleeding, who may have been excluded from the clinical trials.

In practice, thrombolysis is usually reserved as a last resort in cases of hemodynamically unstable PE. The current debate surrounding thrombolysis focuses on patients with submassive PE, with right ventricular dysfunction but without hypotension. Opponents of thrombolysis note that thrombolytic therapy can cause life-threatening bleeding and has not been proven to reduce mortality compared with UFH alone. However, a massive study would be needed to specifically show a reduction in mortality. Moreover, treatment allocation would be blurred when patients assigned to UFH alone suffered clinical deterioration and required rescue thrombolysis. Although MAPPET-3,[48] a randomized study of patients with submassive PE, was not powered to demonstrate a mortality benefit, it showed that tPA plus UFH was superior to UFH alone in preventing the composite primary end point of mortality or treatment escalation. Notably, no fatal or cerebral bleeding episodes were observed in the tPA group.

Potential indications for thrombolytic therapy in PE include hemodynamic instability[31] and right ventricular dysfunction. Thrombolysis should not be used routinely in patients with DVT but may be considered in patients with severe iliofemoral DVT who are at risk for limb ischemia.[31]

RISK STRATIFICATION IN PATIENTS WITH PE

All patients with confirmed PE should receive anticoagulation unless they have a major contraindication, such as active bleeding. There are, however, additional questions after the diagnosis is confirmed:

- Can the patient be treated with LMWH in the outpatient setting, or is continued hospitalization prudent?
- Is the patient at high enough risk of death to justify thrombolytic therapy?
- Is the patient at high risk for long-term complications?

Frank hemodynamic instability (tachycardia or hypotension) and classic electrocardiographic findings of right ventricular strain are insensitive for detecting impending right ventricular failure in patients with PE, but some newer diagnostic tools show promise. These include echocardiography, measurement of cardiac troponins, and measurement of B-type natriuretic peptide (BNP). All of these tests seek to quantify the degree of strain on the right ventricle, since it is the potential for acute right ventricular failure that makes PE deadly. Identification of patients at high risk for hemodynamic collapse and death allows for appropriate triage decisions (such as early discharge with LMWH therapy at home vs observation in the hospital) and may allow for timely escalation of therapy (ie, thrombolytics) in selected patients.[48]

A recent prospective study[49] of the prognostic utility of cardiac troponins and echocardiography in 106 patients with acute PE found that both troponin I and troponin T were associated with right ventricular dysfunction, especially when the enzyme elevations were more than 2 times the upper limit of normal. The study's two end points were in-hospital death or a "complicated" inpatient course (ie, death or the need for thrombolysis, pressor support, intubation, or cardiopulmonary resuscitation). Of the 7 patients who died, 6 (86%) had elevated cardiac enzyme levels at presentation (vs about 20% to 30% of those who survived). Of the 19 patients with a complicated hospital course, more than 70% had elevated enzyme levels, compared with less than 30% of patients with an uncomplicated course. Similar prognostication has been reported with BNP.[50] Evidence of right ventricular dysfunction on echocardiography is also associated with worse prognosis, although definitions of right ventricular dysfunction have been inconsistent.[51]

We suggest that at least two methods of risk stratification (echocardiography plus BNP or troponin measurement) be used in any hemodynamically stable patient with PE who is asymptomatic (not in pain and without dyspnea or hypoxia) in whom early discharge and home treatment are being considered.[51] If there is evidence of right ventricular dysfunction by any of these tests, we favor continued hospitalization for observation until target anticoagulation intensity is achieved. If early discharge treatment is not an option, risk stratification may still be appropriate if thrombolysis is being considered,[49,52] although thrombolysis for submassive PE remains controversial.[52] Finally, although symptomatic pulmonary hypertension may

develop in the months following PE,[53] there is no evidence that early risk stratification helps to predict this complication or influences clinical management.

INFERIOR VENA CAVA FILTERS

Use of inferior vena cava (IVC) filters has grown markedly over the last 2 decades in patients with PE, patients with DVT alone, and at-risk patients who have neither PE nor DVT.[54] We recommend reserving IVC filters for patients with contraindications to anticoagulation or those who develop recurrent thromboembolic disease despite anticoagulant therapy.[55] The FDA recently approved three types of retrievable filters. Although long-term safety data for these devices are not yet available, removable IVC filters may be attractive options for patients with transient contraindications to anticoagulation.

TESTING FOR HYPERCOAGULABILITY

It has long been known that some patients have a proclivity to develop thrombosis, but laboratory techniques to identify these coagulation defects have become available only relatively recently. More such defects are likely to be identified in the near future. But a laboratory diagnosis of a "hypercoagulable state" such as heterozygous factor V Leiden mutation, protein S deficiency, or heterozygous prothrombin gene mutation G20210A often does not change patient care, may not be cost-effective, and may cause needless anxiety among patients who test positive. Therefore, testing for hypercoagulability should be done only when it will directly impact the plan of care.

There is no role for screening for hypercoagulability in the general population, since many patients with so-called hypercoagulable states may never develop VTE[56,57] and since long-term anticoagulation for primary prevention of VTE would be costly and risky in these patients. But what about hypercoagulability testing after an episode of thrombosis? This, too, is usually not indicated. Even in patients with laboratory-diagnosed thrombophilia, thrombotic events are often triggered by a situational risk factor,[58,59] and once the situational factor is resolved and the thrombosis has been treated, there is little reason for indefinite anticoagulation. Most such patients do not suffer recurrent events.[60,61]

Although some authors recommend hypercoagulability testing in patients with unprovoked (idiopathic) thromboses,[62] this strategy is not universally accepted, and no management trials have shown that hypercoagulability testing improves the care of these patients.[63] Moreover, if lifelong anticoagulation is to be recommended solely because the episode was unprovoked,[7] then hypercoagulability testing is superfluous.

Two recent studies suggest that D-dimer elevations shortly after cessation of oral anticoagulation may be a better global indicator of hypercoagulability than any specific marker of thrombophilia.[61,64] In one of these studies, the absence of D-dimer elevations after withdrawal of anticoagulation carried a favorable prognosis, even in the presence of laboratory-confirmed thrombophilia (such as protein C deficiency or combined factor V Leiden/prothrombin mutation).[61] This strategy may help to inexpensively identify patients at risk for recurrent VTE without formal hypercoagulability testing.

In sum, definite indications for hypercoagulability testing remain elusive. It is clear, though, that such testing is not warranted in most patients with VTE and should be ordered selectively until management trials define clear indications for it. Gene assays for factor V Leiden and prothrombin gene mutation and testing for antiphospholipid antibodies can be performed in anticoagulated patients. However, testing for protein C and S levels should be done only after the patient has been off oral anticoagulants for at least 7 to 10 days, and this may be best accomplished after completing the course of warfarin therapy.

CHRONIC MAINTENANCE THERAPY

In 1992, Brandjes et al[65] showed that patients with acute VTE should not receive monotherapy with vitamin K antagonists such as warfarin. These drugs must be combined with an immediate-acting anticoagulant such as heparin since their optimal antithrombotic activity usually takes several days to achieve.

Debate over the appropriate starting dose of warfarin continues, as recent evidence suggests that a starting dose of 10 mg daily may achieve a therapeutic INR faster than 5 mg without increasing the risk of bleeding or thromboembolic complications. This may minimize the time on LMWH therapy.[66] However, previous randomized trials suggested that patients are more likely to have a therapeutic INR 3 to 5 days after initiating warfarin at 5 mg rather than 10 mg, in part because the higher dose carries a higher risk of supratherapeutic INR values.[67,68]

We recommend that clinicians consider patient-specific factors such as age, concomitant medications, and comorbidities when choosing the starting dose. Common medications that may require a lower starting warfarin dose include amiodarone, trimethoprim-sulfamethoxazole, and metronidazole. Lower starting doses may also be reasonable in patients with liver

TABLE 4
Bleeding risk index for outpatient warfarin therapy

What risk factors are present? (check all that apply)

- ❑ Age ≥ 65 years
- ❑ History of stroke
- ❑ History of gastrointestinal bleeding
- ❑ Recent myocardial infarction, hematocrit < 30%, serum creatinine > 1.5 mg/dL, history of diabetes mellitus

Sum the risk factors, classify patient by number of factors

Low bleeding risk: 0 factors
Intermediate bleeding risk: 1 or 2 factors
High bleeding risk: 3 or 4 factors

Estimated risk for major bleeding

	Low risk	Intermed. risk	High risk
In 3 months	2%	5%	23%
In 12 months	3%	12%	48%

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TABLE 5
Recommendations for optimal warfarin therapy duration for symptomatic venous thromboembolism

Indication/risk factor	Duration
Major transient risk factor (eg, surgery within 3 months, hospitalization, immobilization of leg)	3 months
Minor risk factor (eg, air travel, recent hormone replacement therapy, minor trauma or immobilization)	6 months
Unprovoked*, uncontrolled malignancy, or other factors (> 1 unprovoked venous thromboembolic episodes; antiphospholipid antibodies; protein C, protein S, or antithrombin deficiency; homozygous factor V Leiden or G20210A prothrombin mutation; inferior vena cava filter)	Indefinite†
Idiopathic calf vein thrombosis	6 months

*Consider target international normalized ratio of 1.5–2.0 after 6 months of therapy with a target of 2.0–3.0.

†If bleeding risk is high, consider 6 months of therapy instead.

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disease, congestive heart failure, or poor nutritional status, as well as in frail elderly patients. If a 10-mg starting dose is used, it is important that a detailed titration scheme be followed, as outlined in the 10-mg nomogram of Kovacs et al.[66]

Balance risk and benefit on a case-by-case basis

Choosing the duration of warfarin therapy requires estimating the risks of recurrent and fatal VTE if the patient were off warfarin and the competing risks of major and fatal bleeding while on therapy. This requires tailoring the therapy to the individual patient.

The rate of recurrent VTE at 1 year (after 3 months of therapy) is approximately 3% to 5% for patients with reversible risk factors such as surgery, trauma, hormone use, or acute illness. In contrast, the rate of recurrence after an episode of unprovoked VTE, even after 6 months of warfarin therapy, is approximately 10% at 1 year, and as high as 20% in those with cancer. In addition, about 5% to 10% of VTE events are fatal. On the other hand, the rate of major bleeding varies from 1% to 4% per patient-year in clinical trials, and the case-fatality rates for major bleeding range from 9% to 13%. The rate of intracranial bleeding is about 0.65% to 1% per year.[69,70] However, rates of major bleeding are often much higher in clinical practice than in clinical trials, probably owing to common comorbidities that predispose to anticoagulant-associated bleeding.[69] A validated outpatient bleeding risk index is shown in **Table 4**.[71]

Optimal dosing of warfarin for long-term VTE prevention following an unprovoked episode remains controversial. The PREVENT investigators[72] randomized 508 patients with idiopathic VTE to conventional warfarin therapy (target INR of 2.0 to 3.0) or to low-intensity warfarin therapy (target INR of 1.5 to 1.9) after an initial 3- to 6-month course of conventional therapy. This study showed that long-term, low-intensity warfarin therapy is highly effective in preventing recurrent VTE. However, 3 months later, the ELATE trial investigators[73] concluded that conventional warfarin therapy (INR of 2.0 to 3.0) is more effective than low-intensity therapy (INR of 1.5 to 1.9) for the long-term prevention of recurrent VTE following an unprecipitated thrombosis. In this study, low-intensity warfarin did not reduce the risk of clinically important bleeding. It is important to note that neither trial was powered to detect a difference in major bleeding.

These trials indicate that lifelong warfarin therapy for idiopathic VTE may be appropriate in selected patients at low risk of bleeding since these trials enrolled patients whose mean age was in the sixth decade of life (50 to 59 years) and who had few risk factors for bleeding. However, when we apply the outpatient bleeding risk index **(Table 4)** to our medical patients, we often estimate much higher rates of bleeding than observed in the selected patients in these trials.[71] Therefore, our recommendations for the duration of warfarin therapy are similar to those suggested by Kearon,[69] as outlined in **Table 5**.

COMPRESSION STOCKINGS

It is important to appreciate the chronic sequelae of DVT. The postthrombotic syndrome develops in approximately 40% of patients with proximal DVT and is charaterized by chronic venous stasis and sometimes by nonhealing ulcerations. A recent randomized study by Prandoni et al[74] demonstrated a 50% reduction in the risk of postthrombotic sequelae (P = .011) in patients with acute proximal DVT who used compression stockings. We therefore endorse the use of below-knee compression stockings (30 to 40 mm Hg at the ankle) in patients with acute DVT, particularly those who present with significant edema or skin changes.

SUMMARY AND RECOMMENDATIONS

VTE is a common disease. Its diagnosis can be challenging, but it is best approached using a clinical decision model to determine a pretest clinical probability of disease prior to any diagnostic testing. This clinical probability can then be combined with D-dimer testing, diagnostic imaging, or both. Some patients with PE require risk stratification, especially those who may be candidates for outpatient treatment or who may require thrombolysis. We recommend LMWH over UFH in most patients with acute VTE, in light of LMWH's multiple advantages. In addition, newer anticoagulants such as fondaparinux show promise, based on once-daily dosing and the lack of a reported association with HIT. The duration and intensity of warfarin therapy should be tailored to the individual patient, although the optimal target INR is 2.0 to 3.0 at least for the first several months of therapy.

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