Venous thromboembolism (VTE) refers to the pathologic formation of a thrombus within the veins, and includes both pulmonary embolism (PE) and deep venous thrombosis (DVT). VTE is a common disease causing significant morbidity, mortality, and substantial socioeconomic costs. Consequently, many resources have been devoted to improving its diagnosis and management; resulting in an increasing number of well-designed clinical trials over the past decades. These trials have significantly advanced our understanding of the optimal approach toward diagnosis and treatment of VTE, and are helping resolve existing controversies. The clinical landscape of VTE management, however, continues to evolve rapidly as novel medications, imaging techniques, procedures, and devices present new exciting options and challenges.

EPIDEMIOLOGY AND RISK FACTORS

Epidemiology

Although the exact incidence and prevalence of VTE is unknown, modeling based on epidemiologic studies estimates more than 900,000 incident or recurrent cases in the United States alone.\(^1\) PE is a substantial subset of these cases, with hospital-based studies estimating it is responsible for 200,000 to 300,000 hospital admissions per year.\(^2\) The majority of deaths secondary to VTE are caused by PE, with a 3-month disease specific mortality rate of 10% causing an estimated 30,000 to 50,000 deaths annually.\(^3\)–\(^5\) Symptomatic PE carries an 18-fold higher risk of early death when
compared with DVT alone, and the initial clinical presentation is sudden death in 20% of all cases.\textsuperscript{2,6} The epidemiology for Europe and other parts of the world is generally similar.\textsuperscript{7}

Although the incidence of VTE and PE has not changed dramatically over the past 25 years,\textsuperscript{8} the overall mortality rate from PE has decreased substantially in the past several decades.\textsuperscript{2,9,10} This decrease has been attributed to improved detection and treatment of DVT, risk-factor modification including protocolization of VTE prophylaxis, and/or improvements in PE diagnostic tests that have increased the specificity and sensitivity of disease diagnosis. Regardless, the annual hospital mortality has decreased by roughly 30% from 1998 to 2009.\textsuperscript{2}

**Risk Factors**

Rudolph Virchow (1821–1902) first coined the term embolism after observing at autopsy blood clots wedged in the pulmonary arteries.\textsuperscript{11} From his extensive writings and descriptions of VTE, later investigators coined the term Virchow’s Triad, which consists of vascular endothelial injury, hypercoagulability, and venous stasis as the combination of host factors that predispose to VTE.\textsuperscript{12} VTE risk factors are traditionally categorized as either acquired or genetic (inherited thrombophilia).

**Inherited thrombophilia**

Inherited thrombophilias may result in increased levels or function of coagulation factors (activated protein C resistance, factor V Leiden mutation, prothrombin gene mutation, elevated factor VIII levels), defects of coagulation factor inhibitors (antithrombin, protein C, protein S), and defects in fi brolysis, hyperhomocysteinemia, or altered platelet function. The majority of published data regarding the inherited thrombophilias comes from studies of Caucasian populations with VTE.\textsuperscript{13–15} It is generally accepted that patients with a “provoked” VTE, such as those with recent surgery, trauma, immobilization, malignancy, or certain inflammatory disorders such as lupus or inflammatory bowel, do not require screening of the hereditary thrombophilias.\textsuperscript{16} Screening patients with unprovoked VTE, however, is still a matter of debate, and it is recommended to consult with a coagulopathy specialist before initiating an evaluation.

**Acquired risk factors**

Acquired risk factors account for the majority of VTE cases. The most significant acquired risk factor for incident VTE is advancing age, especially as age advances beyond 60 years. The most significant risk factor for recurrent VTE is a previous episode of VTE. Other important acquired risk factors include obesity, malignancy, surgery, trauma, hormone replacement therapy, pregnancy, and heparin-induced thrombocytopenia. Roughly 50% or more of patients with VTE will have multiple risk factors,\textsuperscript{17} both acquired and inherited, validating the pathophysiologic and clinical relevance of Virchow’s Triad.

**DIAGNOSIS AND EVALUATION**

The diagnosis of PE often presents a significant challenge. The clinical presentations of pulmonary embolic disease are diverse and often incongruous; many patients will experience only a subset of the characteristic symptoms, may have atypical symptoms, or may even be asymptomatic. The signs and symptoms of PE, such as tachycardia, dyspnea, chest pain, hypoxemia, and shock, overlap considerably with other common diseases such as coronary artery disease, congestive heart failure, pericarditis, pneumonia, and exacerbations of chronic obstructive pulmonary disease. Further confounding diagnosis and treatment is that many patients may have a PE
in addition to one of the aforementioned diagnoses. The clinical consequences of PE can be equally as diverse, ranging from incidental to catastrophic hemodynamic collapse and sudden death. Consequently, several clinical prediction tools have been developed which, combined with the history and examination, aid clinicians in the choice of appropriate diagnostic tests and therapeutic interventions. Given the high prevalence, diverse symptoms, and mortality associated with PE, it is essential that a high clinical index of suspicion be maintained while using these clinical tools in an efficient and expeditious fashion.

**Medical History**

Given the diversity and complexity in the clinical presentation of PE, it is crucial to identify risk factors for VTE by performing a careful history. Specifically, the patient’s personal and family history of prior VTE, coexisting medical conditions, functional status, travel history, and current medications are fundamental. Recent immobilization, myocardial infarction, cerebrovascular accident, surgery, and recent (within 30 days) trauma are all major risk factors for VTE. Additional major risk factors include advanced age, malignancy, prior VTE, known thrombophilia (inherited or acquired), and indwelling venous catheter. Moderate risk factors include use of estrogen or hormone replacement therapy, obesity, and family history of VTE. These risk factors are used in clinical prediction tools, such as the Wells criteria and the Geneva score, to assess the patient’s pretest probability of PE (see the section Clinical Tools).

**Clinical Assessment**

As previously mentioned, the typical signs and symptoms of PE are nonspecific and include tachypnea, rales, tachycardia, a fourth heart sound, a loud S2, dyspnea, pleuritic chest pain, cough and, in a minority of patients, hemoptysis. Despite, or perhaps because of the complexity in diagnosing PE, clinical judgment is a critical first step in the evaluation and is heavily weighted in diagnostic algorithms. The 1990 PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study first highlighted the importance of a clinician’s suspicion in predicting the probability of PE.18

In PIOPED, prior to ventilation/perfusion (V/Q) scan and pulmonary arteriogram, physicians recorded their clinical suspicion (low, intermediate, or high probability) of PE in patients evaluated for the disease. A very important finding of PIOPED was that diagnosis or exclusion of PE required concordance between the clinical impression and radiographic findings by V/Q (normal, low, intermediate, or high). There have been many subsequent attempts to quantify and standardize the definition of “clinical impression,” 2 of the most widely known being the Wells and Geneva scores, discussed in the Clinical Tools section.

**Electrocardiography and Chest Radiography**

Chest radiographs (CXR) and electrocardiograms (ECG) are commonly used in the initial evaluation of patients with chest pain or dyspnea. Both lack adequate sensitivity or specificity for diagnosis or exclusion of PE, and do not figure prominently in diagnostic algorithms. It is nevertheless important to appreciate findings that are suggestive of PE. In the case of ECG, evidence of right heart strain should raise suspicion for PE. Signs of right ventricular (RV) strain include T-wave inversions in the anterior precordial leads, new right bundle branch block, or the S1Q3T3 complex (deep S-wave in lead I, and a Q-wave with T-wave inversions in lead III, Fig. 1). Other common ECG abnormalities include sinus tachycardia and atrial fibrillation.

Like ECG, CXR is insensitive for PE, but is helpful by excluding other causes of chest pain such as pneumonia or pneumothorax. Although by itself not sensitive or specific
for PE, ipsilateral elevation of the diaphragm on the affected side can be seen. Other suggestive signs of PE include a wedge-shaped infiltrate (Hampton hump), focal oligemia (Westermark sign), or an enlarged right descending pulmonary artery (Palla sign).

Laboratory Tests

The initial evaluation of patients with dyspnea or chest pain includes several laboratory tests that can aid in the diagnosis and/or prognosis of PE. Common tests include D-dimer, arterial blood gas (ABG), B-type natriuretic peptide (BNP), serum sodium, and troponin. D-dimer is included in many diagnostic algorithms, as a normal level carries a high negative predictive value and is helpful to exclude PE in low to intermediate clinical risk groups. Although not a part of official algorithms at this time, an elevation in either troponin or BNP, or a depression in serum sodium (hyponatremia) has been suggested as a poor prognostic indicator.16,19,20 Research indicates these markers can differentiate between low and intermediate risk for PE-related complications, including hemodynamic collapse and death.21,22 Finally, ongoing investigations continue to identify new biomarkers of potential use in the prognosis or diagnosis of PE. One such novel biomarker, growth differentiation factor 15 (GDF-15), is also be discussed herein.23

Arterial blood gas

Obtaining an ABG documenting an elevation in alveolar-arterial (A-a) gradient was thought to aid in the diagnosis of PE. It has subsequently been demonstrated, however, that a normal A-a gradient lacks sufficient negative predictive value to exclude PE.24 Although PE causes increased alveolar dead space and shunt, patients with acute PE will often have hypocapnia and respiratory alkalosis. Also, the partial
pressure of oxygen (PO2) may be decreased, normal, or increased. Thus, although an ABG may be indicated for other reasons (dyspnea, hypoxemia, or hypercapnia), its utility in the evaluation of PE is questionable.

D-dimer
D-dimer is a plasmin-derived fibrin degradation product commonly included in the initial evaluation of patients with dyspnea or chest pain. D-dimer represents a direct method to measure endogenous fibrinolysis following a thrombotic event, such as a PE, and is an important screening tool in patients with suspected VTE.26 Although extremely sensitive, D-dimer lacks specificity for VTE (30%–75%). Many other conditions (eg, trauma, inflammation, surgery) can elevate plasma D-dimer levels; therefore, an abnormal laboratory result has a low positive predictive value for VTE. The strength of the D-dimer is its high sensitivity and ability, with a normal test, to essentially rule out VTE in low-risk and intermediate-risk patients (see Clinical Tools section).

The exact way in which D-dimer is measured has gone through considerable refinement over the past 25 years. Initially several different assays were available, including quantitative enzyme-linked immunosorbent assay (ELISA), quantitative latex agglutination, semiquantitative agglutination latex, and whole blood agglutination. These assays all varied in their sensitivity and specificity, which presented clinicians with a challenge to correctly interpret results. ELISA, however, has now been established as the standard D-dimer test, due to its superior sensitivity and high negative predictive value.26 Typically a level greater than 500 ng/mL is considered abnormal. When combined with a low clinical probability of VTE, a normal D-dimer level (value <500 ng/mL) has a 99% negative predictive value for PE. This finding was demonstrated in the Christopher study, in which the incidence of PE was on 0.5% at 3 months in patients with a low probability score (by the “modified” Wells criteria) and a D-dimer level less than 500 ng/mL.27 Other VTE studies looking at outcomes have had similar results, with D-dimer sensitivities ranging between 92% and 99%. In patients with a high clinical suspicion, however, a normal D-dimer cannot adequately rule out VTE, and additional testing is warranted (see Clinical Tools section).27

B-type natriuretic peptide
Released by ventricular myocardial cells in response to wall stretch and volume overload, BNP is a prognostic (not diagnostic) biomarker for PE. In the presence of PE, elevated BNP levels generally indicate RV strain due to elevated pulmonary vascular resistance in the clot-burdened lungs. Clinically, BNP levels differentiate between low and intermediate risk of PE-related complications, and alert the clinician to patients at increased risk who are otherwise hemodynamically stable. When measured within 4 hours of admission for PE, elevated BNP levels (>90 pg/mL) have a sensitivity of 85% and specificity of 75% in predicting PE-related clinical outcomes such as need for emergent thrombolysis, mechanical ventilation, vasopressor therapy, emergency surgical embolectomy, cardiopulmonary resuscitation, or death.28 Conversely, normal BNP values in the setting of acute PE have a 97% to 100% negative predictive value for in-hospital death.29 Given its short half-life and delay in release, if symptoms have been present for less than 6 hours a repeat test is warranted.

Troponin
Released by damaged myocardial cells, cardiac troponins are extremely sensitive and specific markers of cardiac ischemia and infarction. When elevated in acute PE, troponins are presumed to represent myocyte ischemia and microinfarction due to acute RV strain. Approximately 30% to 50% of patients with large PE will have elevations in troponins I and T that are mild and short-lived when compared with acute coronary
syndromes. Similar to BNP, elevated troponin levels correlate with worse RV function and a high incidence of complications while normal troponin T levels have a 97% to 100% negative predictive value for in-hospital death.\textsuperscript{19,21} Although BNP and troponins are not a part of diagnostic algorithms at this time, this may change in the future given their usefulness in prognosis and triage of patients.

**Growth differentiation factor 15**

GDF-15 is a distant member of the transforming growth factor β family of cytokines, and is upregulated in cardiomyocytes in response to stress such as pressure overload or ischemia. GDF-15 levels may also be elevated because of cancer, diabetes, congestive heart failure, or renal failure. A recent prospective cohort study demonstrated GDF-15 to be an independent predictor of PE-related complications including need for vasopressors, mechanical ventilation, cardiopulmonary resuscitation, or death.\textsuperscript{23} In this cohort, a cutoff of 4600 ng/L had a positive predictive value of 0.52 and negative predictive value of 0.95 for these PE-related complications. Further studies are needed to validate these findings, but GDF-15 is a promising new prognostic biomarker with potentially superior differentiating power to BNP or troponins.

**Hyponatremia**

Hyponatremia has been well described as a poor prognostic indicator in a variety of disease processes including congestive heart failure, liver failure, and pulmonary hypertension. Recently, several publications have discussed the prognostic utility of hyponatremia in acute PE. A retrospective analysis of 13,728 patient hospitalizations found serum sodium levels of less than 135 mmol/L in 2907 patients (21.1%).\textsuperscript{20} Sodium levels less than 130 mmol/L were independently associated with increased 30-day mortality and readmission. The investigators also found serum sodium levels to improve the accuracy of the pulmonary embolism severity index (PESI) classification of patients into low-risk, intermediate-risk, and high-risk groups (see Clinical Tools section). As with GDF-15, validation of these findings awaits further independent prospective studies.

**Advanced Imaging**

**Venous compression ultrasonography**

When initial diagnostic tests are inconclusive, ultrasonography of the deep venous system is a useful adjunctive test in the diagnosis and treatment of PE. Pragmatically the approach to treatment (anticoagulation) of both DVT and submassive PE is the same, and thus a positive ultrasonogram for DVT obviates the immediate need for further diagnostic studies to demonstrate PE. A negative ultrasonogram, however, is a somewhat more complicated result and requires appreciation of several caveats. Ultrasonography of the proximal leg veins detects DVT in roughly 1% to 5% of patients with clinical symptoms consistent with PE but nondiagnostic chest imaging.\textsuperscript{30–33} Also, DVT is detectable by ultrasonography in only approximately 50% of patients with an acute PE. Thus, a negative ultrasonogram does not rule out PE. It does, however, slightly reduce the probability of PE and connotes a lower risk of short-term VTE complications should therapeutic anticoagulation be withheld.\textsuperscript{34}

**Echocardiogram**

Transthoracic or transesophageal echocardiography has limited diagnostic value for PE, due to its low sensitivity and specificity. For critically ill patients too unstable for transport, echocardiography can suggest the diagnosis of PE by demonstrating RV dilatation or hypokinesis. Rarely, thrombus within the pulmonary arteries or right ventricle can be visualized on echo. More commonly, acute changes in the RV
pressure, size, and function are observed, indicating increased RV strain and pulmonary arterial pressures suggestive of PE in the absence of alternative diagnoses (Fig. 2).

Although of limited value in the diagnosis of PE, echocardiography is of great prognostic use in stratifying risk for patients with acute PE. Numerous studies have demonstrated that RV dysfunction or dilatation in acute PE is associated with worse outcomes, including increased mortality.35–37

Ventilation/perfusion lung scan
As previously mentioned, the PIOPED study established the role of the V/Q scan in the diagnosis of PE.18 By correlating the V/Q results (normal, low, high, or indeterminate probability) with a similar clinical impression (low, intermediate, or high probability), the diagnosis or exclusion of PE can be made (Fig. 3). It must be noted that a normal V/Q test essentially rules out PE as a diagnosis. Further testing, often by pulmonary or computed tomography (CT) angiogram, is required in patients with discordant or intermediate results. In recent years CT angiography has replaced the V/Q scan as the favored diagnostic test (see CT Angiogram section). V/Q scan remains, however, an important alternative to CT in patients with pregnancy, contrast allergy, or renal insufficiency. V/Q may be the modality of choice to evaluate patients for chronic thromboembolic pulmonary hypertension (CTEPH) (see Chronic Thromboembolic Disease section).

Fig. 2. Echocardiogram of a patient with an RV dysfunction secondary to pulmonary thromboembolic disease. (A) Color Doppler of the large tricuspid regurgitant jet. (B) M-mode of the tricuspid jet, estimating severely elevated pulmonary arterial pressures. (C) Four-chamber view demonstrating enlarged right ventricle and right atria with a flattened septum indicated elevated right-sided ventricular pressures.
CT angiogram
Over the past 10 years, CT pulmonary angiography (CTA) has become the favored diagnostic study in the evaluation of PE (see Fig. 3). There are several practical advantages of CTA, including: (1) common availability, especially after hours; (2) rapid interpretation; (3) direct visualization of the thrombus; (4) evaluation of the chest for alternative or concomitant diagnoses; and (5) simultaneous evaluation for DVT and PE when both the chest and lower extremity deep veins and pelvic veins are imaged. The ability to evaluate the chest for both PE and alternative pathology is not trivial. Up to 75% of patients with suspected PE will actually have an alternative diagnosis, some of which can be just as serious and readily identifiable by CTA, such as thoracic aortic dissection or pneumonia.27,38

When evaluating the efficacy of CTA to diagnose PE, it is important to appreciate the improvements in CT technology and the extent these have increased the sensitivity and specificity of CTA over the past 10 years. Early publications of CTA used single-detector scanners that were specific (>90%) but relatively insensitive (~72%), meaning they could not reliably exclude PE.39,40 Multidetector scanners have significantly improved the sensitivity and specificity as well as the positive and negative predictive value of CTA. Recent outcome studies such as the Christopher study have found the sensitivity and specificity of CTA to be greater than 95%, and a negative CTA carries a 3-month risk of VTE of 1% to 2%, essentially the same as a negative pulmonary arteriogram.27,30 Current multidetector scanners allow resolution and evaluation of PE down to the sixth-order branches of the pulmonary arteries. In fact, the interobserver agreement for CTA is superior to V/Q scanning, and CTA may be more sensitive than V/Q for subsegmental PE.41,42 As such, CTA is now the predominant imaging modality used in diagnostic algorithms for the evaluation of PE.

Pulmonary arteriogram
Long considered the gold standard, pulmonary angiography, also known as digital subtraction angiography (DSA), is nowadays rarely performed. The reasons for this are both practical and medical. In practical terms DSA is more expensive than CTA,
and is often unavailable in smaller centers. In medical terms outcome studies have found comparable results between DSA and CTA; a negative result with either study confers approximately a 1% VTE rate within 6 months.\(^{18,27,33}\) Also, because of the invasive nature of DSA, it carries a greater risk of complications and mortality. The mortality from DSA has been estimated at 0.5% while 1% may experience major complications including arrhythmias, hypotension, bleeding, and nephrotoxicity. DSA is also less commonly performed, resulting in fewer clinicians who have experience in both performing and interpreting the test. All these factors have recently made DSA a relatively uncommon test in evaluating acute PE. DSA is still an important test, however, in the evaluation of patients with CTEPH, as discussed later (see Chronic Thromboembolic Disease section).

**Magnetic resonance imaging**

The Prospective Evaluation Of Pulmonary Embolic Disease—3 (PIOPED 3) trial recently evaluated the efficacy of magnetic resonance angiography (MRA), venography (MRV), or the combination of the two in the diagnosis of acute PE.\(^ {43}\) The gold standard used for comparison was a composite end point of CTA, CTA-CTV, V/Q scan, lower extremity ultrasonography, D-dimer assay, and clinical assessment. Overall, MRA and MRA-MRV were found to be poor tests in the diagnosis of PE. Approximately 25% of the 371 patients enrolled in the study had a technically inadequate MRA, and 48% had either an inadequate MRV or MRA. Considering all patients enrolled, MRA alone identified only 57% of PEs, and had a sensitivity of only 78% when only patients with adequate studies were considered. The combined MRA-MRV studies had a sensitivity of 92%, but only about half of the patients had technically adequate studies. These poor results are generally ascribed to the technical difficulties of MRA in identifying abrupt vessel termination and capturing adequate images of the chest vessels secondary to motion artifact. At this time, MRA-MRV is recommended only in centers with a great deal of experience, and then only when all other imaging modalities are contraindicated.

**Clinical Tools**

**Wells criteria and Geneva score**

Two of the most widely known and validated diagnostic scoring systems are the Wells criteria (or modified/dichotomous Wells criteria) and Geneva score.\(^ {27,44–46}\) These tools use a combination of physical examination, history, and vital signs to predict the clinical likelihood of VTE, and thereby inform the appropriate choice of laboratory tests and imaging studies to either diagnose or exclude PE. Notable differences include the use of CXR and ABG in the original Geneva score (subsequent versions do not include these tests), while the Wells criteria use a clinical gestalt in their formula by assigning points to PE if an “alternative diagnosis is less likely.” Both scores have been modified and simplified throughout the years, now incorporating many common variables (although scored differently), and have been found to be equally efficacious (Table 1).

**Pulmonary embolism severity index**

Published in 2005 by Aujesky and colleagues,\(^ {47}\) the PESI was originally derived from analysis of 10,354 patients discharged with PE from 186 Pennsylvania hospitals. PESI risk stratifies patients with PE into low (I and II) and high (III, IV, and V) risk groups. In contrast to the Geneva score, which requires an ABG and ultrasonography, PESI only uses data available from a brief history, physical, and vital signs. Low-risk groups have 2% 30-day mortality and are candidates for home-based care, whereas high-risk groups have 14% 30-day mortality and warrant hospitalization and close monitoring.
The accuracy of PESI has been validated in numerous studies.\textsuperscript{48–50} Recently, a simplified version of PESI (sPESI) has been proposed (see Table 1).\textsuperscript{51} Initial studies indicate PESI and sPESI are very similar in most respects, although PESI classifies more patients as low risk than sPESI (41\% vs 37\%). Finally, a recent prospective study has reported a high level of PE-related complications in patients classified as low risk by PESI.\textsuperscript{52} Further investigation is warranted, but generally this report highlights the potential limitations of PESI and other prognostic algorithms, and serves to remind clinicians to exercise their judgment in conjunction with these clinical prediction tools.

The table lists all the clinical variables considered in the most recent published versions of these 3 algorithms. Both the modified Wells criteria and simplified revised Geneva score are used to predict the likelihood of pulmonary embolism as a diagnosis. In the most recent iteration, the modified Wells criteria is split in a dichotomous fashion with pulmonary embolism (PE) being likely if >4 points are assigned. PE can essentially be ruled out with an unlikely score and a negative D-dimer. The simplified revised Geneva score considers PE likely with >2 points. PE is essentially ruled out with 2 or fewer points and a negative D-dimer. The PESI score assigns a prognostic likelihood of poor clinical outcome once the diagnosis of PE is established. A simplified PESI score of 0 is considered low risk, whereas 1 or greater is high risk. Outpatient treatment of PE can be considered in the low-risk group.

\textit{Abbreviations:} DVT, deep venous thrombosis; VTE, venous thromboembolism.

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<table>
<thead>
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<th>Variable</th>
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\textit{Abbreviations:} DVT, deep venous thrombosis; VTE, venous thromboembolism.
Prompt anticoagulation has remained the cornerstone of PE treatment for more than 50 years and is life saving. There have been, however, numerous exciting advances in recent decades, which have added new options with nuanced risks and benefits for clinicians to weigh. For example, the number and types of anticoagulant medications available continues to expand; with newer medications providing the ability to treat PE outside the hospital setting and with the potential to change future recommendations for duration of treatment. In addition to medications, widely available minimally invasive interventional techniques placing mechanical barriers in the inferior vena cava can protect patients otherwise ineligible for anticoagulation. Uncertainties remain, however, regarding the extent of indications for their use and their long-term risks and benefits. In addition to these newer therapies, clinical trials continue to refine the use of older treatments such as thrombolysis. Overall, these advances in care can be categorized into one of two categories: (1) treatment of acute PE or (2) prophylaxis against recurrent VTE.

**Treatment of Acute Pulmonary Embolism**

**Anticoagulation**

**Heparin and vitamin K antagonists** Initial treatment with anticoagulation aims at rapidly blocking the clotting cascade, stabilizing existing clot, and allowing the body’s endogenous thrombolytic system to dissolve preexisting thrombi. For many years now, the standard of care has been to treat nonmassive pulmonary emboli with at least 5 days of heparin concomitant with commencement of an oral vitamin K antagonist (VKA) for long-term anticoagulation, preferably beginning on the first day of treatment. Intravenous unfractionated heparin (UFH) was the anticoagulant of choice until being recently eclipsed by subcutaneous low molecular weight heparin (LMWH) in many situations. LMWH has many advantages over UFH, including more predictable and reliable anticoagulation, increased patient satisfaction, and the ability to be self-administered, making home-based treatment a possibility. LMWH was first studied and approved for the prevention of DVT. Studies with LMWH have subsequently demonstrated it to have similar morbidity and mortality outcomes to UFH in the treatment of DVT and submassive PE. Of interest, a small number of patients in these studies were either discharged early or treated entirely at home, and had similar outcomes to hospitalized patients. Combined with risk stratification tools (see Clinical Tools section) such as PESI, LMWH has revolutionized the treatment of low-risk PE by making home-based treatment possible for some patients. Although heparin and VKA continue to play a major role in the treatment of PE, advancements in anticoagulation medications continue to challenge these existing treatment paradigms.

**Factor Xa inhibitors** Factor Xa is a common factor in both the intrinsic and extrinsic coagulation pathways proximal to fibrin formation, making it ideally positioned as a target for anticoagulation. For many years, the only available factor Xa inhibitor has been subcutaneously administered fondaparinux. With a relatively long half-life (17 hours), fondaparinux can be administered once daily. A newer factor Xa inhibitor with an even longer half-life (80 hours), idraparinux, is currently under evaluation. If approved, idraparinux could dramatically simplify administration to once a week. Both subcutaneous Xa inhibitors undergo renal clearance, and should be used with caution in patients with renal insufficiency.

Recently, new oral factor Xa inhibitors such as rivaroxaban have undergone evaluation for the treatment of VTE, and appear likely to gain approval. Similar to the
subcutaneous LMWH and fondaparinux, these oral preparations have predictable and rapid anticoagulation in addition to excellent bioavailability. The Einstein investigators recently demonstrated “noninferiority” between 3, 6, and 12 months of rivaroxaban compared with 5 days of subcutaneous enoxaparin followed by 3, 6, or 12 months of an oral VKA. Of note, both groups had similar low levels of bleeding complications. Included in this report, the investigators published a long-term continuation study examining patients with VTE who had previously completed 6 to 12 months of treatment with oral VKA and were then randomized to either placebo or rivaroxaban for an additional 6 to 12 months. There was a small increased risk of significant bleeding with rivaroxaban versus placebo, but also a significant decrease in recurrent VTE. Although further study is warranted, the oral Xa inhibitors have the potential to dramatically change the current management of VTE. As with LMWH, the ease of use, efficacy, and predictability of anticoagulation could facilitate outpatient management. For long-term anticoagulation, oral Xa inhibitors would relieve the burden of serial laboratory tests needed with the VKAs. One current point of concern, however, is the lack of an available antidote should rapid reversal of anticoagulation be necessary. The development of a reversal agent, as well as further prospective studies demonstrating efficacy, economy, and safety, will help establish whether outpatient and perhaps prolonged therapy (>6–12 months) with oral Xa inhibitors will become the new treatment of choice.

**Direct thrombin inhibitors** There are currently several direct thrombin inhibitors (DTIs) approved for use in humans, including hirudin, bivalrudin, dabigatran, and argatroban. There are several potential benefits to these medications. For instance, unlike heparin, which requires antithrombin III, the DTIs do not require cofactors for efficacy. The DTIs are also able to inactivate clot-bound thrombin and are unaffected by activated platelet factors such as heparinase and PF4. These potential benefits are offset, however, by the practical difficulties of using most of these medications, including unpredictable anticoagulation, need for intensive laboratory monitoring, continuous intravenous access, and potential drug-drug interactions. The usefulness of the DTIs currently lies in their lack of interaction with platelets and inability to potentiate or cause heparin-induced thrombocytopenia. It is in the treatment of this dangerous condition that the DTIs are primarily used with respect to VTE, although this may change in the future. Dabigatran is a new DTI with an oral preparation that appears not to have these drawbacks. It produces predictable anticoagulation, does not require monitoring, and is approved for treatment of nonvalvular atrial fibrillation, and may gain approval for treatment of VTE as an alternative to VKAs.

**Thrombolysis** Thrombolytics represent a potentially life-saving intervention, but have potential complications. Consequently, numerous trials have examined the safety and efficacy of thrombolitics for VTE and PE. Many trials found that thrombolysis improved hemodynamics, imaging studies, and hastened clot resolution but were unable to demonstrate improved mortality. Of concern, increased risk of severe bleeding was observed with thrombolysis. Given these results, investigators have sought to identify subgroups of patients with PE in whom the benefits of thrombolysis outweigh its risks.

Jerjes-Sanchez and colleagues planned to enroll 40 patients into a small prospective, randomized controlled trial comparing streptokinase with placebo in patients with massive PE and cardiogenic shock. The study was terminated early after enrolling only 8 patients, due to a clear benefit of thrombolysis: all 4 patients receiving streptokinase and heparin survived, whereas the 4 patients who received only heparin died within 1 to...
3 hours of arrival. It is now widely accepted that the use of thrombolytics in patients with cardiogenic shock and massive PE is critical, barring any absolute contraindications. In the vast majority of patients with PE the use of thrombolytics is more nuanced. As discussed, RV dysfunction in otherwise hemodynamically stable patients is a poor prognostic indicator for both morbidity and mortality. It would stand to reason, then, that this group of patients would benefit from thrombolysis. To date two large prospective trials, the Management Strategies and Prognosis of Pulmonary Embolism (MAPPET) and the Management Strategies and Prognosis of Pulmonary Embolism—3 (MAPPET-3), have investigated this issue and have reported potential benefits. Controversy remains, however, because of criticism regarding the design of these studies.

In MAPPET, patients with PE and RV dysfunction received either heparin with thrombolytics (alteplase, streptokinase, or urokinase) or heparin alone as a control group. The use of thrombolytics improved 30-day survival from 11.1% to 4.7%. Recurrent PE was also decreased from 18.7% to 7.7% in the thrombolytic group. The study design, however, was not randomized, and the thrombolytic group was significantly younger and suffered from less cardiovascular and pulmonary disease than controls. These imbalances in patient selection may have inflated the observed benefit of thrombolytics, as age and comorbidities are known risk factors for mortality.

A follow-up study by the same group to address these concerns was the randomized, prospective trial MAPPET-3. Patients with RV dysfunction and PE were randomized to either alteplase and heparin, or a control group receiving only heparin. In contrast to MAPPET whereby the end point was mortality, MAPPET-3 used a combined end point of survival and “escalation in therapy.” At its conclusion, MAPPET-3 demonstrated a significant benefit in this combined end point in favor of thrombolysis. On closer analysis, however, critics have pointed out that there was no survival difference between the two groups; the benefit of thrombolytics was almost entirely attributable to attenuation in “escalation of therapy.” Furthermore, the primary event leading to escalation of therapy in the control group was the later use of thrombolytics. The results of MAPPET-3 continue to generate controversy; several experts cite them as evidence for the benefit of thrombolytics in patients with PE and RV dysfunction, whereas others are skeptical of these conclusions and the significance of the reported benefits.

Pulmonary embolectomy
Pulmonary embolectomy is the surgical removal of an acute PE. It is generally reserved for specific circumstances due to its high reported mortality (up to 30% in some series), in large part a reflection of the severity of the PE and hemodynamic instability before surgery. In general, patients selected for embolectomy have had a large PE resulting in RV dysfunction and shock, and have failed or have contraindications to thrombolytics and anticoagulation.

RECURRENT VTE PROPHYLAXIS
Inferior Vena Cava Filters
Originally conceptualized by Trousseau in 1868, mechanical obstruction of the vena cava is now a safe, reliable procedure with the introduction of inferior vena cava (IVC) filters and minimally invasive placement. More recently, the advent of retrievable IVC filters has broadened the number of patients considered for this procedure. In general, the 2 most common indications for IVC filter placement are (1) contraindications to anticoagulation and (2) inability to adequately anticoagulate patients with VTE. Consideration for IVC filter placement is also given to patients in high-risk situations (despite adequate anticoagulation) such as trauma patients with lower extremity or
pelvis fractures, patients at high risk of death from PE, and patients with severe pulmonary hypertension and a known DVT. This being said, there is a remarkable lack of data regarding the use of IVC filters. There is only one published randomized trial of IVC filter use, demonstrating a decrease in PE incidence in the first 12 days after placement (1.1% vs 4.8%). Follow-up of patients at 2 years found, however, that IVC filters increased the incidence of DVT (20% vs 11.6%) with a small decreased incidence of PE (3.4% vs 6.2%).67 An 8-year follow-up of these same patients found a continuation of the 2-year trends, with an increased incidence of DVT (35.7% vs 27.5%) in patients with IVC filters, but a more dramatic decrease in PE (6.2% vs 15.1%).68 There were no differences in mortality or postphlebitic syndrome between the two cohorts. Most but not all of the patients in the study were on chronic anticoagulation. Given the high rates of VTE in patients with IVC filters left in place, it is recommended they receive indefinite anticoagulation.

In patients with a transient increased risk of VTE, retrievable IVC filters are an option. Retrievable filters theoretically should protect against PE in the short term while avoiding long-term DVT complications. There are, however, no randomized data demonstrating the outcomes or efficacy of retrievable filters. In general, the retrievable filters are placed to cover the days while a patient is off anticoagulation or is at increased risk of VTE, and should be removed as soon as possible to avoid endothelialization. Current recommendations for duration of deployment vary by filter type and center expertise, but are usually 2 to 6 weeks.69 Removal after prolonged use is possible, but comes at increasingly greater risk the longer the device has been in place.70

Management of Inherited Thrombophilia

The acute management of PE in patients with inherited thrombophilia is no different from that for other patients. Long-term treatment and prophylaxis is somewhat less clear, as there are no randomized controlled trials addressing the inherited thrombophilias. Guidelines suggest permanent anticoagulation in patients with spontaneous VTE and multiple prothrombotic mutations (either homozygous for a single mutation or heterozygous for several), any heritable risk factor and a single idiopathic near-fatal thrombosis such as massive PE or portal, mesenteric, or cerebral thrombosis, or a spontaneous thrombosis and an antithrombin deficiency or antiphospholipid antibody syndrome.16,71,72 Less consensus exists regarding the treatment length after the first spontaneous VTE and a single heritable mutation. It is recommended that expert consultation be sought to determine the length of anticoagulation.

Treatment of Cancer-Associated VTE

The incidence of VTE in cancer can be remarkably high, and is affected by several factors unique to cancer including tumor type, stage, and total tumor burden. Renal cell carcinoma, for instance, has a 43% incidence of VTE.73 VTE is also a poor prognostic indicator, with increased 6-month mortality in comparison with similar cancer patients without VTE. The Comparison of LMWH versus Oral anticoagulation Therapy for the prevention of VTE in patients with cancer (CLOT) study randomized patients to receive either 6 months of VKA (warfarin) or LMWH (dalteparin).74 Patients receiving LMWH had less recurrent VTE (9%) than those receiving VKA (17%). Based on these data, the current recommendation for VTE treatment in patients with cancer is to use LMWH as the first-line agent.

Chronic Thromboembolic Disease

In the majority of patients who suffer PE, resolution of the thrombus and restoration of normal pulmonary artery pressures is complete within 30 days of the event. Pengo and
colleagues reported in a prospective incidence study, however, that up to 4% of PE survivors may develop CTEPH. The natural history of CTEPH is unknown, as most patients present late in the clinical course, only after becoming symptomatic with pulmonary artery hypertension (PAH). The predisposing factors to CTEPH are unclear, although an increased incidence of anticardiolipin antibodies and elevated factor VIII levels have been reported. It is thought that CTEPH begins with an acute PE (even an asymptomatic PE) which, instead of undergoing thrombolysis, becomes covered in endothelial cells. Once endothelialization is complete, the thrombus is protected from circulating endogenous or exogenous thrombolytics, and over time obstructs and remolds the pulmonary vasculature, causing PAH.

Overall, untreated severe CTEPH carries a poor prognosis, with 5-year survival estimated at as low as 10%. Chronic anticoagulation is part of the treatment, but will not resolve the organized, endothelialized thrombi. Instead, clot must be physically removed via pulmonary endarterectomy (PEA), a process by which the endothelialized thrombi are carefully dissected from the pulmonary artery wall. PEA is the treatment of choice for CTEPH, but comes with significant morbidity and 5% to 10% postoperative mortality. Given the complexity and magnitude of PEA, it is recommended to be performed only at experienced centers.

Many patients, in some cases up to half, may be ineligible for PEA because of comorbidities or distal clot position. Furthermore, some patients may have persistent or exercise-limiting PAH even after PEA. In such cases, medical therapy is an alternative. Medical therapy can be divided into two categories: general therapies and those specific to PAH. General therapies include correcting hypoxemia with supplementary oxygen, diuresis, indefinite anticoagulation, and digoxin to augment RV contractility. PAH-specific therapies include 3 categories of medications designed for the treatment of idiopathic pulmonary arterial hypertension, and include the phosphodiesterase-5 inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (ambrisentan, bosentan), and the prostacyclin analogues (epoprostenol, treprostinil, and iloprost). The evidence, however, supporting the use of these medications in CTEPH is generally limited to retrospective studies, case series, and prospective cohort series. When subjected to randomized controlled trials, medical therapies such as iloprost, bosentan, and sildenafil have not shown significant clinical benefit.

SUMMARY

VTE is a rapidly evolving field, with advances in biomarkers, imaging, clinical algorithms, devices, and medications improving our ability to diagnose and treat PE. For instance, the development of LMWH, CTA, D-dimer, and clinical scoring tools have all substantially improved diagnostic accuracy and have decreased morbidity and mortality associated with PE. Questions in the diagnosis and management of PE persist, however, such as the significance of heritable thrombophilias or the optimal use of thrombolytics in hemodynamically stable patients with RV dysfunction. In some cases such as CTEPH, medical therapy is inadequate. Ongoing study and advancement in clinical care will attempt to address these deficiencies while continuing to improve clinical care overall.

REFERENCES


