Deep venous thrombosis (DVT) is a common diagnosis in the United States, with an annual incidence exceeding 100 per 100,000 individuals—or approximately 170,000 to 200,000 new cases each year. One in every 5 of these patients will develop DVT again within 5 years. Thus, the total number of new or recurrent DVT cases in any given year in the United States is thought to be in the range of 300,000 to 600,000. Elderly, hospitalized, and immobile patients are at highest risk. DVT can cause significant acute pain, swelling, and discoloration, as well as chronic venous insufficiency. Pulmonary embolism (PE), the major clinical consequence of DVT, has an annual incidence estimated at 69 per 100,000 individuals, with an annual mortality rate of 9.4 per 100,000 individuals. Ninety percent of PEs originate in one of the deep veins of the leg. The risk of death from venous thromboembolism (VTE) can be significantly reduced with timely anticoagulation; however, the clinical presentations of DVT and PE are highly variable, depending on the size and location of the clot as well as the underlying cardiovascular status of the patient.
the patient. Because the warning signs and symptoms are notoriously subtle, or even nonexistent, most individuals who die from acute PE have never been diagnosed or treated. The key to timely anticoagulation therapy for DVT and PE is an understanding of the risk factors for thromboembolic disease and the appropriate use of diagnostic tests in a practical and evidence-based algorithm. This article will update current diagnostic approaches to VTE and then review the major treatment and prophylaxis options.

DIAGNOSIS

The main diagnostic tests for VTE are the ventilation/perfusion (V/Q) lung scan, ultrasonography of the lower extremities for DVT, helical computed tomography (CT), the D-dimer assay, and pulmonary angiography. The results of any of these tests should be interpreted in combination with the clinician's clinical suspicion, or pretest probability. A scoring system can help clinicians objectively determine the pretest probability of PE based on clinical criteria (Table 1).

VENTILATION-PERFUSION LUNG SCAN

The landmark Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study of the V/Q scan in the evaluation of suspected PE illustrated how clinical suspicion can be combined with imaging results to confirm or rule out a diagnosis of PE in at least a minority of patients.

As shown in Figure 1, the combination of V/Q scan results and clinical impression was most helpful in ruling in or ruling out PE when clinical suspicion was consistent with the V/Q result. For example, 96% of patients for whom there was both a high clinical suspicion of PE and a high-probability V/Q scan result had PE confirmed on angiogram. For these patients, anticoagulation is indicated with no further workup required. Of patients for whom there was a low clinical suspicion and a low-probability V/Q scan result, only 4% actually had angiographically confirmed PE. In the latter category of patients, and in those with a completely normal V/Q scan, PE can be ruled out and other sources for the patients' complaints can be sought.

Unfortunately, the majority of patients fall into an indeterminate category, with either an intermediate-probability V/Q scan or a clinical suspicion inconsistent with the V/Q result. In PIOPED, the combination of clinical impression and V/Q result was nondiagnostic in 72% (640/887) of patients. For such patients, additional testing is required.

ULTRASOUND

DVT and PE are now considered different manifestations of the single systemic disorder of VTE. Among patients with DVT and no pulmonary symptoms, 40% are found to have asymptomatic PE on testing. Half of proximal lower-extremity DVTs eventually embolize to the lung. In contrast, only 20% to 25% of calf vein DVTs migrate to the proximal lower extremity. Thus, only about 10% of calf DVTs will cause a PE. Because most PEs originate in lower-extremity DVTs, ultrasound has become a valuable test not only for diagnosing DVT but also as part of the workup for PE.

Ultrasound is safe and noninvasive and has a higher specificity than impedance plethysmography for the evaluation of suspected DVT. With color flow Doppler and compression ultrasound, a DVT is diagnosed based on the inability to compress the common femoral or popliteal veins. With a first symptomatic DVT, sensitivity is 95% and specificity 96%. The diagnostic accuracy of ultrasound in patients with first asymptomatic DVT, recurrent DVT, or isolated calf DVT is less reliable.

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg swelling, tenderness</td>
<td>3</td>
</tr>
<tr>
<td>Pulse &gt;100 bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization, surgery</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>No other more likely diagnosis</td>
<td>3</td>
</tr>
</tbody>
</table>

<2 = Low probability
2-6 = Moderate probability
>6 = High probability

*Data from Wells PS, et al.†

Bpm = beats per minute; DVT = deep vein thrombosis; PE = pulmonary embolism.

Figure 1. Which Patients Have Pulmonary Embolism? Combining V/Q Scan Results With Clinical Suspicion to Diagnose PE.†

*Data from The PIOPED Investigators.†

†The shaded area represents an intermediate category, in which V/Q was nondiagnostic in 72% of patients in the PIOPED study.

V/Q = ventilation/perfusion; PE = pulmonary embolism.
The sensitivity of ultrasound improves with serial testing in untreated patients. Repeat testing at 5 to 7 days will identify another 2% of patients with clots not apparent on the first ultrasound.\textsuperscript{16} Serial testing can be particularly valuable in ruling out proximal extension of a possible calf DVT. Because the accuracy of ultrasound in diagnosing calf DVT is acknowledged to be lower (81% for DVT below the knee versus 99% for proximal DVT),\textsuperscript{17} follow-up ultrasounds at 5 to 7 days are reasonable because most calf DVTs that extend proximally will do so within days of the initial presentation. Monitoring with serial ultrasound is not appropriate in patients with diminished cardiopulmonary reserve due to underlying heart failure or lung disease.

Ultrasound after a nondiagnostic V/Q scan is particularly effective in excluding PE in stable patients. In one study of patients with nondiagnostic V/Q scans, the negative predictive value of serial ultrasound (performed at days 3, 7, and 14) was 99.5%.\textsuperscript{9} Serial ultrasound after a nondiagnostic V/Q scan can thus reduce the percentage of patients who need angiography from 73% to 29%.\textsuperscript{18}

**D-DIMERS**

D-dimers are degradation products of cross-linked fibrin, and assays for D-dimers can serve as a noninvasive blood test for evaluating suspected VTE. These assays have high sensitivity, with measurements below 500 ng/mL making the likelihood of PE much less probable. On the other hand, D-dimers have poor specificity, particularly in the settings of hospitalization, pregnancy, cancer, or postoperative state.\textsuperscript{19}

Each of the many types of D-dimer assays has advantages and disadvantages. This variation should remind clinicians who analyze the literature to seek data generated with the test available at their own institution. The enzyme-linked immunoorbent assay (ELISA) has a 95% negative predictive value with a cutoff of 500 mcg/L, but it is slow. The rapid ELISA has test characteristics similar to the standard ELISA.\textsuperscript{20} The latex agglutination assay is faster but carries a lower negative predictive value. The SimpliRED assay involves whole blood agglutination and can be performed at the bedside. Immunofiltration is just one of several newer D-dimer assays for which fewer data are available. As documented in a review of 29 clinical studies, D-dimer testing varies widely, not only in terms of assays used and patients analyzed, but also in the methodology employed to define DVT and PE.\textsuperscript{21}

The D-dimer test should not be used alone to rule in a diagnosis of VTE. Nevertheless, despite its failings as a stand-alone test, the D-dimer assay can be useful in low-risk patients as part of a diagnostic algorithm for ruling out DVT or PE. The role of the D-dimer in diagnosing DVT or PE should be in conjunction with clinical findings or with imaging results in ambulatory or emergency department settings to rule out the diagnosis. In patients for whom there is a low clinical suspicion of DVT, a normal SimpliRED whole blood D-dimer test has a negative predictive value of 99.4% (95% CI, 96.9%-100%).\textsuperscript{22} The use of D-dimer as part of a diagnostic algorithm for suspected PE was recently evaluated in 930 patients who presented to the emergency department.\textsuperscript{23} Clinicians determined their clinical suspicion of PE using the Wells criteria. Among 527 patients for whom there was a low clinical suspicion of PE, the D-dimer assay was negative in 437 patients, and no further testing was performed, meaning that PE was ruled out without need for a V/Q scan. Only one of these 437 patients developed PE during the 3-month follow-up period (ie, negative predictive value of 99.5%), which again suggests that the D-dimer test may be most valuable in eliminating the need for expensive additional testing in low-risk patients. For patients in whom clinical suspicion was not low, or in whom the D-dimer was positive, additional testing starting with a V/Q scan was performed.

**HELICAL COMPUTED TOMOGRAPHY**

The helical CT—also called spiral-volumetric CT—is less studied than the V/Q scan but has nonetheless become a first-line diagnostic test for PE in some institutions. The technique requires contrast media and involves moving patients through the gantry while the scanner rotates continuously to acquire 3-dimensional data. The procedure is rapid, acquiring data during a single breath-hold. The imaging results are reported as a definitive yes or no for PE, as opposed to the probability that is reported by a V/Q scan, and they may also provide information about other lung diseases. Helical CT has lower sensitivity for subsegmental (peripheral) emboli, although the clinical significance of these emboli is still undetermined. The quality of interpretation varies markedly with the radiologist’s expertise and the quality of the scanner.

Two meta-analyses that evaluated helical CT in the diagnosis of PE found that sensitivity ranged from 53% to 100% and specificity from 81% to 100%.\textsuperscript{24,25} The results varied considerably by reader and, in several studies, were methodologically flawed by nonblinded study design. Also, the sensitivity for subsegmental PE was only 29%, a potentially important limitation for patients with underlying cardiopulmonary disease in whom small clots may cause symptoms or in other patients in whom subsegmental PE may portend a future risk of larger emboli.

A recent prospective, multicenter study provided strong evidence for helical CT as a first-line diagnostic test for PE in institutions with the appropriate radiology expertise. Five hundred ten patients with suspected PE underwent helical CT as the initial diagnostic test.\textsuperscript{26} In 124 (24%) patients, PE was diagnosed; in 130 (26%), an alternative diagnosis, such as pneumonia, malignancy, pleural effusion, or heart failure, was diagnosed; and in the remaining 248 (49%), the CT results were normal. All patients with negative CT scans underwent serial lower-extremity ultrasound testing on presentation and on days 4 and 7 to ensure that clots were not missed on CT. Ultrasound revealed only 2 patients with
DVT at presentation and none at follow-up. Further, only 1 patient (0.4%) developed VTE over the subsequent 3 months. Helical CT was thus useful for diagnosing PE and for identifying other diagnoses missed on traditional x-rays or V/Q images. Based on their finding of only 2 cases of DVT among the 247 patients with negative helical CT scans, the authors recommended stopping testing after a negative CT.

In light of the current evidence, a positive helical CT result rules in PE, especially for large central emboli. A normal helical CT is usually sufficient to stop the diagnostic PE workup and withhold anticoagulation. However, in patients who lack any other diagnosis and who are at high risk for PE, particularly those with poor cardiopulmonary reserve, the possibility of subsegmental PE must still be considered. As illustrated in the algorithm in Figure 2, the V/Q scan remains a first-line diagnostic test for most outpatients with no other underlying lung disease and a normal chest x-ray. Helical CT is an alternative first-line test in institutions with radiologists experienced in interpreting the results with a low degree of interobserver variability. For the two thirds of patients with nondiagnostic V/Q scans, subsequent testing may include serial ultrasound, although the delayed testing can be unsafe in unstable patients at risk for PE in the interim. Other options include D-dimer assays, which may be of limited value if positive, or helical CT. Pulmonary angiography remains the gold standard invasive diagnostic option. The helical CT is indicated for unstable patients as the first-line test in place of the V/Q scan (Table 2).

**RISK FACTORS**

Approximately 80% of patients with VTE have an acquired risk factor such as malignancy, surgery, pregnancy or estrogen use, trauma, immobilization, congestive heart failure, nephrotic syndrome, or the antiphospholipid antibody syndrome. A full discussion of acquired risk factors is beyond the scope of this article, but clinicians should be aware of these associations because they may impact decisions about genetic screening, length of hospital monitoring, or duration of therapy. Background and general management approaches related to estrogen and malignancy are discussed here.

Oral contraceptives (OCs) increase the risk of VTE. The relative risk of VTE is increased 3 to 4 times with OCs that contain first- or second-generation progestogens such as levonorgestrel and norethindrone, and 6 to 9 times with third-generation agents such as desogestrel. In women with inherited hypercoagulability, use of OCs may increase VTE risk 6 to 40 times. Hormone replacement therapy increases the risk of VTE by 2 to 3 times, but the risk is lower with transdermal estrogen.

Based on these risk estimates, third-generation OCs are not recommended as first-line OC agents. A personal history of VTE remains an absolute con-
trandinication to OCs, and family history is a relative contraindication.\textsuperscript{39} Routine screening for inherited hypercoagulability before initiating OCs is not recommended because it would be expensive, the absolute risk of mortality from PE among OC users is quite low, and the available screening tests would not detect all patients with inherited causes of thrombophilia that are caused by as-yet-identified factors.\textsuperscript{31}

Cancer is another important risk factor for VTE. About 20% of patients with cancer will develop VTE. About 75% will already have a diagnosed cancer at the time of VTE diagnosis.\textsuperscript{32} Among patients with cancer, those with VTE have relatively poorer prognoses, with a higher 1-year rate of metastases than in controls without thromboembolism (40% vs 32%, respectively) and reduced 1-year survival rate from that of controls (38% vs 47%, respectively).\textsuperscript{41} Conversely, in patients with VTE who do not have known cancer, the near-term risk of subsequent cancer diagnosis is increased. Within 6 months, the relative risk of cancer diagnosis is 3 times; after 6 months, however, the risk is only slightly higher than that for controls without VTE.\textsuperscript{36} Among patients with VTE, older age and idiopathic VTE increase the cancer risk slightly.\textsuperscript{42} The most common cancers diagnosed at or shortly after the time of diagnosis of VTE involve the lung, prostate, colon and rectum, breast, and pancreas. Given the association between cancer and VTE, the recommendations for performing evaluations of patients with idiopathic VTE are to: 1) perform a careful history and physical examination; 2) follow up any new symptoms or signs identified; and 3) apply routine age- and sex-appropriate cancer screening.\textsuperscript{39} For treatment, low molecular weight heparin (LMWH) is superior to oral anticoagulants in the secondary prevention of VTE in cancer patients.\textsuperscript{43}

**Inherited Risk Factors**

Up to one third of patients with VTE have an inherited tendency for thrombophilia, which compares to about 10% of the general population. Patients with inherited hypercoagulability often have their first presentation as a consequence of an acquired risk factor such as surgery or OC use. Clues to an underlying genetic risk factor among patients with VTE include age under 50 years at thrombosis onset, family history, recurrent thrombosis (with or without anticoagulation), idiopathic thrombosis, thrombosis in unusual locations (eg, cerebral or visceral clots), or thrombosis of extreme severity.

The most common forms of inherited hypercoagulability are listed in Table 3. Heterozygosity for the factor V Leiden mutation is the most prevalent, occurring in 12% to 21% of Caucasians presenting with VTE (vs 5% in the general Caucasian population; relative risk of thrombosis is 2-2.7).\textsuperscript{47} This mutation is autosomal dominant and causes factor V to be resistant to inhibition by activated protein C, an endogenous anticoagulant. The factor V Leiden mutation accounts for approximately 40% of idiopathic thromboses. The prothrombin mutation elevates prothrombin levels by about 30% and is seen in 4% to 8% of patients with DVT (relative risk = 3-4).\textsuperscript{48} Both the Leiden and prothrombin mutations are uncommon in African Americans and Asians. Elevation of homocysteine can be either inherited or acquired (eg, because of deficiencies of B vitamins such as folate, B\textsubscript{12}, or pyridoxine). Elevated homocysteine increases the risk of both arterial and venous thrombosis. Elevated factor VIII levels have been associated with VTE, although the mechanism of increase is not known.\textsuperscript{49}

Screening for thrombophilia may benefit patients with clues to inherited hypercoagulability and VTE by allowing for family testing and counseling, longer duration of anticoagulation therapy, prophylactic anticoagulation in high-risk settings, or avoidance of synergistic risk factors such as OCs. These potential benefits must be weighed against the test costs and the lack of definitive data to guide the optimal duration of anticoagulation therapy. Focusing genetic testing on patients with the highest suspicion of inherited thrombophilia may be the most cost-effective approach. Testing for factor V Leiden mutation, prothrombin mutation, and hyperhomocysteinemia targets the most common disorders. Testing for the factor V Leiden and prothrombin mutations can be performed at the time of presentation with acute thrombosis. Because protein C and S levels and antithrombin levels are measured with functional assays, and the levels may be decreased by the acute clot and by anticoagulants, testing for these disorders should be deferred until after treatment of the acute thrombosis. Protein C and S levels should return to baseline 2 to 4 weeks after warfarin discontinuation.

**TREATMENT**

Therapy of VTE with unfractionated heparin (UFH) or LMWH for approximately 5 to 7 days plus oral anticoagulation continuing for at least 3 months leads to an 80% to 90% risk reduction for both recurrent thrombosis and death.\textsuperscript{4} Heparin and warfarin can usually be initiated simultaneously, except in patients with

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**Table 3. Inherited Hypercoagulability**

<table>
<thead>
<tr>
<th>Inherited Risk Factor</th>
<th>Prevalence With VTE</th>
<th>Prevalence Without PE</th>
<th>Means of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>12%-21%</td>
<td>6%</td>
<td>PCR</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>6%-8%</td>
<td>2%</td>
<td>PCR</td>
</tr>
<tr>
<td>Homocysteinemia</td>
<td>Homocysteine level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein C, S deficiency</td>
<td>2%-4%</td>
<td>&lt;1%</td>
<td>Protein C, S levels</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>1%-2%</td>
<td>&lt;1%</td>
<td>ATIII level</td>
</tr>
<tr>
<td>Any thrombophilia</td>
<td>2%-37%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism; PE = pulmonary embolism; PCR = polymerase chain reaction; ATIII = antithrombin III.
known protein C deficiency, in whom heparin should be started first to avoid protein C depletion and the associated risk of skin necrosis. Heparin and warfarin are continued together until a therapeutic international normalized ratio (INR) of 2 to 3 is achieved for 24 hours, after which heparin is discontinued.

**Initiating Warfarin**

The recommended initial dose of warfarin is 5 mg, a level shown to achieve the target INR of 2 to 3 as soon as, if not faster than would a 10-mg loading dose.42,43 One recent study of outpatients found that dosing with 10 mg warfarin on days 1 and 2 led to more rapid achievement of a therapeutic INR; however, the 10-mg loading dose risks excessive anticoagulation and bleeding complications.44

**Choosing Heparin Therapy**

UFH is a heterogeneous mixture of polysaccharides (molecular weight, MW, 5000-30 000 d) whose activity is measured with the activated partial thromboplastin time (APTT). There are multiple LMWH preparations, with molecular weights of 2000 to 10 000 d, and there are variable ratios of anti-factor Xa to antithrombin activity, depending on the LMWH preparation. These differences among the LMWHs may not translate into significant differences in clinical efficacy or safety, yet the advantages of LMWH over UFH are clear:

- Longer half-life: up to 6 hours vs 1 to 2 hours for subcutaneous UFH
- Predictable anticoagulant response: no need to monitor APTT or adjust dose
- Better bioavailability after subcutaneous injection: immediate effect vs 1- to 2-hour delay in onset of UFH due to plasma protein binding
- Less heparin-induced thrombocytopenia (HIT); in a study of immunologically mediated type II HIT, no hip fracture patients who received LMWH developed HIT vs 2.7% of those treated with UFH
- Potentially lower rates of bleeding and lower risk of osteoporosis with long-term therapy.

One disadvantage of LWMH is that protamine incompletely reverses its effects, a particular concern in patients at high bleeding risk. Also, with renal failure or obesity, the response to LMWH may be unpredictable, and use of either UFH or monitoring of anti-Xa activity in patients weighing more than 100 kg or for those with a serum creatinine over 2 mg/dL while on LMWH is recommended.

Several studies that compared LMWH with UFH in patients with VTE have confirmed the efficacy of LMWH in preventing recurrent thrombosis, limiting bleeding complications, and reducing hospital stay. Two of these studies involved a total of 900 patients with acute DVT who received outpatient heparin therapy.45 Many patients in the LMWH groups did not need to be hospitalized at all. A third randomized trial that involved patients with PE also showed equivalent rates of recurrent VTE, major bleeding, and mortality in the LMWH and UFH treatment groups.46 A meta-analysis of 13 randomized controlled trials that compared LMWH with UFH in the treatment of acute VTE found no statistically significant differences in recurrent VTE, PE, major or minor bleeding, or thrombocytopenia (Figure 3).47 Mortality was significantly reduced with LMWH (relative risk = 0.76; 95% CI, 0.59-0.98).

**Continuing Warfarin**

The goal with warfarin is to maintain the INR between 2 and 3. An INR greater than 5 is associated with a markedly increased bleeding risk. Over a decade ago, researchers showed that a 3-month course of anticoagulation in patients with DVT and/or PE led to a 1-year recurrence rate of 4% compared to a 7.8% rate in those treated for 4 weeks.48 Recently, there has been increasing recognition that VTE is a chronic and systemic disease. Approximately 40% of recurrent lower-extremity DVTs occur in the leg of the side opposite the site of the original clot.49 Consequently, investigators have evaluated the potential benefits of longer courses of warfarin to reduce DVT recurrence.

Two recent studies compared short-term warfarin therapy (3 to 6 months) followed by placebo with extended therapy (up to 2 years or more). With a first idiopathic VTE, the recurrence rate with the 3-month warfarin regimen was 27% per patient-year compared with 1.3% on extended anticoagulation.50 With recurrent VTE, the 4-year recurrence rate after 6 months of warfarin was 20.7%, compared with 2.6% with extended warfarin treatment, with no difference in

![Figure 3. Meta-Analysis of Treatment for Venous Thromboembolism: Comparing Low Molecular Weight Heparin With Unfractionated Heparin*](image)

*Data from Dolovich LR, et al.51

**DVT = deep venous thrombosis; PE = pulmonary embolism; LMWH = low molecular weight heparin; UFH = unfractionated heparin.**
Thromboembolic Event | Duration of Treatment for VTE
--- | ---
1st event, reversible risk factor (trauma, immobilization, surgery) | 3-6 months
1st event, idiopathic | 26 months
1st event, spontaneous, and life-threatening | Consider indefinite
1st event, spontaneous, and >1 genetic risk abnormality | Consider indefinite
1st event and active cancer | Lifelong or until cancer inactive
2nd event | 2-12 months
2nd spontaneous event | Lifelong
3rd event | Lifelong


With permission from the American College of Cardiology Foundation.

VTE = venous thromboembolism.

mortality. The incidence of major hemorrhage was 4% with warfarin compared with 0% with placebo.

Despite the benefits of extended anticoagulant therapy, the protection disappears after discontinuation of anticoagu-
lation. In a clinical trial that compared the DVT recurrence rate in patients with a first episode of idiopathic DVT treated for 3 months vs 1 year of warfarin, the recurrence rate at 9 months in the 3-month group was 8.3%, compared with a 0.7% rate in the group with ongoing therapy (P = .003). However, after about 3 years, the DVT recurrence rate was approximately 16% in both groups.

Low-intensity warfarin for secondary prevention has been studied in an attempt to achieve the protective effects of anticoagulation while limiting the risk of hemorrhage. In the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial, patients with idiopathic VTE received 6 months of warfarin with the standard INR goal of 2 to 3 and then were randomized either to placebo or a regimen of warfarin with an INR goal of 1.5 to 2. After 4 years, 37 of 253 patients (7.2 per 100 person-years) who took placebo had recurrent VTE, compared with 14 of 255 patients (2.6 per 100 person-years) on low-intensity warfarin (risk reduction of 64%, P < .001). Major bleeding occurred in 2 patients who took placebo and 3 who took warfarin (P = .25). In light of recent data that show a 0.6% annual recurrence rate with extended warfarin therapy at full-intensity (ie, INR 2-3), the PREVENT data indicate that long-term low-intensity warfarin provides much but not all of the benefit of full-intensity warfarin. However, in both trials, bleeding rates with low-intensity warfarin were comparable to those with full-intensity warfarin. Because these results indicate that low-intensity warfarin is slightly less effective than warfarin at full intensity, without a meaningful difference in bleeding rates, the role of low-intensity warfarin is not clear. The clinician may thus incorporate the individual patient’s bleeding risk and adherence to therapy and monitoring in electing a low-intensity as opposed to a full-intensity INR goal.

Current treatment guidelines for VTE emphasize individualizing the duration of anticoagulant therapy based on the patient’s risks for recurrence and bleeding. As shown in Table 4, those patients with a first DVT and reversible risk factors such as surgery, immobilization, or trauma can receive 3 to 6 months of warfarin. Spontaneous or recurrent events require longer therapy and some individuals, such as those with a third event or with ongoing nonmodifiable risk factors such as cancer or inherited thrombophilia, should be considered for lifelong treatment.

Thrombolytics for Pulmonary Embolism

Thrombolytic therapy is an alternative to anticoagulation for more rapid lysis of PE. Although streptokinase and urokinase are also approved by the Food and Drug Administration (FDA) for treatment of PE, recombinant tissue plasminogen activator (t-PA) 100 mg over 2 hours is now considered the agent of choice. It is approved for treatment of massive PE, defined as PE with hemodynamic instability. A recent study showed that hemodynamically stable patients with submassive PE, defined as PE with right ventricular dysfunction due to pulmonary hypertension manifested on electrocardiogram or echocardiogram, also benefit from t-PA. In this study, 34 of 118 patients with submassive PE who received heparin alone died or had clinical deterioration, compared with 13 of 138 patients who received both t-PA plus heparin (P = .006), yet there was no mortality difference between the 2 groups. Any potential benefits of t-PA must be balanced against the risk of major hemorrhage. One review of thrombolytic therapy in major trials showed an average 6.3% incidence (range, 0%-48%) of major hemorrhage, compared with 1.8% in patients who received heparin, and a risk of intracranial hemorrhage with thrombolitics of 1.2%. On the other hand, rates of major bleeding in more recent trials have been lower—as in the t-PA trial described above in which the major bleeding rate was 0.8%. Given the risks of thrombolytics, the primary care provider should make the decision to administer thrombolitics in conjunction with a cardiologist or intensivist.

Inferior Vena Cava Filters

The inferior vena cava (IVC) filter is a therapeutic option for patients with acute VTE and active bleeding, VTE despite adequate anticoagulation, or an absolute contraindication to anticoagulation, and possibly in patients with PE and underlying poor cardiopulmonary reserve. Potential complications of filter insertion...
include filter migration, IVC obstruction, insertion-site DVT, trauma to the IVC wall, recurrent DVT, and death (<0.5%). In one review of more than 1700 IVC filter placements, the rate of postplacement PE was 5.6% (3.7% fatal), with 2.7% of patients developing IVC-related thrombosis. In a review of past case series, also uncontrolled, 2400 patients received IVC filters and the rate of PE was approximately 2%; mortality from filter complications was 0.16%.

One controlled trial of anticoagulation with IVC filters has tempered enthusiasm for widespread use of these devices. This study randomized 200 patients with proximal DVT to receive an IVC filter with anticoagulation and another 200 to receive only anticoagulation. Anticoagulation was continued at least 3 months. Half of all patients had PE at presentation. Though the very early outcomes favored the filter group, the 2-year outcomes showed that there was no significant difference in PE. In fact, filters increased the risk of DVT at 2 years, confirming the thrombogenicity of IVC filters and suggesting that clinicians should evaluate the indications for filter placement carefully in each patient. New retrievable IVC filters allow for short-term IVC interruption, with removal of the filter within 2 weeks, or perhaps longer, of insertion.

**NEW AGENTS**

Ximelagatran is an oral direct thrombin inhibitor with attractive dosing characteristics that is under study as an alternative to warfarin. It is administered twice daily as a fixed dose with no need for laboratory monitoring. Because ximelagatran reaches its peak effects within 2 to 3 hours, bridging with heparin therapy is not required, which simplifies the initial management of VTE. Elevated liver function tests in approximately 6% of patients in phase II studies and the lack of an easily accessible antidote have raised concerns about safety. A synthetic factor Xa inhibitor, fondaparinux, is a commercially available direct inhibitor of factor Xa that is FDA approved for prevention of VTE and as an alternative to heparin for treatment of acute VTE while warfarin is initiated. It is administered once daily as a weight-based subcutaneous injection without need for laboratory monitoring. In large trials, it was shown to be approximately 55% more effective than LMWH in preventing VTE, as identified by mandatory venography or symptoms after hip fracture or knee surgery.

**Prophylaxis of VTE**

The prevention of VTE is critically important in hospital and surgical settings. Current guidelines for DVT prophylaxis in surgical patients (Table 5) provide specific recommendations for low-, moderate-, and high-risk patients. Low-risk patients generally require only early ambulation. Moderate-risk patients should receive UFH or LMWH with or without intermittent pneumatic compression or compression hose, and high-risk patients warrant LMWH, which can be combined with mechanical methods.

Prophylaxis of DVT in hospitalized medical patients is also very effective but, unfortunately, often overlooked. A meta-analysis of 7 controlled trials (N = 15095) in inpatient medicine settings showed that heparin reduced the risk of DVT and PE by 56% and 58%, respectively, as opposed to placebo (P < .0001). There were no differences in mortality, although LMWH was associated with a lower risk of major hemorrhage than was UFH (P = .049). A placebo-controlled study of LMWH in 866 moderate- to high-risk medical patients (respiratory failure, infection, and congestive heart failure) showed that enoxaparin 40 mg/day reduced the rate of DVT at day 14 (5.5% vs 15% for both placebo and enoxaparin 20 mg/day; P < .001). Mortality and side effects were similar in all groups. Thus, whereas LMWH may reduce bleeding complications slightly in comparison with UFH, either form of heparin reduces the risk of DVT by approximately 60% in at-risk medical patients.

**CONCLUSION**

The diagnostic workup for suspected DVT or PE should integrate clinical suspicion with imaging and laboratory results. New data indicate that CT angiography can serve as the first-line test in the evolving diagnostic algorithm for DVT/PE. Awareness of inherited thrombophilia is increasing, and clinicians must now consider targeted

<table>
<thead>
<tr>
<th>Table 5. Deep Venous Thrombosis Prophylaxis in Surgical Patients*</th>
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<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Anesthesia duration</td>
</tr>
<tr>
<td>Medical disease risk†</td>
</tr>
<tr>
<td>Surgery type</td>
</tr>
<tr>
<td>Risk of proximal DVT without prophylaxis</td>
</tr>
<tr>
<td>Risk of fatal PE</td>
</tr>
<tr>
<td>Prophylaxis</td>
</tr>
</tbody>
</table>

*Data from Geerts WH, et al.†Thrombophilia, congestive heart failure, malignancy.

DVT = deep venous thrombosis; PE = pulmonary embolism; UFH = unfractionated heparin; bid = twice daily; LMWH = low molecular weight heparin; IPC = intermittent pneumatic compression; INR = international normalized ratio.
testing for genetic factors that will, along with acquired risk factors, help in assessing the risk of recurrent VTE. For initial treatment, LMWH is equivalent in efficacy, and perhaps superior to, UFH. Warfarin treatment is now being continued for longer durations, and in some cases indefinitely, to prevent recurrence. Whereas patients who present with acute DVT or PE remain the natural focus of clinician attention, prophylaxis of DVT in appropriately selected medical and surgical patients must not be neglected. Emerging data suggest that new anticoagulants such as fondaparinux and ximelagatran offer promise as alternatives to traditional treatment and prophylaxis regimens.

REFERENCES


14. Massuda EM, Kessler DM, Kistner RL, et al. Testing for genetic factors that will, along with acquired risk factors, help in assessing the risk of recurrent VTE. For initial treatment, LMWH is equivalent in efficacy, and perhaps superior to, UFH. Warfarin treatment is now being continued for longer durations, and in some cases indefinitely, to prevent recurrence. Whereas patients who present with acute DVT or PE remain the natural focus of clinician attention, prophylaxis of DVT in appropriately selected medical and surgical patients must not be neglected. Emerging data suggest that new anticoagulants such as fondaparinux and ximelagatran offer promise as alternatives to traditional treatment and prophylaxis regimens.


