The field of venous thromboembolism (VTE) has seen tremendous growth since the last edition of the “Venous Thromboembolism Guidebook.” This fifth edition incorporates contemporary concepts in diagnosis, management, and prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE) into a practical and user-friendly format. The purpose of the guidebook is to provide a literature-based review of the current clinical approach to VTE as well as up-to-date references for further study.

**DISCLAIMER**

The authors caution that the information contained here is intended solely to serve as a guideline for the evaluation and management of patients with VTE. Readers are strongly encouraged to consider the individual patient situation and use their best clinical judgment when particular questions arise. Although we make every effort to keep the information contained within the guidebook updated, the field is rapidly changing.

**Epidemiology**

The overall incidence of VTE, which includes DVT and PE, has remained relatively constant across cohort studies. In the Olmsted County population, the estimated annual incidence of DVT during the 25-year period from 1966 to 1990 was 117 per 100,000 person-years compared with 117.7 per 100,000 person-years during the 7-year period between 1991 and 1997. The incidence rates for overall VTE rise sharply after age 60 for both men and women with PE accounting for the majority of the increase. The annual incidence of DVT among persons aged 15 years or older has been estimated to be 61 per 100,000.

**Risk Factors for Venous Thromboembolism**

Risk factors for VTE include several inherited thrombophilias as well as a multitude of acquired conditions of endothelial injury, stasis, and hypercoagulability. The majority of patients present with a combination of risk factors that results in the development of VTE.

**Inherited Risk Factors**

Inherited thrombophilias should be suspected in patients with VTE at a young age, multiple family members with VTE, idiopathic or recurrent VTE, or a history of recurrent spontaneous abortions. The prevalence of inherited thrombophilias varies by population. Major inherited thrombophilias include factor V Leiden mutation resulting in activated protein C resistance, prothrombin gene mutation, and deficiencies of antithrombin III, protein C, and protein S (Table 1). Recently identified polymorphisms in other genes such as those encoding the β2-adrenergic receptor and lipoprotein lipase may prove to be significant risk factors for VTE.

**Acquired Risk Factors**

Acquired risk factors for VTE are greater in number and far more common than inherited thrombophilias (Table 2). Well-established risk factors include advancing age, smoking, obesity, personal or family history of VTE, and recent surgery, trauma, or hospitalization. Acute infectious illnesses such as urinary tract infections have recently been correlated with a transiently increased risk of VTE in the community setting. Long-haul air travel appears to result in activation of coagulation in addition to physical immobility, thereby leading to an increased risk of VTE. Although the link between established malignancy and risk of VTE has been well recognized, occult malignancy has also been associated with an increased incidence of DVT and PE. In fact, the incidence of newly diagnosed cancer is significantly elevated for several years after an initial episode of VTE.
TABLE 1. Major Inherited Risk Factors for Venous Thromboembolism

- Factor V Leiden resulting in activated protein C resistance
- Prothrombin gene mutation 20210
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

TABLE 2. Major Acquired Risk Factors for Venous Thromboembolism

- Advancing age
- Smoking
- Obesity
- Personal or family history of venous thromboembolism
- Recent surgery, trauma, or hospitalization
- Acute infection
- Long-haul air travel
- Malignancy
- Antiphospholipid antibody syndrome
- Hyperhomocystinemia (less commonly inherited secondary to a mutation in methylenetetrahydrofolate reductase)
- Pregnancy, oral contraceptive pills, or hormone replacement therapy
- Atherosclerotic disease
- Pacemaker or implantable cardiac defibrillator leads and indwelling venous catheters

An acquired hypercoagulable state, antiphospholipid antibody syndrome, increases the risk for arterial and venous thromboembolism as well as recurrent spontaneous abortions. Hyperhomocystinemia is also associated with an increased risk of arterial and venous thromboembolism. Although it may be secondary to an inherited deficiency in methylenetetrahydrofolate reductase, hyperhomocystinemia is most often acquired through a deficiency of folate.

VTE is an important women’s health concern. Pregnancy is well recognized as a state of increased risk for VTE. The use of oral contraceptive pills, especially containing third-generation progestins, has been associated with an elevated risk of VTE. In the Women’s Health Initiative, women receiving estrogen plus progestin hormone replacement therapy demonstrated a 2-fold increase in the risk of VTE compared with those receiving placebo.

Patients with evidence of atherosclerotic disease have been shown to have an increased risk of VTE compared with control subjects. Chronically indwelling central venous foreign bodies such as a pacemaker or internal cardiac defibrillator leads as well as venous catheters increase the risk of upper extremity DVT.

Hypercoagulable Evaluation

A workup for hypercoagulable states should be reserved for patients in whom there is a high suspicion for thrombophilia and in whom the results of the evaluation will guide management. A high-yield initial workup should focus on the most common thrombophilias, which include factor V Leiden, prothrombin gene mutation, antiphospholipid antibody syndrome, and hyperhomocystinemia. If the initial evaluation is negative and suspicion for a hypercoagulable state persists, testing for less prevalent disorders such as deficiencies of antithrombin III, protein C, and protein S may be pursued.

PATHOPHYSIOLOGY

Pathophysiology of Deep Vein Thrombosis

DVT results from a combination of pathophysiological states of endothelial injury, stasis, and hypercoagulability. Although the deep veins of the lower extremity are the most common site for formation of DVT, thrombosis may also develop within the upper extremity veins and deep veins of the pelvis.

Pathophysiology of Pulmonary Embolism

The majority of pulmonary emboli originate from the deep veins of the lower extremities and pelvis. Thrombi embolize from these veins and travel through the inferior vena cava and right heart to lodge in the pulmonary arterial tree where they cause hemodynamic and gas exchange abnormalities.

The size of the embolus, the patient’s underlying cardiopulmonary reserve, and compensatory neurohumoral adaptations determine the hemodynamic impact of PE. Acute PE results in an increase in pulmonary vascular resistance and subsequent right ventricular (RV) afterload through direct physical obstruction, hypoxemia, and release of pulmonary artery vasoconstrictors. This sudden increase in RV afterload can lead to RV dilatation and hypokinesis, tricuspid regurgitation, and ultimately acute RV failure. Patients with RV failure may rapidly decompensate to systemic arterial hypotension and cardiac arrest.

RV pressure overload can also result in interventricular septal flattening with deviation toward the left ventricle (LV) in diastole, thereby impairing LV filling. This phenomenon of interventricular dependence also leads to abnormal transmural flow with left atrial contraction, represented by the A wave on Doppler echocardiography, making a greater contribution to LV diastole than passive filling, represented by the E wave. RV pressure overload may also result in increased wall stress and ischemia by increasing myocardial oxygen demand while simultaneously limiting supply.

Impaired gas exchange in PE may result from ventilation to perfusion mismatch, increases in total dead space, and right-to-left shunting. The 2 most common abnormalities of gas exchange include arterial hypoxemia and an increased alveolar-arterial oxygen gradient. Patients may also hyperventilate leading to hypocapnia and respiratory alkalosis. Hypercapnia suggests massive PE resulting in increased anatomic and physiological dead space and impaired minute ventilation.

DIAGNOSIS

Diagnosis of Deep Vein Thrombosis

Clinical Clues

Although it is most commonly described in the lower extremities, DVT may also be seen in the upper extremities in the setting of chronically indwelling central venous foreign bodies such as catheters and syndromes of thoracic outlet ob-
Patients with lower extremity DVT will often report a cramping or pulling sensation of the lower calf that may worsen with ambulation. Physical examination findings of warmth, edema, and tenderness of the lower extremity may be present. Occasionally, a palpable cord or prominent venous collaterals may be appreciated. Importantly, some patients may not demonstrate any abnormalities on physical examination.

Alternative diagnoses to DVT include phlebitis without thrombosis, superficial thrombophlebitis, venous insufficiency without acute thrombosis, ruptured Baker cyst, muscle or soft tissue injury, hematoma, cellulitis, lymphangitis, lymphedema, and peripheral edema secondary to congestive heart failure (CHF), liver disease, renal failure, or nephrotic syndrome.

**Laboratory Evaluation**

A nonspecific marker of ineffective endogenous fibrinolysis, D-dimer is elevated in VTE, including DVT, as well as many other systemic illnesses and conditions such as surgery and pregnancy. D-dimer is most useful in the evaluation of outpatients or emergency department patients with suspected VTE because many inpatients will have elevated levels secondary to other conditions. A systematic review of D-dimer studies in patients with suspected DVT demonstrated that the quantitative D-dimer enzyme-linked immunosorbent assay (ELISA) had negative likelihood ratios similar to those for negative duplex venous ultrasonography. D-dimer for the evaluation of patients with suspected DVT offers the greatest accuracy when used in conjunction with an assessment of clinical probability. In patients with low probability, a negative D-dimer can exclude the diagnosis of DVT without the need of further testing such as ultrasonography. Among patients with a higher clinical suspicion for DVT, further diagnostic evaluation may be indicated despite negative D-dimer results.
Imaging Studies

Venous Ultrasonography

Venous ultrasonography is the initial imaging test of choice in the evaluation of suspected lower as well as upper extremity DVT. Venous ultrasonography is superb for both the diagnosis and exclusion of an initial episode of DVT in both symptomatic and asymptomatic patients.²²,²³ Duplex venous ultrasonography combines vein compression (B-mode imaging) and pulsed Doppler spectrum analysis with and without color. Failure to compress a vein is diagnostic of DVT.

Other Imaging Modalities

Alternative imaging modalities for assessment of patients with suspected DVT include computed tomography (CT), magnetic resonance (MR), and contrast venography. These imaging techniques are used when the evaluation by duplex venous ultrasonography is inadequate. Anatomic limitations hinder ultrasonic evaluation of the pelvic veins and the upper extremity veins proximal to the clavicle. Under these circumstances, alternative imaging modalities such as MR or CT venography are preferred. If a high clinical suspicion persists despite negative venous ultrasonography or if acute-on-chronic thrombosis is suspected, MR, CT, or contrast venography may also be indicated. MR venography provides excellent resolution of the venous system, can estimate the age of the thrombus, and is particularly useful for the evaluation of suspected pelvic vein or upper extremity DVT.²⁴ CT venography can be simultaneously performed with chest CT and increases the diagnostic sensitivity for PE when compared with chest CT alone.²⁵

Diagnosis of Pulmonary Embolism

The prompt diagnosis of acute PE requires the integration of a careful history and physical examination with appropriate laboratory testing and imaging as indicated by an assessment of clinical probability.

Clinical Clues

Acute PE can present as a spectrum of diseases with symptoms and signs that vary widely from patient to patient. Dyspnea is the most frequently reported symptom. Severe dyspnea, cyanosis, or syncope suggests a massive PE, whereas pleuritic pain, cough, or hemothorax may indicate a smaller peripherally located PE. Because acute coronary syndromes are so common and clinical suspicion is often high, clinicians may overlook the possibility of a life-threatening acute PE and inadvertently discharge these patients from the hospital after exclusion of myocardial infarction with serial cardiac enzymes and electrocardiograms.

On physical examination, tachypnea is the most common sign. Patients without underlying cardiopulmonary disease may appear anxious but well compensated even with an anatomically large PE. Patients with massive PE may present with systemic arterial hypotension, cardiogenic shock, or cardiac arrest. Submassive PE describes patients who fall between these 2 extremes. These patients demonstrate preserved systolic blood pressure but may exhibit evidence of RV failure such as tachycardia, distended neck veins, tricuspid regurgitation, and an accentuated sound of pulmonic closure (P2).

Alternative diagnoses to PE include acute coronary syndromes, exacerbations of chronic obstructive pulmonary disease, aortic dissection, pneumonia, acute bronchitis, decompensated congestive heart failure, pulmonary hypertension, pericardial disease, intrathoracic malignancy, musculoskeletal pain, pneumothorax, anxiety, and hepatobiliary or splenic pathology, which may lead to referred pleuritic discomfort.¹⁶

Laboratory Evaluation

The laboratory evaluation of patients with suspected acute PE should focus on the use of D-dimer testing in appropriately selected patients. Although it is a nonspecific marker of fibrinolysis, D-dimer, as measured by ELISA, can be a very helpful test in the evaluation of patients with suspected PE, especially in the emergency room setting. A study of patients with suspected PE in the high-volume emergency department setting demonstrated that the D-dimer ELISA had a sensitivity of 96.4% and negative predictive value of 99.6%.²⁶ Because of its high negative predictive value, the D-dimer ELISA can be used to exclude PE in outpatients with low to moderate pretest probability without the need for further costly testing.²⁰ Inpatients should proceed directly to an imaging study as the initial test for PE because most will already have elevated D-dimers secondary to comorbid illnesses.

Electrocardiogram

The electrocardiogram constitutes an important part of the evaluation of patients with suspected PE because it may reveal the presence of RV strain while also suggesting alternative diagnoses such as myocardial infarction. Signs of RV strain secondary to PE include incomplete or complete right bundle branch block, T wave inversions in the anterior precordium, as well as an S wave in lead I and a Q wave and T wave inversion in lead III (S1Q3T3) (Table 3). Some patients may simply demonstrate signs of increased adrenergic tone with a resting sinus tachycardia. Of note, the electrocardiogram may be entirely normal in young, previously healthy patients.

<table>
<thead>
<tr>
<th>TABLE 3. Electrocardiographic Findings in Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia</td>
</tr>
<tr>
<td>Incomplete or complete right bundle branch block</td>
</tr>
<tr>
<td>T wave inversions in leads III and aVF or in leads V1–V4</td>
</tr>
<tr>
<td>S wave in lead I and a Q wave and T wave inversion in lead III (S1Q3T3)</td>
</tr>
<tr>
<td>QRS axis greater than 90° or an indeterminate axis</td>
</tr>
<tr>
<td>S waves in lead I and aVL greater than 1.5 mm</td>
</tr>
<tr>
<td>Q waves in lead III and aVF, but not in lead II</td>
</tr>
<tr>
<td>Transition zone shift toward V5</td>
</tr>
<tr>
<td>Low voltage in the limb leads</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>

**Sinus tachycardia**
- Incomplete or complete right bundle branch block
- T wave inversions in leads III and aVF or in leads V1–V4
- S wave in lead I and a Q wave and T wave inversion in lead III (S1Q3T3)
- QRS axis greater than 90° or an indeterminate axis
- S waves in lead I and aVL greater than 1.5 mm
- Q waves in lead III and aVF, but not in lead II
- Transition zone shift toward V5
- Low voltage in the limb leads
- Atrial fibrillation

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Imaging Studies

**Chest X-ray**

Like the electrocardiogram, the chest x-ray serves an important role in suggesting alternative diagnoses to PE such as pneumonia. A normal or near-normal chest x-ray in a patient with dyspnea or hypoxemia may suggest PE. However, the majority of patients with PE will have some abnormality such as cardiomegaly or pleural effusion on chest x-ray. Classic findings such as focal oligemia (Westmark sign), a peripheral wedge-shaped opacity (Hampton hump), or an enlarged right descending pulmonary artery (Palla’s sign) are rare.

**Chest Computed Tomography**

Chest CT with intravenous contrast has emerged as the dominant diagnostic imaging technique to evaluate suspected PE. The improved resolution of the newer multidetector CT scanners has increased the detection rate of subsegmental PE and has dramatically reduced the frequency of nondiagnostic studies when compared with older single-detector models. An overview of chest CT in the assessment of patients with suspected acute PE demonstrated negative predictive values of 99.1% and 99.4% for PE and PE-attributable mortality, respectively. Based on these data, chest CT appears to be at least as accurate as invasive contrast pulmonary angiography.

**Ventilation-Perfusion Lung Scanning**

In general, ventilation–perfusion lung scans are reserved for patients with major renal impairment, anaphylaxis to intravenous iodinated contrast, or pregnancy. Although a high probability scan in the setting of moderate to high clinical suspicion virtually guarantees the diagnosis and a normal scan excludes it, the majority of patients have intermediate or indeterminate probability scans. Patients with nondiagnostic scans require further imaging to evaluate for PE.

**Magnetic Resonance Angiography**

MR angiography is a promising modality for the detection of PE in the proximal pulmonary arteries. MR angiography offers the additional benefit of avoiding the risks of iodinated contrast and ionizing radiation.

**Echocardiography**

Although insensitive for diagnosis, transthoracic echocardiography (TTE) plays a critical role in the risk stratification of patients with proven acute PE. TTE is superb for detecting RV dysfunction in the setting of PE with RV pressure overload. Characteristic echocardiographic findings among patients with acute PE include RV dilatation and hypokinesis, paradoxical interventricular septal motion toward the LV, tricuspid regurgitation, and pulmonary hypertension as identified by a tricuspid regurgitant jet velocity greater than 2.6 m/s (Table 4). Regional RV dysfunction with severe free wall hypokinesis and apical sparing (McConnell sign) is a specific finding for PE. RV dysfunction is a clinically important echocardiographic finding among normotensive patients with acute PE because RV hypokinesis has been shown to be an independent risk predictor for early death. In hemodynamically unstable patients, TTE can be performed rapidly at the bedside and may demonstrate evidence of RV failure suggestive of acute PE in addition to alternative diagnoses such as myocardial infarction, aortic dissection, and pericardial tamponade.

Transthoracic echocardiography (TTE) may diagnose PE by direct visualization of the proximal pulmonary arteries. TEE is also useful in determining the extent of thrombus and surgical accessibility in patients being considered for surgical embolectomy.

**Contrast Pulmonary Angiography**

Invasive contrast pulmonary angiography is reserved for the diagnosis of acute PE in the rare circumstance when other imaging modalities are nondiagnostic and a high clinical suspicion remains.

**Venous Ultrasonography**

Lower extremity duplex venous ultrasonography revealing DVT may support a clinical diagnosis of PE when suspicion remains high and other imaging modalities are nondiagnostic.

**An Integrated Diagnostic Approach**

A diagnostic algorithm that integrates an assessment of clinical probability with appropriate laboratory testing and imaging modalities is essential (Fig. 2). The recent Christopher Study used an algorithm consisting of a dichotomized clinical decision rule, D-dimer testing, and chest CT to prospectively evaluate a cohort of patients with suspected acute PE. A modified version of the Wells clinical decision rule assigned 3 points for clinical symptoms and signs of DVT, 3 points for an alternative diagnosis less likely than PE, 1.5 points for a heart rate greater than 100 beats per minute, 1.5 points for recent immobilization or surgery, 1.5 points for previous VTE, 1 point for hemoptysis, and 1 point for malignancy receiving treatment or palliative care within the last 6 months.

TABLE 4. Echocardiographic Findings in Patients With Pulmonary Embolism

<table>
<thead>
<tr>
<th>Description</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular dilatation and hypokinesis</td>
<td>Indirect evidence of RV overload</td>
</tr>
<tr>
<td>Interventricular septal flattening and paradoxic motion toward the left ventricle</td>
<td>Indirect evidence of RV overload</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>Indirect evidence of RV overload</td>
</tr>
<tr>
<td>Pulmonary hypertension as identified by a tricuspid regurgitant jet velocity greater than 2.6 m/s</td>
<td>Indirect evidence of RV overload</td>
</tr>
<tr>
<td>Loss of respiratory phasic collapse of the inferior vena cava with inspiration</td>
<td>Indirect evidence of RV overload</td>
</tr>
<tr>
<td>Decrease in the difference between left ventricular area during diastole and systole (indicates low cardiac output state)</td>
<td>Indirect evidence of RV overload</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>Indirect evidence of RV overload</td>
</tr>
</tbody>
</table>
derwent D-dimer testing and were only referred for chest CT if the D-dimer was abnormal. PE was considered to be excluded in patients classified as "pulmonary embolism unlikely" with negative D-dimer results and in patients with negative chest CT scans. The use of this simple clinical algorithm permitted a management decision in 98% of patients and was associated with a low risk of VTE.

The recent Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial evaluated the accuracy of multidetector chest CT alone and combined with venous phase imaging for the diagnosis of acute PE after assessment of the patient using a clinical decision rule. Among patients with a low to intermediate clinical probability of acute PE, a negative chest CT had a high negative predictive value (96% for patients with a low probability and 89% for patients with an intermediate probability), whereas the negative predictive value was low (60%) for patients with a high clinical probability.

TABLE 5. A Generally Accepted Clinical Decision Rule for the Evaluation of Patients With Suspected Pulmonary Embolism

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms and signs of deep vein thrombosis</td>
<td>3.0</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than pulmonary embolism</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate greater than 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Recent immobilization or surgery</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy receiving treatment or palliative care within the last 6 months</td>
<td>1.0</td>
</tr>
</tbody>
</table>

"Pulmonary embolism unlikely" ≤4 points.
"Pulmonary embolism likely" >4 points.

FIGURE 2. An integrated approach to the evaluation of patients with suspected pulmonary embolism. PE, pulmonary embolism; ECG, electrocardiogram; CT, computed tomography.
The addition of venous phase imaging to chest CT added diagnostic sensitivity and modestly increased the negative predictive value when compared with chest CT alone.25,38 PIOPED II also suggested that additional testing may be necessary to confirm or exclude the diagnosis of PE when the clinical probability is discordant with the test results.25,38

Both the Christopher Study and PIOPED II trial highlighted the importance of an algorithm that integrates the use of a clinical decision rule with appropriate laboratory testing and imaging with chest CT. The use of such an algorithm allows for a management decision to be made in the majority of patients with suspected PE and is associated with a low risk of VTE.

**RISK STRATIFICATION OF PULMONARY EMBOLISM**

PE may present as a broad spectrum of clinical syndromes. Some patients may present with pleuritic pain resulting from small peripheral emboli, whereas others may experience massive PE resulting in cardiogenic shock or cardiac arrest. The majority of patients with acute PE present with normal blood pressure. However, a subset of these patients may abruptly deteriorate and experience systemic arterial hypotension, cardiogenic shock, and sudden death despite therapeutic levels of anticoagulation. Risk stratification to identify such patients has become a crucial part of the management of acute PE.

**Clinical Clues**

The history and physical examination can provide important clues for risk stratification. The International Cooperative Pulmonary Embolism Registry (ICOPER) described several significant clinical predictors of increased mortality, including congestive heart failure, chronic lung disease, cancer, systolic blood pressure less than or equal to 100 mm Hg, age greater than 70 years, and heart rate greater than 100 beats per minute (Table 6).35

**Cardiac Biomarkers**

Cardiac biomarkers such as troponin and brain-type natriuretic peptide (BNP) have emerged as important tools in the risk stratification of patients with acute PE. Elevated cardiac biomarkers correlate with the presence of RV dysfunction, which has been established as a powerful independent predictor of early mortality.35 The myocardium releases cardiac troponin as a result of microinfarction resulting from RV pressure overload, whereas cardiac myocytes increase secretion of BNP in response to RV shear stress.39 Both cardiac troponins and BNP accurately identify a low-risk subset of patients with PE with negative predictive values for in-hospital death ranging from 97% to 100%.30 However, in contrast to cardiac troponins, which have well-established ranges associated with the presence of RV dysfunction, the levels at which BNP correlates with RV dysfunction have only been determined in post hoc analyses. A TTE to evaluate for the presence of RV dysfunction should be performed in patients with acute PE and elevated cardiac biomarkers.39

### Imaging Studies

**Chest Computed Tomography**

Although it is most often used for the diagnosis of PE, chest CT can also assess for evidence of RV dysfunction in the setting of acute PE. A marker of RV dysfunction, RV enlargement as detected by chest CT, has been evaluated as a risk stratification tool in the management of patients with acute PE.46 Based on measurements from a reconstructed CT 4-chamber view, RV enlargement, defined as a ratio of RV to LV dimension of greater than 0.9, was found to be a significant independent predictor of mortality at 30 days.40 Chest CT detection for RV enlargement is a particularly convenient risk stratification tool because it may be performed using the data from the initial diagnostic scan.

**Echocardiography**

Echocardiography remains the imaging study of choice for the risk stratification of patients with acute PE. Normotensive patients with acute PE and evidence of RV dysfunction on echocardiography demonstrate an increased risk of systemic arterial hypotension, cardiogenic shock, and death, whereas those without evidence of RV dysfunction generally have a benign clinical course.33,35 Echocardiography should be performed in patients with acute PE and clinical evidence of RV failure, elevated cardiac biomarkers, unexpected deterioration, or suspicion of other comorbid cardiac disease.36

### An Integrated Approach to Risk Stratification

A risk stratification algorithm that integrates clinical prognostic indicators, cardiac biomarkers, and evidence of RV dysfunction as detected by either echocardiography or chest CT is essential for identifying patients with acute PE and an elevated risk of adverse outcomes (Fig. 3).41

### MANAGEMENT

**Spectrum of Disease: Deep Vein Thrombosis**

Deep venous thrombosis encompasses a wide spectrum of diseases, including massive DVT, proximal lower extremity DVT, isolated calf DVT, and upper extremity DVT.

**Massive Deep Vein Thrombosis**

Massive DVT most often describes thrombus that originates in the proximal veins of the lower extremity and extends into the pelvic veins. Such extensive thrombus may result in severe chronic venous insufficiency if not treated with primary therapy such as fibrinolysis or thrombectomy.

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**TABLE 6. Clinical Predictors of Increased Mortality at 30 Days in Patients With Acute Pulmonary Embolism**

<table>
<thead>
<tr>
<th>Congestive heart failure</th>
<th>Chronic lung disease</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure less than or equal to 100 mm Hg</td>
<td>Age greater than 70 years</td>
<td>Heart rate greater than 100 beats per minute</td>
</tr>
</tbody>
</table>

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Proximal Lower Extremity Deep Vein Thrombosis

Proximal DVT is the most common type of DVT and generally describes thrombus involving the common femoral, superficial femoral, profunda femoris, or popliteal veins.

Isolated Calf Deep Vein Thrombosis

The previous practice of serial observation with lower extremity ultrasound has been replaced by routine anticoagulation of isolated calf DVT. Patients with isolated calf DVT are at elevated risk for proximal propagation of the thrombus as well as for development of PE.

Upper Extremity Deep Vein Thrombosis

Upper extremity DVT most often affects the subclavian, internal jugular, and axillary veins as a result of chronic indwelling foreign bodies such as central venous catheters and pacemaker or defibrillator leads. Superior vena cava syndrome may complicate an upper extremity DVT secondary to venous foreign bodies or may result from thoracic malignancy with extrinsic compression of the upper extremity veins.

Spectrum of Disease: Pulmonary Embolism

Acute pulmonary embolism describes a number of clinical syndromes, including massive PE, submassive PE, and PE with normal blood pressure and preserved RV function.

Massive Pulmonary Embolism

Massive pulmonary embolism describes a subset of patients with PE who present with syncope, systemic arterial hypotension, cardiogenic shock, or cardiac arrest.

Submassive Pulmonary Embolism

Normotensive patients with acute pulmonary embolism and evidence of RV dysfunction are classified as having submassive PE. These patients represent a population at increased risk of adverse events and early mortality.

Pulmonary Embolism With Normal Blood Pressure and Preserved Right Ventricular Function

Patients with acute PE presenting with normal systemic blood pressure and no evidence of RV dysfunction generally...
have a benign hospital course when treated with standard anticoagulation alone.

### Pulmonary Hypertension Secondary to Chronic Thromboembolic Disease

Both single and recurrent episodes of PE may result in pulmonary hypertension secondary to chronic thromboembolic disease. An often debilitating condition, pulmonary hypertension secondary to chronic thromboembolic disease may be treated with surgical pulmonary thromboendarterectomy.

### Primary Therapy

#### Fibrinolysis

**Deep Vein Thrombosis**

Although not proven, fibrinolysis should, in theory, provide a greater chance of preserving venous valve patency and function, thereby preventing postphlebitic syndrome and chronic venous stasis disease. Fibrinolysis in DVT is used most commonly to treat upper extremity thrombosis or iliofemoral DVT in young, otherwise healthy patients with severe symptoms. Although fibrinolytics for the primary therapy for PE are administered peripherally, fibrinolysis should be catheter-directed in DVT to gain access to the obstructed deep venous system.

#### Pulmonary Embolism

Primary therapy with fibrinolysis is reserved for patients presenting with either massive or submassive acute PE. However, because of a paucity of conclusive randomized, controlled trials, the use of fibrinolytics as primary therapy in the treatment of submassive PE remains controversial.

In general, fibrinolysis is well accepted to be a lifesaving therapy in patients presenting with massive PE. However, the magnitude of the clinical benefit in these patients remains unclear.

The rationale for fibrinolysis in submassive PE centers on the observation that normotensive patients with RV dysfunction have a significantly increased risk of adverse clinical events such as recurrent PE and higher early mortality. The goal of fibrinolysis is to prevent clinical deterioration in this high-risk subset of patients and thereby reduce mortality. The Management Strategies and Prognosis of Pulmonary Embolism-3 (MAPPET-3) evaluated the benefit of primary therapy with t-PA (alteplase) in patients with submassive PE. The MAPPET-3 trial demonstrated a reduction in the need for escalation of therapy among patients receiving alteplase.

#### Administration

The U.S. Food and Drug Administration (FDA) has approved 100 mg t-PA (alteplase) as a continuous infusion over 2 hours for the fibrinolysis of massive PE. All patients being considered for fibrinolysis should be meticulously screened for contraindications (Table 7). In contrast to fibrinolysis in myocardial infarction, intravenous unfractionated heparin is withheld during the infusion of t-PA. The activated partial thromboplastin time (aPTT) should be checked at the conclusion of the fibrinolytic infusion. Unfractionated heparin infusion should be restarted without a bolus when the aPTT has fallen to less than twice the upper limit of normal.

If still greater than twice the upper limit of normal, the aPTT should be rechecked every 4 hours until it falls into the range at which heparin can be safely restarted. Although the efficacy of fibrinolytics in PE appears to be inversely proportional to the duration of symptoms, effective fibrinolysis can be administered up to 2 weeks after an acute PE.

#### Complications

Bleeding, in particular intracranial hemorrhage, comprises the most feared complication of fibrinolytic therapy. ICOPER has reported that the risk of intracranial hemorrhage may be as high as 3.0% among patients receiving fibrinolitics for PE.

### Surgical Interventions

Surgery may be considered in the primary therapy for both DVT and PE. Surgical thrombectomy is generally considered in patients with massive or severely symptomatic DVT in whom fibrinolysis has failed or is contraindicated. Surgical embolectomy may be considered in patients with massive or submassive PE in whom fibrinolysis has failed or is contraindicated. Other indications include paradoxical embolism, persistent right heart thrombi, “clot-in-transit,” and hemodynamic or respiratory compromise requiring cardio-pulmonary resuscitation. In specialized centers with experience in the care of such patients, surgical embolectomy has been shown to be a safe and effective technique in the treatment of massive PE.

### Catheter-Assisted Techniques

Catheter-assisted techniques have been applied to both DVT and PE. Catheter-based pulmonary embolectomy is an emerging technique for the primary therapy for acute PE. Catheter-assisted techniques should be considered when fibrinolysis and surgical intervention are contraindicated. In general, catheter-assisted techniques are most effective when applied to fresh thrombi within the first 5 days of symptoms of DVT or PE.

### Supportive Care of Patients with Massive Pulmonary Embolism

The supportive care of patients with massive PE can be particularly challenging even with the institution of primary therapy (Table 8). While considering primary therapy, high-dose unfractionated heparin should be administered as soon as massive PE is suspected. The majority of patients will require at least a 10,000-unit bolus of unfractionated heparin followed by a continuous infusion of at least 1250 units/hour with a target aPTT of at least 80 seconds. The rationale for

---

**TABLE 7. Major Contraindications to Fibrinolytic Administration in Pulmonary Embolism**

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial disease</td>
</tr>
<tr>
<td>Recent surgery</td>
</tr>
<tr>
<td>Recent trauma</td>
</tr>
<tr>
<td>Severe or uncontrolled hypertension</td>
</tr>
<tr>
<td>Recent prolonged cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>Active or recent bleeding</td>
</tr>
</tbody>
</table>

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LV filling and reducing systemic cardiac output. An interventricular septal shift toward the LV, thereby worsening volume loading may overdistend the RV, increase wall stress, be the first step in hemodynamic support. An initial trial of volume is most likely to be successful in patients without signs of increased right-sided preload such as those with central venous pressures of less than 12 to 15 mm Hg. In patients with central venous pressures of greater than 12 to 15 mm Hg, volume loading should be avoided and the administration of vasopressors and inotropes should be the first step in hemodynamic support. Norepinephrine, epinephrine, and dopamine are favorable agents for the initial support of patients with massive PE. If an inotrope such as dobutamine is necessary to enhance cardiac output, the addition of a vasopressor may help compensate for inotrope-induced vasodilation and thereby maintain systemic perfusion pressure. In some patients with massive PE and tachycardia, a strict vasopressor such as a phenylephrine may be most appropriate to avoid accelerating the heart rate further.

**TABLE 8. Tips for the Supportive Care of Patients With Massive Pulmonary Embolism**

While considering primary therapy, high-dose unfractionated heparin should be administered as soon as massive pulmonary embolism (PE) is suspected. High doses of heparin are often necessary because standard doses frequently fail to achieve adequate therapeutic anticoagulation in patients with massive PE. Care must be taken to avoid excessive volume resuscitation that may worsen right ventricular failure. An initial trial of volume is most likely to be successful in patients with central venous pressures of less than 12 to 15 mm Hg. In patients with central venous pressures of greater than 12 to 15 mm Hg, volume loading should be avoided and the administration of vasopressors and inotropes should be the first step in hemodynamic support. Norepinephrine, epinephrine, and dopamine are favorable agents for the initial support of patients with massive PE. If an inotrope such as dobutamine is necessary to enhance cardiac output, the addition of a vasopressor may help compensate for inotrope-induced vasodilation and thereby maintain systemic perfusion pressure. In some patients with massive PE and tachycardia, a strict vasopressor such as a phenylephrine may be most appropriate to avoid accelerating the heart rate further.

**Secondary Therapy**

**Anticoagulation**

**Overview**

Whether or not patients receive primary therapy, anticoagulation remains the foundation of therapy for patients with VTE. Currently used agents for anticoagulation in VTE include unfractionated heparin, low-molecular-weight heparin, fondaparinux, and warfarin.

**Unfractionated Heparin**

The majority of patients with VTE will receive intravenous unfractionated heparin administered as a bolus followed by a continuous infusion titrated to a goal aPTT of 2 to 3 times the upper limit of normal, or approximately 60 to 80 seconds. Weight-based protocols such as the modified Raschke nomogram are widely used and may achieve therapeutic levels of anticoagulation more quickly (Table 9).

Because it can be discontinued and reversed rapidly, unfractionated heparin is preferred in patients undergoing fibrinolysis, catheter-based intervention, or surgery for VTE. Although unfractionated heparin is continued during fibrinolysis for myocardial infarction, anticoagulation is withheld during the administration of t-PA for VTE and is not restarted until the aPTT has fallen to less than twice the upper limit of normal.

**Low-Molecular-Weight Heparin**

Low-molecular-weight heparins (LMWHs) offer several advantages over unfractionated heparin, including longer half-life, more consistent bioavailability, and a more predictable dose response. LMWHs are dosed according to weight, administered subcutaneously, and do not require dose adjustments or laboratory monitoring under usual circumstances. Several trials have demonstrated that LMWHs are at least as safe and effective as continuous infusion unfractionated heparin in the prevention of recurrent VTE after DVT. A meta-analysis of randomized, controlled trials using high doses of heparin is derived from the observation that standard doses often fail to achieve adequate therapeutic anticoagulation, and in patients with massive PE, subtherapeutic heparin dosing can be fatal.

Although the initial reaction to hemodynamic instability is often to augment RV preload with bolus administration of intravenous fluids such as normal saline, care must be taken to avoid excessive volume resuscitation, which may worsen RV failure. In the setting of RV pressure overload, volume loading may overdistend the RV, increase wall stress, worsen RV ischemia, decrease contractility, and cause further interventricular septal shift toward the LV, thereby worsening LV filling and reducing systemic cardiac output. An initial trial of volume is most likely to be successful in patients without signs of increased right-sided preload such as those with central venous pressures of less than 12 to 15 mm Hg. In patients with central venous pressures of greater than 12 to 15 mm Hg, volume loading should be avoided and the administration of vasopressors and inotropes should be the first step in hemodynamic support.

The ideal agent for the hemodynamic support of patients with massive PE should augment RV function through positive inotropic effects while also maintaining systemic arterial perfusion.

Norepinephrine, epinephrine, and dopamine have dual mechanisms of action as both inotropes and vasopressors and therefore may be favorable agents for the initial support of patients with massive PE. Inotropes such as dobutamine may be necessary to enhance cardiac output but may also cause systemic arterial hypotension. In these cases, the addition of a vasopressor may be required to maintain systemic perfusion while administering inotropes. In some patients with massive PE and tachycardia, a strict

**TABLE 9. A Modified Raschke Weight-Based Heparin Nomogram**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heparin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial heparin dose</td>
<td>80 U/kg bolus, then 18 U/kg/h</td>
</tr>
<tr>
<td>aPTT &lt;35 seconds (&lt;1.2 × control)</td>
<td>80 U/kg bolus, then increase infusion by 4 U/kg/h</td>
</tr>
<tr>
<td>aPTT 35–59 seconds (1.2–1.9 × control)</td>
<td>40 U/kg bolus, then increase infusion by 2 U/kg/h</td>
</tr>
<tr>
<td>aPTT 60–89 seconds (2.0–2.9 × control)</td>
<td>No change</td>
</tr>
<tr>
<td>aPTT 90–100 seconds (3.0–3.3 × control)</td>
<td>Decrease infusion by 3 U/kg/h</td>
</tr>
<tr>
<td>aPTT &gt;100 seconds (&gt;3.3 × control)</td>
<td>Hold infusion 1 hour; then decrease infusion rate by 4 U/kg/h</td>
</tr>
</tbody>
</table>

Adapted with permission from Ann Intern Med. 1993;119:874–881. aPTT, activated partial thromboplastin time.
comparing LMWH therapy with intravenous unfractionated heparin for the treatment of DVT demonstrated a 30% reduction in mortality and 40% reduction in risk of major bleeding associated with LMWH use.56 The FDA has approved enoxaparin and tinzaparin for treatment of DVT as “bridge” to therapeutic oral anticoagulation (Table 10).

LMWHs have also been shown to be as safe and effective as intravenous unfractionated heparin in the prevention of recurrent VTE among patients with acute PE.58,59 LMWH monotherapy without transition to oral anticoagulation appears to be promising and may be preferable in patients with active malignancy.60–62

In contrast to unfractionated heparin, which is largely eliminated by the liver, LMWHs are cleared renally. Patients with impaired renal clearance, massive obesity, pregnancy, or unanticipated bleeding or thromboembolism despite correct weight-based dosing of LMWH may benefit from laboratory monitoring. Although the aPTT is checked to monitor the level of anticoagulation with unfractionated heparin therapy, anti-Xa levels, often called heparin levels, are used to determine the level of anticoagulation with LMWHs. The goal therapeutic range for anti-Xa levels is 0.5 to 1.0 anti-Xa IU/mL. Anti-Xa levels should be drawn 4 to 6 hours after the second or third dose of LMWH to ensure a steady-state value. The use of anti-Xa testing remains the subject of considerable debate because the correlation of anti-Xa levels to antithrombotic effect and risk of bleeding has come into question.63,64

**Adverse Effects of Heparin**

Bleeding is a common and important adverse effect of heparin therapy. Although in most cases, discontinuation of heparin therapy is sufficient, protamine sulfate may be necessary to reverse the effects of heparin in the setting of life-threatening hemorrhage. Protamine sulfate is administered as a slow infusion in a dose of 1 mg for every 100 units of heparin administered over the preceding 4 hours up to a maximum dose of 50 mg. A potentially severe allergic reaction may be observed in patients who have been exposed to heparin who present with thromboembolism and experience thrombocytopenia once HIT has developed and may lead to worsening thrombocytopenia and thrombosis.

**Fondaparinux**

Fondaparinux is a synthetic pentasaccharide with anti-Xa activity approved by the FDA for the initial therapy for VTE, including DVT and PE. Fondaparinux has been shown to be at least as safe and effective as enoxaparin in the initial treatment of patients with symptomatic DVT.56 Among hemodynamically stable patients with acute symptomatic PE, fondaparinux is as safe and effective as intravenous unfractionated heparin.67 Fondaparinux is administered subcutaneously on a once-daily basis in fixed doses of 5 mg for body weight less than 50 kg, 7.5 mg for body weight of 50 to 100 kg, and 10 mg for body weight greater than 100 kg. Fondaparinux is as safe and effective as intravenous unfractionated heparin and LMWH for the treatment of DVT demonstrated a 30% reduction in mortality and 40% reduction in risk of major bleeding associated with LMWH use.56 The FDA has approved enoxaparin and tinzaparin for treatment of DVT as “bridge” to therapeutic oral anticoagulation (Table 10).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg</td>
<td>Subcutaneously</td>
<td>Every 12 hours</td>
<td>Inpatient and outpatient</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1.5 mg/kg</td>
<td>Subcutaneously</td>
<td>Daily</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>175 units/kg</td>
<td>Subcutaneously</td>
<td>Daily</td>
<td>Inpatient and outpatient</td>
</tr>
</tbody>
</table>

**TABLE 10.** U.S. Food and Drug Administration-Approved Dosing Regimens for the Use of Low-Molecular-Weight Heparins in Venous Thromboembolism

Heparin-induced thrombocytopenia (HIT) is caused by heparin-dependent IgG antibodies directed against heparin-platelet factor 4 complex. Although bleeding is rarely a complication of HIT, devastating arterial and, more commonly, venous thromboembolic complications may result in limb-threatening and life-threatening ischemia. Although the risk is lower with LMWH, both unfractionated heparin and LMWH are associated with the development of HIT. HIT must be distinguished from transient early decreases in the platelet count that most often normalize within 3 days despite ongoing administration of heparin. A decrease in the platelet count of greater than 50% of baseline or a new thromboembolic event in the setting of any heparin product, including heparin flushes, should raise concern for true HIT and lead to the discontinuation of all heparin-containing products. HIT typically occurs within 4 to 14 days from the initial heparin exposure but may occur earlier if the patient has been exposed to heparin in the past. Clinicians should consider the diagnosis of delayed-onset HIT in patients recently exposed to heparin who present with thromboembolism and experience thrombocytopenia on re-exposure.65

When HIT is confirmed or even suspected, a direct thrombin inhibitor such as argatroban or lepirudin should be administered. Unlike lepirudin, argatroban does not require dose adjustment for renal insufficiency. However, argatroban is heptatically cleared and should be used with caution in patients with impaired liver function. Several other pitfalls in the management of HIT must be avoided. Warfarin as monotherapy should not be used for anticoagulation because it may worsen the procoagulant state and precipitate limb gangrene. Platelet transfusions simply “add more fuel to the fire” and are contraindicated. Inferior vena cava (IVC) filter placement in place of anticoagulation can result in devastating caval, pelvic, and lower extremity venous thrombosis. LMWH, although less likely to initiate HIT, will often crossreact with the IgG antibodies once HIT has developed and may lead to worsening thrombocytopenia and thrombosis.
Warfarin

Oral vitamin K antagonists such as warfarin continue to be the mainstay of outpatient anticoagulation for VTE. Oral anticoagulation is started concurrently with heparin, LMWH, or fondaparinux and overlapped for a minimum of 5 days until full therapeutic efficacy has been achieved. For the majority of patients with VTE, the target international normalized ratio (INR) is between 2.0 and 3.0. Most patients achieve a therapeutic INR with initial warfarin doses of 5 mg daily.

Management of warfarin anticoagulation can often be challenging because of many drug-food, drug-alcohol, and drug-drug interactions. Commonly implicated warfarin potentiators include acetaminophen, quinolone antibiotics, amiodarone, and antiplatelet agents such as clopidogrel. A subset of patients with a genetic mutation in cytochrome P450 2C9 that leads to very slow metabolism of warfarin and lower maintenance dose requirements presents an additional challenge.

The effect of polymorphisms in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) on the response to warfarin has been evaluated. Ten common noncoding VKORC1 single-nucleotide polymorphisms and 5 major haplotypes were identified. These 5 major haplotypes were classified as either a low-dose haplotype group (A) or a high-dose haplotype group (B). Warfarin maintenance doses differed significantly among the 3 combinations of these 2 haplotype groups: low dose (A/A), intermediate dose (A/B), and high dose (B/B). Interestingly, Asian-Americans had a higher proportion of group A haplotypes, whereas blacks demonstrated a higher frequency of group B haplotypes. Based on these data, VKORC1 haplotypes may explain differences in warfarin maintenance doses across various patient populations and may provide an important tool for stratification of patients into low-, intermediate-, or high-dose groups.

An individual patient’s risk of recurrent VTE determines the optimal duration of anticoagulation. The risk of recurrent VTE persists after completion of standard anticoagulation in patients with idiopathic DVT or PE. In these patients without reversible causes for DVT or PE, VTE represents a chronic illness that may require indefinite therapy.

Several studies have established the efficacy of indefinite anticoagulation for patients with idiopathic, unprovoked VTE. In the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial, 508 patients with idiopathic VTE who had completed standard full-dose anticoagulation were randomized to placebo or low-intensity warfarin (target INR, 1.5–2.0). Over a mean follow-up of 2.1 years, a 64% risk reduction in recurrent VTE was observed in the low-intensity warfarin group without an increase in major bleeding. The risk reduction was similar across all subgroups, including those with and without thrombophilia. In the subsequent Extended Low-intensity Anticoagulation for Thrombo-Embolism (ELATE) study, 738 patients who had completed standard anticoagulation for idiopathic VTE were randomized to indefinite conventional-intensity warfarin (target INR, 2.0–3.0) or low-intensity warfarin (target INR, 1.5–2.0). Over an average follow-up period of 2.4 years, 16 patients in the low-intensity group had recurrent VTE compared with 6 in the conventional-intensity group without any significant difference in the risk of bleeding. In the randomized, controlled Thrombin Inhibitor in Venous Thromboembolism III (THRIVE III), patients were randomly assigned to receive 18 months of the investigational oral direct thrombin inhibitor ximelagatran or placebo for the secondary prevention of VTE after 6 months of standard anticoagulation. Compared with placebo, ximelagatran reduced the rate of recurrent VTE by 84% without significantly increasing the rate of major bleeding.

Based on these data, a therapeutic algorithm that considers indefinite anticoagulation for patients with idiopathic VTE is crucial.

Correction of Excessive Oral Anticoagulation

In the event of minor excessive oral anticoagulation without active bleeding, one to 2 doses of warfarin should be held and the INR should be rechecked serially until it falls into the therapeutic range. For more severe cases of excessive oral anticoagulation without active bleeding, 2.5 mg oral vitamin K can be safely administered to expedite the return of the INR to the therapeutic range. Fresh-frozen plasma or recombinant factor VIIa should be used to reverse excessive oral anticoagulation in the setting of active bleeding.

Tips for Outpatient Anticoagulation

Management of outpatient anticoagulation can present a unique challenge to even the most experienced of healthcare providers. Several important interventions such as the use of patient-centered educational materials and centralized anticoagulation clinics may help avoid many of the management pitfalls of outpatient anticoagulation therapy (Table 11).

<table>
<thead>
<tr>
<th>TABLE 11. Tips for Management of Outpatient Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insist on detailed and explicit communication between all of the patient’s healthcare providers and clearly designate who will manage the anticoagulation</td>
</tr>
<tr>
<td>Clearly explain to the patient and family the rationale for anticoagulation and the major risks from supratherapeutic (bleeding) and subtherapeutic levels (thromboembolism)</td>
</tr>
<tr>
<td>Define the relationship between important terms such as prothrombin time, international normalized ratio (INR), and dose adjustment of the anticoagulant</td>
</tr>
<tr>
<td>Use a software-supported electronic surveillance system that will keep track of prior anticoagulation levels and flag patients in whom an expected laboratory value has not been reported</td>
</tr>
<tr>
<td>Consider the use of centralized anticoagulation clinics</td>
</tr>
<tr>
<td>Avoid warfarin dose adjustments of greater than 20% of the previous dose</td>
</tr>
<tr>
<td>Changes in the INR are most reflective of the warfarin dose given 3 to 5 days previously</td>
</tr>
</tbody>
</table>

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Inferior Vena Cava Filters

IVC filters should be considered for patients in whom anticoagulation is contraindicated, those who experience recurrent PE despite adequate anticoagulation, and those undergoing surgical embolectomy. IVC filters have been associated with an increased incidence of DVT. Although further studies are required, a recent analysis from ICOPER noted a significant reduction in 90-day mortality associated with the use of IVC filters. Retrievable IVC filters offer a safe and effective alternative in patients with transient contraindications to anticoagulation.
An Integrated Approach to Management of Pulmonary Embolism

An overall therapeutic algorithm that considers primary therapy for appropriate patients with PE and integrates indefinite anticoagulation for those with idiopathic VTE is critical (Fig. 4).41

PREVENTION

Overview

Although the use of VTE prophylaxis should be virtually universal among hospitalized patients, implementation of both mechanical and pharmacologic techniques continues to be inconsistent. Accordingly, the incidence of VTE among inpatients remains unacceptably high.

Mechanisms of Prophylaxis

Current prophylactic regimens use mechanical and pharmacologic modalities.78 Mechanical prophylactic devices such as graduated compression stockings and intermittent pneumatic compression boots increase venous blood flow and may augment endogenous fibrinolysis, thereby leading to reductions in VTE.79 Pharmacologic agents for the prevention of VTE include subcutaneously administered unfractionated heparin, LMWH, warfarin, and fondaparinux. In certain high-risk populations such as neurosurgical and thoracic surgery patients, a combination of mechanical and pharmacologic modalities may be beneficial.

Computerized provider order entry programs offer a unique opportunity to assist healthcare providers in the prevention of VTE among hospitalized patients. A computer alert program at Brigham and Women’s Hospital was recently shown to increase physician utilization of VTE prophylaxis resulting in a 41% risk reduction in the incidence of symptomatic DVT or PE.80

Duration of Prophylaxis

The risk of VTE persists after hospital discharge with a significant number of patients, especially those who are postoperative, experiencing DVT or PE while at a rehabilitation center or even at home. Several studies have validated the use of extended VTE prophylaxis for up to 4 to 6 weeks in high-risk patient populations such as those undergoing oncologic or orthopedic surgery.81–83

Recommendations for Specific Patient Populations

Medical Patients

VTE prophylaxis continues to be underused among hospitalized medical patients. The DVT Free Registry demonstrated that only 42% of patients who had a DVT diagnosed while in the hospital had received prophylaxis within the 30 days before diagnosis.3 Several studies have established the safety and efficacy of various regimens for the prevention of VTE among hospitalized medical patients. Enoxaparin, administered as a daily subcutaneous injection, has been shown to safely and effectively reduce the risk of VTE among patients admitted with acute medical illnesses.84

A large randomized, controlled trial of acutely ill medical patients demonstrated that the LMWH dalteparin (5000 IU subcutaneously once daily) halved the rate of VTE with a low risk of bleeding.85 In the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS), fondaparinux (2.5 mg subcutaneously once daily) reduced the incidence of VTE among medical patients by 47%.86

Orthopedic Patients

The risk of VTE among orthopedic patients remains significantly elevated even after discharge from the hospital. Extended out-of-hospital prophylaxis with warfarin or LMWH has been established as safe and effective in the prevention of VTE among orthopedic patients.81,82,87 Fondaparinux (2.5 mg subcutaneously once daily) has been shown to safely reduce the risk of VTE in patients undergoing hip replacement, major knee surgery, and hip fracture repair.88–91

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>Unfractionated heparin 5000 units subcutaneously 2 or 3 times a day or</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 40 mg subcutaneously daily or</td>
</tr>
<tr>
<td></td>
<td>Dalteparin 2500 or 5000 units subcutaneously daily</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Warfarin (target INR 2.0–3.0) or</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 30 mg subcutaneously 2 times a day or</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Dalteparin 2500 or 5000 units subcutaneously daily or</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux 2.5 mg subcutaneously daily</td>
</tr>
<tr>
<td>Oncologic surgery</td>
<td>Unfractionated heparin 5000 units subcutaneously 2 times a day or</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>Enoxaparin 40 mg subcutaneously daily and</td>
</tr>
<tr>
<td>Medical patients</td>
<td>Graduated compression stockings/intermittent</td>
</tr>
<tr>
<td></td>
<td>pneumatic compression</td>
</tr>
<tr>
<td></td>
<td>Consider surveillance lower extremity ultrasonography</td>
</tr>
</tbody>
</table>

| TABLE 12. Regimens for Venous Thromboembolism Prevention |

INR, international normalized ratio.

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Abdominal or Pelvic Surgery for Malignancy

Patients who have undergone abdominal or pelvic surgery for malignancy have a significantly elevated risk of postoperative VTE. In the Enoxaparin and Cancer (ENOXACAN) II study, extended-duration prophylaxis with enoxaparin significantly reduced the risk of VTE in patients undergoing open surgery for abdominal or pelvic cancer.83

An Overview of Prophylactic Regimens

The approach to VTE prevention among hospitalized and postoperative patients must consider the patient population and individual risk while integrating the use of mechanical, pharmacologic, and combined modalities when indicated (Table 12).41

REFERENCES


77. Turpie AG, Gallus AS, Hoes JA. Apixaban: a synthetic pentasaccharide for the

