REVIEW ARTICLE

MEDICAL PROGRESS

Acute Pulmonary Embolism

Victor F. Tapson, M.D.

From the Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, NC. Address reprint requests to Dr. Tapson at the Division of Pulmonary and Critical Care Medicine, Rm 351, Bell Bldg, Box 31175, Duke University Medical Center, Durham, NC, 27710, or at tapso001@mc.duke.edu.

N Engl J Med 2008;358:1037-52.

Pulmonary embolism, most commonly originating from deep venous thrombosis of the legs, ranges from asymptomatic, incidentally discovered emboli to massive embolism causing immediate death. Chronic sequelae of venous thromboembolism (deep venous thrombosis and pulmonary embolism) include the post-thrombotic syndrome[1] and chronic thromboembolic pulmonary hypertension.[2] Acute pulmonary embolism may occur rapidly and unpredictably and may be difficult to diagnose. Treatment can reduce the risk of death, and appropriate primary prophylaxis is usually effective. Patients treated for acute pulmonary embolism appear to be almost four times as likely to die of recurrent thromboembolism in the next year as patients treated for deep venous thrombosis (rate of death, 1.5% vs. 0.4%).[3] The primary focus of this review is acute pulmonary embolism of thrombotic origin.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Pulmonary embolism and deep venous thrombosis represent the spectrum of one disease. Thrombi commonly form in deep veins in the calf and then propagate into the proximal veins, including and above the popliteal veins, from which they are more likely to embolize. About 79% of patients who present with pulmonary embolism have evidence of deep venous thrombosis in their legs; if deep venous thrombosis is not detected in such patients, it is likely that the whole thrombus has already detached and embolized.[4] Deep venous thrombosis with resultant pulmonary embolism is shown in Figure 1. Conversely, pulmonary embolism occurs in up to 50% of patients with proximal deep venous thrombosis. Because of the dual pulmonary circulation arising from the pulmonary and bronchial arteries, pulmonary infarction is not usually present. In acute pulmonary embolism, anatomical obstruction is undoubtedly the most important cause of compromised physiology, but the release of vasoactive and bronchoactive agents such as serotonin from platelets may lead to deleterious ventilation–perfusion matching.[5] As right ventricular afterload increases, tension in the right ventricular wall rises and may lead to dilatation, dysfunction, and ischemia of the right ventricle. Death results from right ventricular failure.

Although less common in certain regions, such as Asia, venous thromboembolism is a worldwide problem, particularly in people with known risk factors.[6] A study using an inception cohort of patients in Olmsted County, Minnesota, estimated that the average annual incidence in the United States was 1 episode per 1000 registered patients.[7] Annually, as many as 300,000 people in the United States die from acute pulmonary embolism,[7,8] and the diagnosis is often not made until autopsy.[4,9] Hospitalized patients are at particularly high risk, although thromboembolism often is not manifested until after discharge.[9]

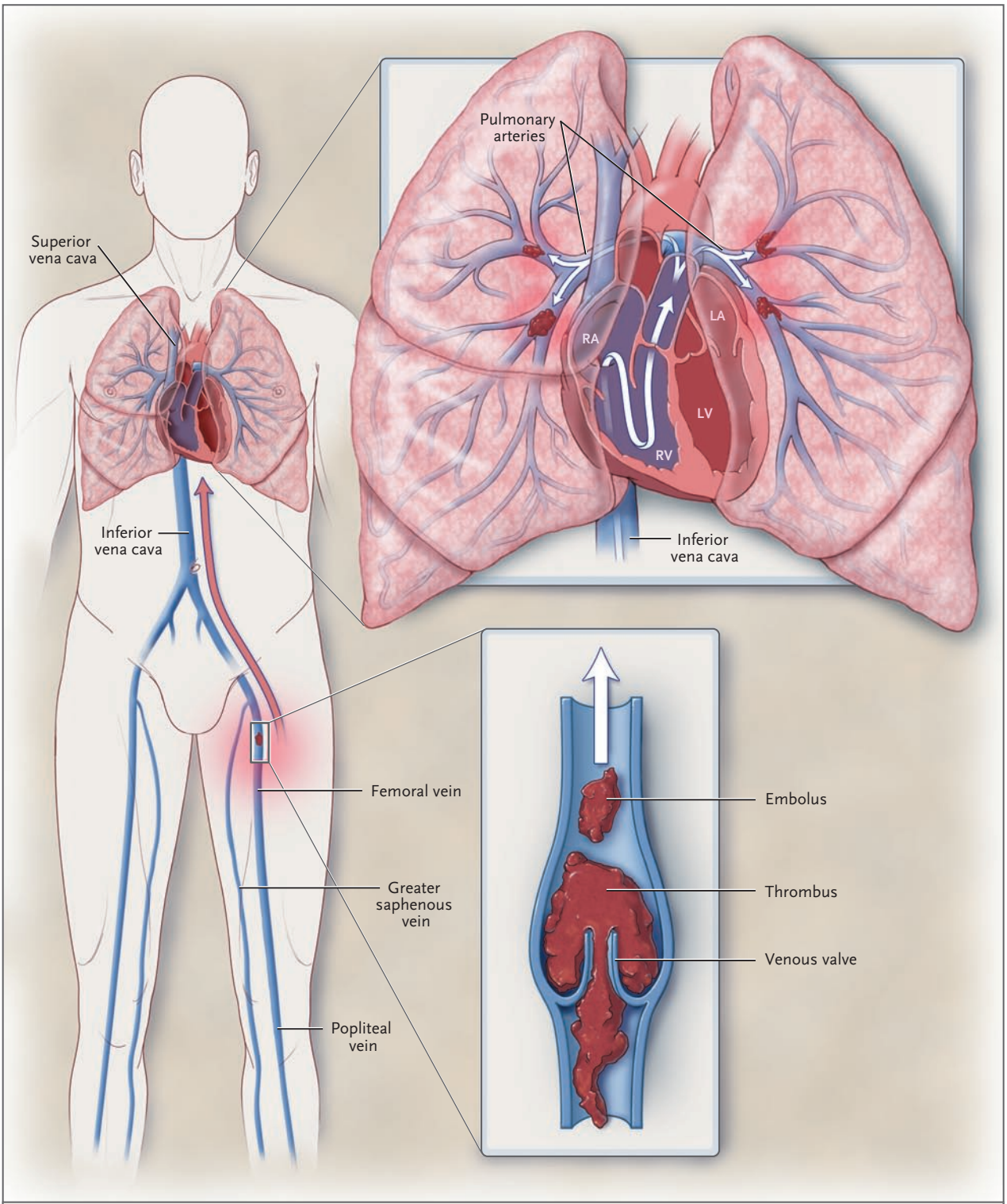

Figure 1. Pathophysiology of Pulmonary Embolism.

Pulmonary embolism usually originates from the deep veins of the legs, most commonly the calf veins. These venous thrombi originate predominantly in venous valve pockets and at other sites of presumed venous stasis (inset, bottom). If a clot propagates to the knee vein or above, or if it originates above the knee, the risk of embolism increases. Thromboemboli travel through the right side of the heart to reach the lungs. LA denotes left atrium, LV left ventricle, RA right atrium, and RV right ventricle.

RISK FACTORS

ACQUIRED RISK FACTORS

Certain risk factors increase the likelihood of acute deep venous thrombosis and thus pulmonary embolism.[8] Total hip and knee replacement, surgery for hip fracture, and surgery for cancer impart particularly high risks, as do trauma and spinal cord injury; overall, acute medical illness may be the most common setting in which thromboembolism occurs.[10] Markedly reduced mobility also confers an increased risk, though the degree and duration of reduced mobility that trigger the increase in risk remain unclear, often depending on concomitant risk factors. Prolonged air or ground travel increases the risk of thromboembolism. A sedentary lifestyle and occupations involving long periods of sitting merit awareness; in fact, the term eThrombosis has been coined to describe thrombotic events related to extended periods of sitting at a computer terminal.[11] Advancing age is another clear risk factor, with the risk increasing after the age of 40 years.

In patients with conditions such as cancer and the thrombophilias, acquired risk and genetic predisposition may overlap. In cancer, the procoagulant effects of the particular tumor or its treatment may increase the risk of thromboembolic events, as can venous obstruction by the tumor, reduced mobility, the presence of central venous catheters, and chemotherapy.[12] Antiphospholipid antibodies are associated with thrombosis and recurrent, unexplained fetal loss.[13] Hereditary and acquired risk factors for venous thromboembolism are listed in Table 1.

Table 1. Risk Factors for Venous Thromboembolism.*

Hereditary factors
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden
Activated protein C resistance without factor V Leiden
Prothrombin gene mutation
Dysfibrinogenemia
Plasminogen deficiency
Acquired factors
Reduced mobility
Advanced age
Cancer
Acute medical illness
Major surgery
Trauma
Spinal cord injury
Pregnancy and postpartum period
Polycythemia vera
Antiphospholipid antibody syndrome
Oral contraceptives
Hormone-replacement therapy
Heparins
Chemotherapy
Obesity
Central venous catheterization
Immobilizer or cast
Probable factors
Elevated levels of lipoprotein(a)†
Low levels of tissue factor–pathway inhibitor
Elevated levels of homocysteine; factors VIII, IX, and XI; fibrinogen; and thrombin-activated fibrinolysis inhibitor

* It remains unclear whether some of the disorders listed are hereditary, acquired, or both.
† At present, the associated risk of venous thromboembolism is not clear.

GENETIC DISORDERS AND THROMBOEMBOLIC RISK

Deficiencies in protein C, protein S, and antithrombin substantially increase the risk of thrombosis and thromboembolic events. Factor V Leiden, which causes activated protein C resistance, is the most common genetic risk factor for thrombophilia.[14] The question of whether to test for these disorders most often arises in patients with recurrent thromboembolism, in young patients, in patients with apparently unprovoked thrombotic or thromboembolic episodes, and in those with thrombosis in an unusual location (e.g., in cerebral, mesenteric, portal, or hepatic veins). In summary, Virchow's classic triad of risk[15] — stasis, venous injury, and hypercoagulability — is still relevant in assessing patients, reflecting the influence of genetic and environmental risk factors and their interactions.[16] Knowing the risk factors for a given patient should help the physician choose appropriate diagnostic and prophylactic strategies.

DIAGNOSTIC APPROACHES

CLINICAL MANIFESTATIONS

Being cognizant of the symptoms and signs of venous thromboembolism may reduce diagnostic delays.[17] Leg pain, warmth, or swelling may serve

as a clue that a patient has deep venous thrombosis. Patients with acute pulmonary embolism often have dyspnea or chest pain, either sudden in onset or evolving over a period of days to weeks. Pleuritic chest pain and hemoptysis occur more frequently in patients with pulmonary infarction, which is characterized by smaller, more peripheral emboli, and in such patients, a pleural rub may be evident. Symptoms of cough, palpitations, and light-headedness and signs including fever, wheezing, and rales may result from pulmonary embolism or from concomitant illnesses. Tachypnea and tachycardia are common but nonspecific findings. Signs of pulmonary hypertension caused by pulmonary embolism may include elevated neck veins, a loud P_2, a right-sided gallop, and a right ventricular lift. Signs and symptoms of both deep venous thrombosis and pulmonary embolism may be highly suggestive but are neither sensitive nor specific. Thus, when either condition is suspected, further testing must be considered. Often the extent of symptoms depends on the thromboembolic burden. However, even very large thrombi in the periphery may evolve silently and then present as symptomatic or even fatal pulmonary embolism, whereas smaller emboli may be associated with major symptoms, particularly if cardiovascular reserve is already poor. The possibility of massive pulmonary embolism should be considered in patients who have a sudden onset of near syncope or syncope, hypotension, extreme hypoxemia, electromechanical dissociation, or cardiac arrest.

PRELIMINARY LABORATORY TESTING AND PRETEST PROBABILITY

If pulmonary embolism is suspected, a careful assessment based on the history, physical examination, and known risk factors is necessary; additional studies, including electrocardiography, chest radiography, and arterial blood gas analysis, should also be considered. Electrocardiographic abnormalities, including unexplained tachycardia, are common in acute pulmonary embolism but nonspecific. Electrocardiographic manifestations of acute cor pulmonale, such as an S1, Q3, T3 pattern, right bundle-branch block, P-wave pulmonale, or right axis deviation, are more common with massive embolism than with smaller emboli, but these findings are also nonspecific.[18] The chest radiograph is generally nondiagnostic, though it may uncover an alternative diagnosis. Patients with acute pulmonary embolism usually have hypoxemia, but the arterial oxygen tension may be normal. On rare occasions, the alveolar–arterial oxygen difference is also normal.[18] A sudden or unexplained change in arterial oxygen saturation should raise suspicion.

Additional studies may also be useful. Although a positive D-dimer test (which measures plasma levels of a specific derivative of cross-linked fibrin) indicates that venous thrombosis and pulmonary embolism are possible diagnoses, this test is nonspecific, since it may be positive in patients with infection, cancer, trauma, and other inflammatory states and thus cannot inform decisions about treatment.[19,20] The enzyme-linked immunosorbent assay (ELISA)–based D-dimer tests have superior sensitivity (96 to 98%). D-dimer testing is best considered together with clinical probability, and the latter can be estimated on the basis of one of two clinical-prediction scores that assess the likelihood that a patient has acute pulmonary embolism (Table 2).[21-24] These methods, which predominate in the evidence-based literature on clinical-probability assessment, are based on information from the history and physical examination. The scores have been best used in patients presenting to the emergency room. When an ELISA-based D-dimer test is negative in patients with a low or moderate pretest probability, the likelihood of deep venous thrombosis and pulmonary embolism is low and precludes the need for specific imaging studies.[20,25] In patients with a high pretest probability, however, imaging should be performed instead of D-dimer testing.[26,27] The tool used for clinical-probability assessment may be less important than the principle that each patient must undergo a careful assessment based on the individual clinical probability of actually having pulmonary embolism.

Other biomarkers may offer useful clinical information. Cardiac troponin levels may be elevated, particularly in patients with massive acute pulmonary embolism.[28] An elevated troponin level is most commonly used in risk stratification in patients with established pulmonary embolism, but it is not sensitive as a diagnostic tool when used alone.[28] Plasma levels of brain natriuretic peptide increase with ventricular stretching but may be elevated in patients with congestive heart failure or various other conditions that cause pulmonary hypertension.[29]

IMAGING STUDIES

Many types of imaging studies have been used in diagnosing acute pulmonary embolism, including ventilation–perfusion scanning, contrast-enhanced computed tomographic (CT) arteriography, magnetic resonance imaging (MRI), standard pulmonary arteriography, and imaging for detecting deep venous thrombosis as a surrogate for acute pulmonary embolism (ultrasonography, CT venography, MRI, and standard venography).

Contrast-enhanced CT arteriography has advantages over ventilation–perfusion scanning, including speed, characterization of nonvascular structures, and detection of venous thrombosis. If a patient has either acute or chronic renal insufficiency, caution in using contrast agents is imperative, given the possibility of inducing nephropathy associated with contrast material. CT arteriography has the greatest sensitivity and specificity for detecting emboli in the main, lobar, or segmental pulmonary arteries. The use of multidetector CT arteriography has led to decreased section thickness, reduced scanning times, and markedly improved visualization of segmental and subsegmental vessels.[30] Systematic reviews and prospective randomized trials suggest that outpatients with suspected pulmonary embolism and negative CT arteriographic studies have excellent outcomes without therapy, although additional imaging studies that included leg ultrasonography were usually part of the evaluation that led to the management decision.[31]

In a recent large, prospective trial conducted with outpatients with suspected acute pulmonary embolism, the investigators reported an excellent outcome when anticoagulation therapy was not initiated after a negative finding on multidetector CT arteriography (which was the sole imaging study).[22] Nonetheless, it is prudent to consider additional imaging in cases of high clinical suspicion, even if CT arteriography is negative. When either single-detector or multidetector CT arteriography suggests acute pulmonary embolism, treatment is nearly always mandated; false positive CT arteriographic studies appear to be unusual. A CT arteriographic study in a patient with acute pulmonary embolism is shown in Figure 2.

The combination of CT arteriography and CT venography has been assessed in some trials.[32,33] Most recently, the Prospective Investigation of Pulmonary Embolism Diagnosis II trial compared the use of multidetector CT arteriography alone with its use in combination with CT venography for detecting suspected acute pulmonary embolism.[33] The sensitivity of spiral CT arteriography alone was 83%, whereas the combination of CT arteriography and CT venography increased the sensitivity to 90%, suggesting that a combined approach might facilitate clinical management, particularly for the treatment of inpatients with complex cases.

Ventilation–perfusion scanning is most likely to be diagnostic in the absence of cardiopulmonary disease.[34] A normal perfusion lung scan effectively rules out acute pulmonary embolism. A scan suggesting a high probability of acute pulmonary embolism should be considered diagnostic, unless clinical suspicion is low or there is a history of pulmonary embolism with an identical previous scan.[34,35] However, if the clinical story strongly suggests pulmonary embolism despite a nondiagnostic ventilation–perfusion scan, the diagnosis should be rigorously pursued.[34,36] If the ventilation–perfusion scan is nondiagnostic in a patient with a low clinical probability of acute pulmonary embolism or in a patient with a moderate clinical probability but negative results on D-dimer testing, no additional testing or therapy is indicated.[34-36] In a recent study of 221 consecutive patients with suspected acute pulmonary embolism, multitechnique thoracic MRI of the lung followed by magnetic resonance venography was used successfully to search for both deep venous thrombosis and pulmonary embolism.[37]

Echocardiography may reveal findings that strongly support hemodynamically significant pulmonary embolism,[38] offering the potential to guide treatment. Emboli moving through the heart to the lungs are occasionally confirmed with this technique; in addition, intravascular ultrasonography has been used at the bedside to visualize large emboli.[39] A diagnostic algorithm for suspected pulmonary embolism is shown in Figure 3.

TREATMENT

ANTICOAGULATION

Bed rest is not recommended for deep venous thrombosis unless there is substantial pain and swelling. However, the data for pulmonary em-

Table 2. Clinical Prediction Scores for Suspected Acute Pulmonary Embolism.*

Canadian (Wells) prediction score

Variable and score

- DVT symptoms and signs — 3.0
- PE as likely as or more likely than alternative diagnosis — 3.0†
- Heart rate >100 beats/min — 1.5
- Immobilization or surgery in previous 4 wk — 1.5
- Previous DVT or PE — 1.5
- Hemoptysis — 1.0
- Cancer — 1.0

Total score‡

- <2.0 — low pretest probability
- 2.0 to 6.0 — moderate pretest probability
- >6.0 — high pretest probability

Dichotomized Wells score§

- ≤4 — PE unlikely
- >4 — PE likely

Original Geneva (Wicki) score¶

Variable and score

- Age
  - 60–79 yr — 1
  - ≥80 yr — 2
- Previous DVT or PE — 2
- Recent surgery — 3
- Heart rate >100 beats/min — 1
- $PaCO_2$
  - <36.2 mm Hg (<4.8 kPa) — 2
  - 36.2–38.9 mm Hg (4.8–5.19 kPa) — 1
- PaO_2
  - <48.8 mm Hg (<6.5 kPa) — 4
  - 48.8–59.9 mm Hg (6.5–7.99 kPa) — 3
  - 60–71.2 mm Hg (8.0–9.49 kPa) — 2
  - 71.3–82.4 mm Hg (9.5–10.99) — 1
- Chest radiograph
  - Platelike atelectasis — 1
  - Elevation of hemidiaphragm — 1

Revised Geneva score‖

Variable and score

- Age >65 yr — 1
- Previous DVT or PE — 3
- Surgery or lower limb fracture in previous wk — 2
- Active cancer — 2
- Unilateral lower limb pain — 3
- Hemoptysis — 2

Table 2. (Continued.)

Heart rate
75–94 beats/min — 3
≥95 beats/min — 5
Pain on leg palpation or unilateral edema — 4

* DVT denotes deep venous thrombosis, $PaCO_2$ partial pressure of carbon dioxide in arterial blood, PE pulmonary embolism, and PaO_2 partial pressure of oxygen in arterial blood.
† Physicians used clinical information, chest radiography, electrocardiography, and laboratory results.
‡ In the study by Wells et al., the pretest probability of PE was low, moderate, and high in 527, 339, and 64 patients (1.3%, 16.2%, and 37.5% had PE), respectively. Of the 437 patients with a negative D-dimer result and a low clinical probability, only 1 had PE during follow-up; thus, the negative predictive value for the use of the clinical model combined with D-dimer testing in these patients was 99.5%.[21]
§ In the Christopher study, PE was classified as unlikely in 2206 patients (66.7%). Here, the score was dichotomized. A total of 1057 patients (32.0%) had both a score indicating that PE was unlikely and a normal D-dimer test result, and 1028 of these patients were not treated with anticoagulants; subsequent nonfatal venous thromboembolism occurred in 5 patients (0.5% [95% confidence interval, 0.2–1.1]).[22]
¶ Results were based on 986 patients.[23] A probability score ranging from 0 to 16 was calculated by adding points assigned to the variables. A cutoff score of 4 best identified patients with a low probability of PE. A total of 486 patients (49%) had a low clinical probability of PE (score, ≤4), of whom 50 (10%) had proven PE. The prevalence of PE was 38% in the 437 patients with an intermediate probability (score, 5 to 8) and 81% in the 63 patients with a high probability (score, ≥9).
‖ The score consisted of 8 entirely clinically based variables with points assigned. In the validation set, the prevalence of PE was 8% in the low-probability category (0 to 3 points), 28% in the intermediate-probability category (4 to 10 points), and 74% in the high-probability category (≥11 points). This prediction score has been internally and externally validated and awaits testing for clinical usefulness in an outcome study.[24]

bolism are not sufficient to support this recommendation.[40,41] Thus, when pulmonary embolism is diagnosed, inpatient therapy with initial bed rest for 24 to 48 hours is often recommended. Similarly, although the use of low-molecular-weight heparin as outpatient therapy is well established for deep venous thrombosis, improving the quality of life and reducing the health care costs,[42,43] the data on outpatient therapy for acute pulmonary embolism are less robust.

When acute pulmonary embolism is present, parenteral anticoagulation with low-molecular-weight heparin, the pentasaccharide fondaparinux, or standard, unfractionated heparin should be initiated unless contraindicated. Although they are not thrombolytic, these drugs allow the fibrinolytic system to function unopposed, ultimately decreasing the thromboembolic burden. Anticoagulation clearly improves survival among patients with symptomatic pulmonary embolism, but the risk of recurrent, nonfatal venous thromboembolism is estimated at 5% to 10% during the first year after diagnosis.[40] If the suspicion of pulmonary embolism is high, parenteral anticoagulation should be considered even before imaging, as long as the risk of bleeding does not appear to be excessive.[40] Warfarin can be initiated on the first day of therapy. Subcutaneous low-molecular-weight heparin, fondaparinux, or weight-based intravenous unfractionated heparin should be administered for at least 5 days, preferably until the international normalized ratio is in the therapeutic range (2.0 to 3.0) for 2 consecutive days. With standard heparin administration, the activated partial-thromboplastin time should be measured at 6-hour intervals until it is consistently in the therapeutic range (1.5 to 2.5 times control). Achieving a therapeutic activated partial-thromboplastin time within 24 hours appears to reduce the risk of recurrence.[44] Although no evidence-based recommendations can be made for the treatment of isolated subsegmental pulmonary emboli that have been documented by CT arteriography, they are generally treated, because it may be difficult to definitively exclude the possibility of a clot remaining in the leg and because there may also be an ongoing risk of such a clot.[45]

A number of low-molecular-weight heparin preparations have been studied and approved worldwide. The low-molecular-weight heparin and pentasaccharide preparations have advantages over unfractionated heparin, including greater bioavailability, more predictable dosing, subcutaneous delivery (usually without the need for monitoring), and a lower risk of heparin-induced

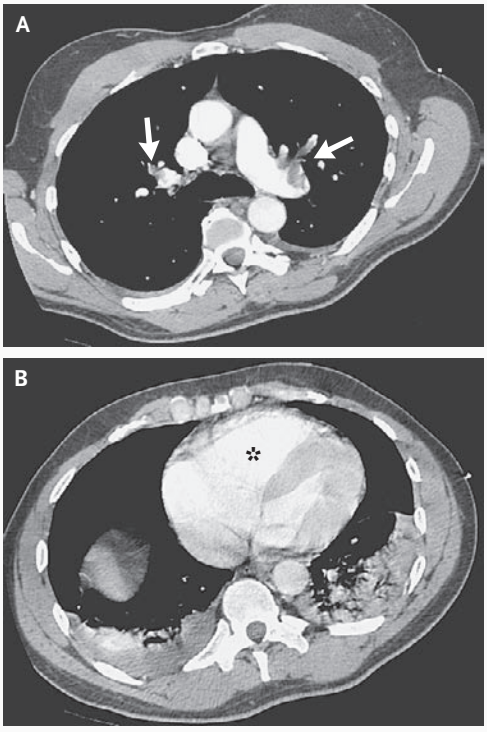

Figure 2. Contrast-Enhanced CT Angiograms Showing Acute Pulmonary Embolism.

Panel A shows bilateral pulmonary embolism (arrows). Panel B shows an enlarged right ventricle (asterisk), caused by acute pulmonary embolism. Angiograms provided by Lynne M. Hurwitz Koweek, M.D., Duke University Medical Center.

thrombocytopenia.[46] Monitoring low-molecular-weight heparin by measuring the level of activity against activated factor X (anti–factor Xa) may be considered in patients who are morbidly obese (weighing >150 kg) or very small (<40 kg), in patients who are pregnant, and in patients with either very severe renal insufficiency or rapidly changing renal function.[47] Fondaparinux should not be used in patients with severe renal insufficiency (creatinine clearance <30 ml per min), given renal excretion and a prolonged half-life with renal insufficiency.[40]

Randomized trials support the use of low-molecular-weight heparin or fondaparinux for symptomatic pulmonary embolism[40,48-51] and for deep venous thrombosis with or without pulmonary embolism.[40,52,53] Low-molecular-weight heparin may be superior to unfractionated heparin for the treatment of deep venous thrombosis, and it is at least as effective as unfractionated heparin in reducing the risk of death and the risk of major bleeding during initial therapy for pulmonary embolism.[40,54] In patients with acute nonmassive pulmonary embolism, the American College of Chest Physicians recommends the use of low-molecular-weight heparin rather than standard heparin on the basis of grade 1A evidence (data are from randomized clinical trials without important limitations).[40]

A potential disadvantage of low-molecular-weight heparin is the acquisition cost for hospital pharmacies in the United States; however, analyses have suggested that even in the inpatient setting, this agent is less costly than unfractionated heparin.[43] Although preparations of low-molecular-weight heparin have common characteristics, different compounds in this class are distinct, so clinical-trial results and specific indications for one drug may not apply to others.[55]

Patients with acute venous thromboembolism require long-term anticoagulation to prevent symptomatic extension and recurrence of thrombosis. Documented thromboembolism in patients with transient risk factors should be treated for 3 to 6 months, but more extended treatment is appropriate when significant risk factors persist, when thromboembolism is idiopathic, or when previous episodes of venous thromboembolism have been documented.[40,56] Recent data suggest that D-dimer levels may help guide decisions about the duration of therapy; persistently elevated levels appear to be associated with an increased recurrence rate.[57] Long-term treatment of thrombosis with the low-molecular-weight heparin dalteparin, as compared with warfarin, in patients with cancer has been shown to be associated with fewer thromboembolic recurrences.[58]

Treatment with a direct thrombin inhibitor (e.g., argatroban or lepirudin) should be considered for heparin-induced thrombocytopenia with thrombosis. Treatment with warfarin should not be initiated until the disease process has been controlled and the platelet count has returned to the normal range because of the potential for worsening thrombotic complications, including venous limb gangrene and warfarin-induced skin necrosis. Lepirudin is excreted by the kidneys, and argatroban is metabolized in the liver —

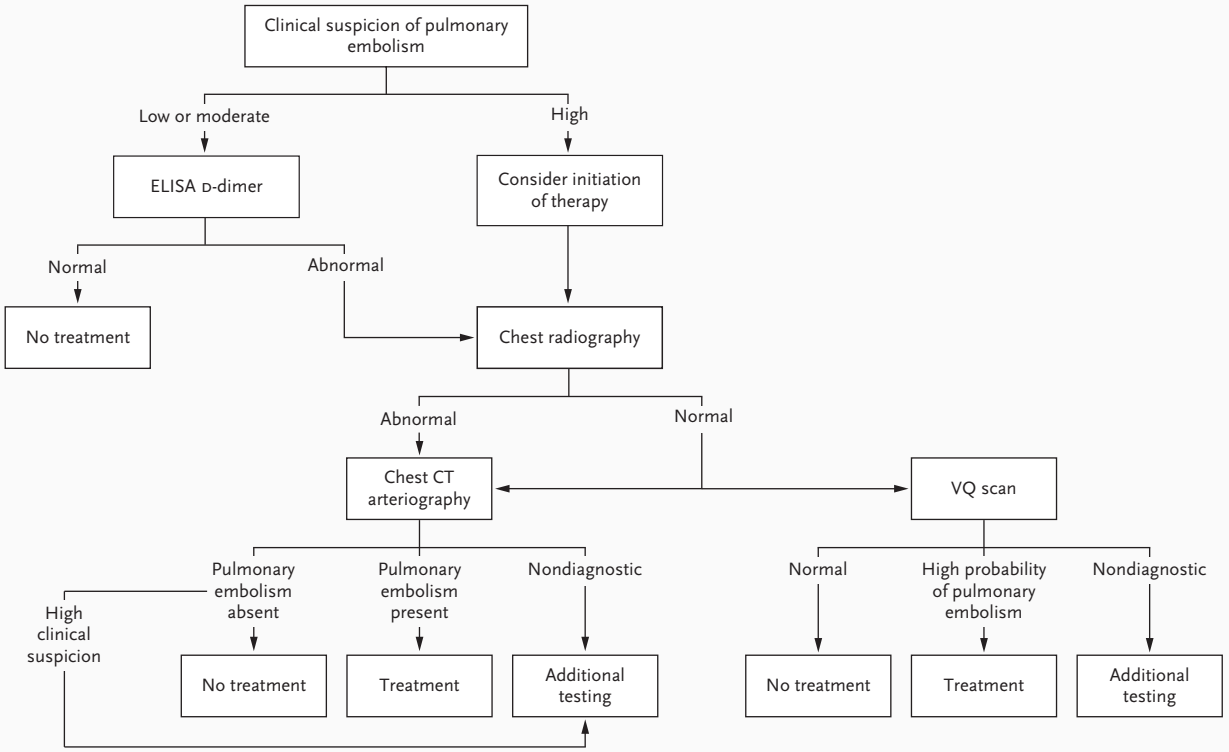

Figure 3. Diagnostic Approach to Suspected Acute Pulmonary Embolism.

The use of prediction rules and D-dimer testing may reduce the need for imaging. If the risk of bleeding is deemed to be low, initiation of therapy before a proven diagnosis of pulmonary embolism should be considered.[40] At this juncture, the chest radiograph and other specific imaging may already be completed. A ventilation–perfusion (VQ) scan is more likely to yield a diagnosis when there is no associated cardiopulmonary disease. A scan indicating a high probability of pulmonary embolism is confirmatory except when there has been a prior pulmonary embolism, in which case a previous VQ scan may be useful in proving that defects are new.[34,36] As with computed tomographic arteriography (CTA), the approach to a nondiagnostic scan includes evaluation of clinical probability as well as consideration of additional testing. Deep venous thrombosis discovered by leg ultrasonography, CT venography, or magnetic resonance venography suggests concomitant pulmonary embolism.[36,37] Standard pulmonary arteriography or venography is rarely needed. Adding CT venography to CT arteriography enhances the overall sensitivity for detecting venous thromboembolism,[33] although an excellent outcome has been demonstrated without additional testing when CTA is negative.[22] With the use of CTA or CT venography, caution is advised when the creatinine level rises above 1.5 mg per deciliter; the patient's age relative to the creatinine clearance should be considered.[36] ELISA denotes enzyme-linked immunosorbent assay.

important considerations when renal or hepatic disease is present. Oral direct thrombin inhibitors, such as dabigatran, and oral anti–factor Xa inhibitors, such as rivaroxaban and apixaban, are in phase 3 trials, as is biotinylated idraparinux, a reversible parenteral anti–factor Xa inhibitor requiring dosing only once a week.[59] Aptamers, derived from nucleic acid templates, act as reversible antagonists of coagulation factors, have the potential to be developed together with a specific antidote, and appear to be promising anticoagulants, but none are approved for commercial use.[60]

PLACEMENT OF A VENA CAVAL FILTER

The primary indications for placement of an inferior vena caval filter include contraindications to anticoagulation, major bleeding complications during anticoagulation, and recurrent embolism while the patient is receiving adequate therapy.[40] Filters are sometimes placed in the case of massive pulmonary embolism, when it is believed that additional emboli might be lethal, particularly if thrombolytic therapy is contraindicated. However, this latter indication is not based on firm trial data. Although filters are effective in reducing the incidence of pulmonary embolism, they increase

the subsequent incidence of deep venous thrombosis and have not been shown to increase overall survival.[61] Optional (retrievable) filters may be left in place permanently or retrieved if patients no longer require vena caval interruption. Certain models can be retrieved several months after placement, and removal approximately 1 year after placement has been reported,[62,63] although there is little published information about very late retrieval. Recommendations for the use of vena caval filters have recently been published.[63]

TREATMENT OF MASSIVE PULMONARY EMBOLISM

Pulmonary embolism causing hemodynamic instability is termed massive; once it is suspected, a diagnostic plan and supportive measures are essential. The physiological effect of massive pulmonary embolism[64,65] is such that resulting right ventricular failure may lead to compromised left ventricular preload, which may be life-threatening. If saline is infused for hypotension, it should be done with caution. Vasopressor therapy (e.g., dopamine) should be considered if the blood pressure is not rapidly restored; there is little information about the use of inotropic agents in general.[66] Oxygen supplementation, intubation, and mechanical ventilation are instituted as necessary for respiratory failure.

COMPLICATIONS OF THROMBOLYTIC THERAPY

The most widely accepted indication for thrombolytic therapy is proven pulmonary embolism with cardiogenic shock; therapy is also frequently considered when a patient presents with systemic hypotension without shock.[67-69] The use of thrombolysis in submassive embolism — that is, pulmonary embolism causing right ventricular dilatation and hypokinesis without systemic hypotension — is debated.[40,67-69] Clinical trials have not been sufficiently large to provide definitive data on the survival benefit in such cases. When t-PA is administered with heparin, as compared with the use of heparin alone, escalation of therapy is less likely to be needed.[69] Streptokinase, urokinase, and recombinant tissue plasminogen activator (t-PA) have been studied extensively; the more rapidly infused t-PA has been the most widely used thrombolytic agent.

An elevated serum troponin level may identify a subgroup of normotensive patients who may benefit from more aggressive treatment.[27] Thrombolytic therapy may also be considered in patients with severely compromised oxygenation or a massive embolic burden identified by imaging studies — even without hemodynamic instability — or in patients with extensive venous thrombosis that accompanies nonmassive embolism. However, the evidence base supporting these indications is inadequate, and individualized care is necessary.

The most devastating complication of thrombolytic therapy is intracranial hemorrhage, although it has been reported in less than 1% of patients in clinical trials and in about 3% of patients in a large registry.[70] Other complications include retroperitoneal and gastrointestinal hemorrhage and bleeding from surgical wounds or sites of recent invasive procedures. Contraindications to consider include intracranial, spinal, or ocular surgery or disease, recent major surgery or other invasive procedures, active or recent major bleeding, pregnancy, and clinically obvious risks of bleeding. Intracranial bleeding is the clearest, strongest contraindication. Clinical judgment that weighs risks and benefits is imperative. Catheter-based mechanical pulmonary embolectomy, local intraembolic thrombolytic therapy, or both can be considered.[71] Pulmonary embolectomy may be successful in patients with proven massive pulmonary embolism and hemodynamic instability or in those in whom thrombolytic therapy has failed or is contraindicated.[40,72,73] However, the condition of these patients is very compromised, and the risk of death may be high with this approach.[73] Surgery is sometimes considered when there are right heart thrombi, with or without paradoxical embolism, but no data from randomized trials are available to support this approach; thrombolysis is commonly considered in such cases. A general treatment algorithm is shown in Figure 4.

PROGNOSIS

Most patients with acute pulmonary embolism who receive adequate anticoagulant therapy survive. The 3-month overall mortality rate has been reported to be about 15 to 18%.[70] Shock at pre-

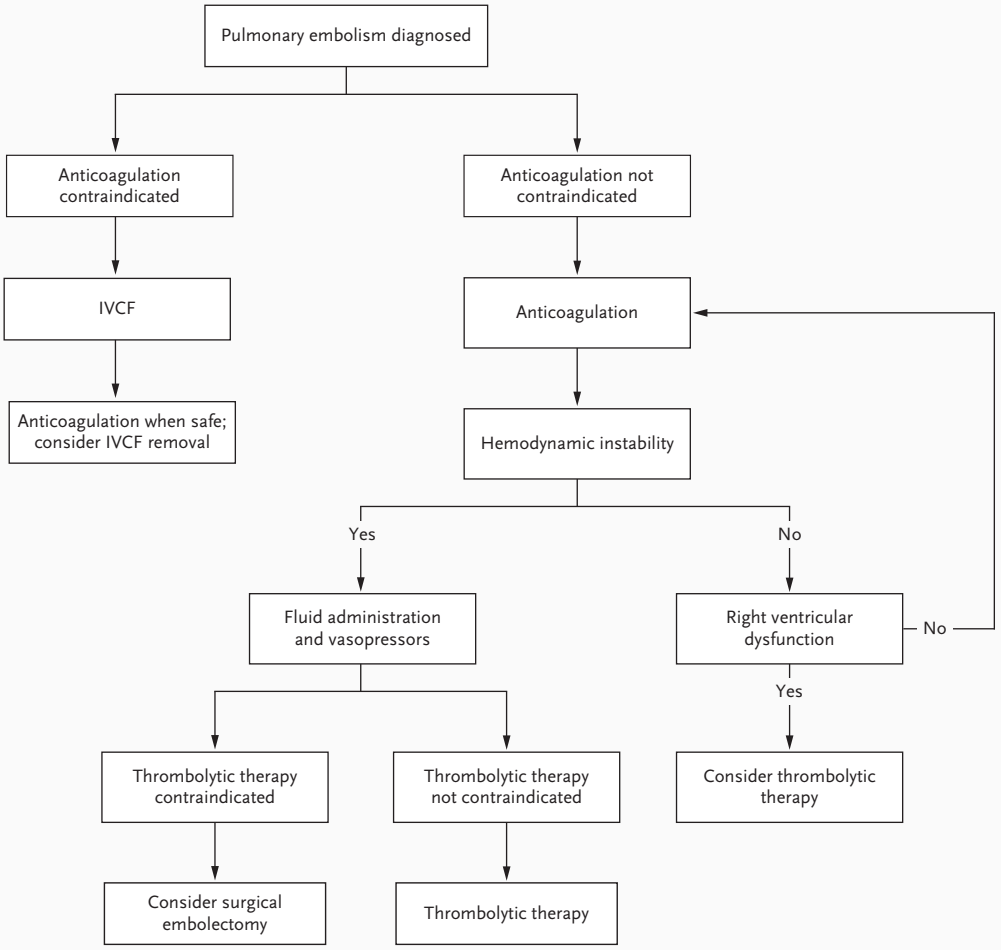

Figure 4. Treatment of Acute Pulmonary Embolism.

Low-molecular-weight heparin is preferable to unfractionated heparin in most settings.[40] Use of an optional (retrievable) inferior vena caval filter (IVCF) offers the potential for removal when risk factors are deemed transient.[63] Although filter placement may be considered in patients with massive embolism in order to prevent additional emboli, this indication has not been studied in prospective, randomized clinical trials. Anticoagulation should be initiated when the risk of bleeding subsides. Although the clearest indication for thrombolytic therapy is hemodynamic instability with cardiogenic shock caused by acute pulmonary embolism, hypotension, particularly if refractory to initial supportive measures (e.g., cautious fluid administration), also merits consideration of this approach. Some clinicians consider right ventricular dysfunction to be an indication for thrombolysis,[68,69] but no study has been large enough to prove that thrombolytic therapy reduces mortality in this setting or in the setting of severe hypoxemia and respiratory failure. Each case must be considered individually. Thrombolytic agents with shorter infusion times, such as tissue plasminogen activator (t-PA) (100 mg given intravenously over a period of 2 hours) have been recommended.[40,68,69] Local thrombolytic therapy, catheter embolectomy, or both can be considered in centers with experience with these techniques.[40] Potential contraindications for thrombolytic therapy include previous intracranial or ophthalmic surgery or disease, clinically significant active or recent bleeding or risk of bleeding, and recent surgery (within 1 to 2 weeks, depending on the procedure). Consideration of the severity of the pulmonary embolism and the perceived risk of bleeding should contribute to the decision to use thrombolytic therapy. Intracranial abnormalities are generally considered to be absolute contraindications.

sentation is associated with an increase in mortality by a factor of three to seven; a majority of the deaths among patients presenting in shock occur within the first hour after presentation.[74] Both chronic leg pain and swelling (the postthrombotic syndrome) and chronic thromboembolic pulmonary hypertension are possible long-term sequelae of acute pulmonary embolism.[1,2]

PREVENTION

The risk of venous thromboembolism is substantial in hospitalized patients but can be reduced significantly when patients receive appropriate prophylaxis.[75] Heparin, low-molecular-weight heparin, fondaparinux, warfarin, and mechanical prophylaxis have proven effective in various clinical settings. Unfortunately, prophylactic measures appear to be grossly underused, as determined in both U.S. and international studies.[76-79] Anticoagulant prophylaxis is more effective than lower-limb mechanical prophylaxis, but the risks of both thrombosis and bleeding should be considered in a given patient.[80]

Consensus statements offer important guidelines for various clinical scenarios.[75,80] Certain patient populations are at particularly high risk for venous thrombosis and thus pulmonary embolism. After total hip or knee replacement, the risk of venous thrombosis is 50% or higher without prophylaxis.[75,81,82] Trauma and spinal cord injury also represent very-high-risk scenarios.[83,84] The superiority of prophylaxis with low-molecular-weight heparin as compared with standard, unfractionated heparin has been demonstrated in these four settings.[75,81-84] Fondaparinux is also effective prophylaxis for total joint replacement and surgery for hip fracture.[75] In other settings, such as abdominal surgery, low-dose unfractionated heparin appears to be adequate, although the advantages of low-molecular-weight heparin for most indications, with regard to both patients and nursing, should be considered.

A large study using venographic end points indicate that without preventive measures, the risk of venous thromboembolism among acutely ill, hospitalized medical patients may be as high as 15%.[85] Well-designed, prospective, randomized trials in this population have demonstrated that enoxaparin,[85] dalteparin,[86] and fondaparinux[87] are each superior to placebo in preventing acute venous thromboembolism. In medical patients, enoxaparin given once daily is at least as effective as heparin delivered every 8 hours,[88] and in patients with stroke, prophylaxis with enoxaparin is associated with significantly lower rates of deep venous thrombosis than is prophylaxis with 5000 U of unfractionated heparin delivered every 12 hours.[89] Patients with stroke or congestive heart failure are at particularly high risk, and in the latter group, the degree of left ventricular dysfunction may correlate with the risk of thrombosis.[90] Extended prophylaxis with enoxaparin (for approximately 38 days) as compared with 7 to 10 days of prophylaxis appears to reduce the rate of deep venous thrombosis, among medically ill patients with limited mobility[91]; such extended prophylaxis has already proven effective in certain high-risk populations, such as patients undergoing total hip replacement or surgery for cancer.[75]

As with therapy for venous thromboembolism, a dose decrease should be considered for prophylaxis with low-molecular-weight heparin in patients with significant renal insufficiency; otherwise, standard heparin should be used. Combining anticoagulant and mechanical methods is reasonable in medical, surgical, or critically ill patients at exceptionally high risk. Consensus recommendations have advised against the use of inferior vena caval filters as primary prophylaxis in patients with trauma and in those undergoing neurosurgery,[75] although others have recommended prophylactic placement in selected patients with trauma.[92]

Every hospitalized patient should be assessed for the need for prophylactic measures, and all hospitals should formulate their own written guidelines for each particular clinical setting, based on the available medical literature.[93] In the United States, several projects have been undertaken in an effort to optimize the prevention and treatment of acute venous thromboembolism. The Surgical Care Improvement Project — sponsored by the Centers for Medicare and Medicaid Services, the American Medical Association, and other health-related organizations — has included prophylaxis against venous thromboembolism as a target area for improvement,[94] and the National Quality Forum, together with the Joint Commission on Accreditation of Healthcare Organizations (now called the Joint Commission), is in the process of finalizing performance measures to ensure that the risk of thromboem-

bolism and prophylaxis against it are considered in hospitalized patients.[95] The unacceptable rate of fatal pulmonary embolism has not served to ensure optimal prophylaxis use in these patients.

PREGNANCY AND ACUTE PULMONARY EMBOLISM

Women who are pregnant or in the postpartum period and women receiving hormonal therapy are all at increased risk for venous thromboembolism, and these groups deserve special mention. Recent U.S. epidemiologic data showed a relative risk of venous thromboembolism among pregnant or postpartum women of 4.29, with an overall incidence of 199.7 cases per 100,000 woman-years.[96] Furthermore, the risk of a first episode of venous thromboembolism was 5 times as high in the postpartum period as during pregnancy, and the risk of pulmonary embolism was 15 times as high during the postpartum period as during pregnancy. Low-dose oral contraceptives increase the risk of venous thrombosis by a factor of two to five,[97] and hormone-replacement therapy appears to increase the risk of thromboembolism by a factor of two to four.[98] In pregnant patients with suspected acute pulmonary embolism, the use of noninvasive diagnostic methods without imaging may appear to be ideal, but concern about exposure to radiation should not deter clinicians from using CT arteriography or ventilation–perfusion scanning when necessary. Pregnant patients with acute venous thromboembolism require the same initial approach as other patients with regard to the need for parenteral anticoagulation, placement of an inferior vena caval filter, or embolectomy. In a patient with life-threatening pulmonary embolism, thrombolytic therapy should not be withheld solely because of pregnancy. Long-term anticoagulation may be best achieved with low-molecular-weight heparin, since warfarin is a teratogen.

CONCLUSIONS

Untreated pulmonary embolism is associated with high mortality. Suspected pulmonary embolism demands prompt diagnostic testing and assessment of risk factors and clinical probability, with empirical clinical assessment and a validated clinical prediction score when possible. Clinical assessment, together with D-dimer testing, may sometimes circumvent the need for imaging. Otherwise, there should be a low threshold for diagnostic imaging. Treatment of acute pulmonary embolism has been shown to reduce mortality. Risk stratification of patients with this disease is necessary to optimize decision making with regard to the use of thrombolytic therapy. Preventive efforts are crucial.

Dr. Tapson reports receiving grant support from Sanofi-Aventis, Actelion, Encysive, Pfizer, and United Therapeutics and consulting fees from Sanofi-Aventis, Bayer, Eisai, Stack, Actelion, Gilead, and United Therapeutics. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Schulman S, Lindmarker P, Holmström M, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. J Thromb Haemost 2006;4:734-42.
2. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257-64.
3. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998;279:458-62.
4. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J R Soc Med 1989;82:203-5.
5. Elliott CG. Pulmonary physiology during pulmonary embolism. Chest 1992;101:Suppl:163S-171S.
6. Leizorovicz A, Turpie AGG, Cohen AT, Wong L, Yoo MC, Dans A. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis: the SMART Study. J Thromb Haemost 2005;3:28-34.
7. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158:585-93.
8. Heit JA, Cohen AT, Anderson FA, VTE Impact Assessment Group. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the U. S. Blood 2005;106:267a. abstract.
9. Bergqvist D, Lindblad B. A 30-year survey of pulmonary embolism verified at autopsy: an analysis of 1274 surgical patients. Br J Surg 1985;72:105-8.
10. Francis CW. Prophylaxis for thromboembolism in hospitalized medical patients. N Engl J Med 2007;356:1438-44. [Erratum, N Engl J Med 2007;357:203.]
11. Beasley R, Raymond N, Hill S, Nowitz M, Hughes R. eThrombosis: the 21st century variant of venous thromboembolism associated with immobility. Eur Respir J 2003;21:374-6.
12. Bick RL. Coagulation abnormalities in malignancy: a review. Semin Thromb Hemost 1992;18:353-72.
13. Ginsberg JS, Wells PS, Brill-Edwards P, et al. Antiphospholipid antibodies and venous thromboembolism. Blood 1995;86:3685-91.
14. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for

factor V Leiden (activated protein C resistance). Blood 1995;85:1504-8.
15. Virchow R. Phlogose und Thrombose im Gefäßsystem: Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt, Germany: Staatsdruckerei, 1856.
16. Rosendaal FR. Venous thrombosis: the role of genes, environment, and behavior. Hematology Am Soc Hematol Educ Program 2005:1-12.
17. Elliott CG, Goldhaber SZ, Jensen RL. Delays in diagnosis of deep vein thrombosis and pulmonary embolism. Chest 2005; 128:3372-6.
18. Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 1991;100:598-603.
19. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med 2004; 140:589-602.
20. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost 2007;5:296-304.
21. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med 2001;135:98-107.
22. Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006;295:172-9.
23. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Arch Intern Med 2001;161:92-7.
24. Le Gal G, Righini M, Roy P-M, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144:165-71.
25. Kearon C, Ginsberg JS, Douketis J, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. Ann Intern Med 2006;144:812-21.
26. Righini M, Aujesky D, Roy P-M, et al. Clinical usefulness of D-dimer depending on clinical probability and cutoff value in outpatients with suspected pulmonary embolism. Arch Intern Med 2004;164:2483-7.
27. Kruip MJ, Söhne M, Nijkeuter M, et al. A simple diagnostic strategy in hospitalized patients with clinically suspected pulmonary embolism. J Intern Med 2006;260: 459-66.
28. Pruszczyk P, Bochowicz A, Torbicki A, et al. Cardiac troponin T monitoring identifies a high-risk group of normotensive patients with acute pulmonary embolism. Chest 2003;123:1947-52.
29. Melanson SE, Laposata M, Camargo CA Jr, et al. Combination of D-dimer and amino-terminal pro-B-type natriuretic Peptide testing for the evaluation of dyspneic patients with and without acute pulmonary embolism. Arch Pathol Lab Med 2006; 130:1326-9.
30. Schoepf U, Holzknecht N, Helmberger TK, et al. Subsegmental pulmonary emboli: improved detection with thin-collimation multi-detector row spiral CT. Radiology 2002;222:483-90.
31. Moores LK, Jackson WL Jr, Shorr AF, Jackson JL. Meta-analysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. Ann Intern Med 2004;141:866-74.
32. Loud PA, Katz DS, Bruce DA, Klippenstein DL, Grossman ZD. Deep venous thrombosis with suspected pulmonary embolism: detection with combined CT venography and pulmonary angiography. Radiology 2001;219:498-502.
33. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 2006;354:2317-27.
34. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990;263:2753-9.
35. Perrier A, Bounameaux H, Morabia A, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. Arch Intern Med 1996;156:531-6.
36. Tapson VF, Carroll BA, Davidson BL, et al. The diagnostic approach to acute venous thromboembolism: clinical practice guideline. Am J Respir Crit Care Med 1999;160:1043-66.
37. Kluge A, Mueller C, Strunk J, Lange U, Bachmann G. Experience in 207 combined MRI examinations for acute pulmonary embolism and deep vein thrombosis. AJR Am J Roentgenol 2006;186:1686-96.
38. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507-11.
39. Tapson VF, Davidson CJ, Kisslo KB, Stack RS. Rapid visualization of massive pulmonary emboli utilizing intravascular ultrasound. Chest 1994;105:888-90.
40. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:Suppl:401S-428S. [Erratum, Chest 2005;27:416.]
41. Partsch H, Blättler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg 2000;32:861-9.
42. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996;334:677-81.
43. Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a cost-effectiveness analysis. Ann Intern Med 1999;130:789-99.
44. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. Arch Intern Med 1997;157:2562-8.
45. Le Gal G, Righini M, Parent F, van Strijen M, Couturaud F. Diagnosis and management of subsegmental pulmonary embolism. J Thromb Haemost 2006;4:724-31.
46. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106:2710-5.
47. Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost 2004; 2:547-50.
48. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997;337:663-9.
49. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997;337:657-62.
50. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003;349:1695-702. [Erratum, N Engl J Med 2004;350:423.]
51. Hull RD, Raskob GE, Brant RF, et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. Arch Intern Med 2000; 160:229-36.
52. Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 2001;134:191-202.
53. Büller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep ve-

nous thrombosis: a randomized trial. Ann Intern Med 2004;140:867-73.
54. Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB.. Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med 2007;146:211-22. [Erratum, Ann Intern Med 2007;146:369.]
55. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:188S-203S.
56. Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HG, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. BMJ 2007;334:674.
57. Palareti G, Cosmi B, Legnani C, et al. D-Dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006;355:1780-9. [Erratum, N Engl J Med 2006;355:2797.]
58. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53.
59. Bauer K. New anticoagulants. Hematology Am Soc Hematol Educ Program 2006:450-6.
60. Rusconi CP, Scardino E, Layzer J, et al. RNA aptamers as reversible antagonists of coagulation factor IXa. Nature 2002;419:90-4.
61. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med 1998;338:409-15.
62. Mismetti P, Rivron-Guillot K, Quenet S, et al. A prospective long-term study of 220 patients with a retrievable vena cava filter for secondary prevention of venous thromboembolism. Chest 2007;131:223-9.
63. Kaufman JA, Kinney TB, Streiff MB, et al. Guidelines for the use of retrievable and convertible vena cava filters: report from the Society of Interventional Radiology multidisciplinary consensus conference. J Vasc Interv Radiol 2006;17:449-59.
64. Dalen JE, Haynes FW, Hoppin FG Jr, Evan GL, Bhardwaj P, Dexter L. Cardiovascular responses to experimental pulmonary embolism. Am J Cardiol 1967;20:3-9.
65. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002;121:877-905.
66. Layish DT, Tapson VF. Pharmacologic hemodynamic support in massive pulmonary embolism. Chest 1997;111:218-24.
67. Witty LA, Krichman A, Tapson VF. Thrombolytic therapy for venous thromboembolism: utilization by practicing pulmonologists. Arch Intern Med 1994;154:1601-4.
68. Goldhaber SZ. Thrombolytic therapy for patients with pulmonary embolism who are hemodynamically stable but have right ventricular dysfunction: pro. Arch Intern Med 2005;165:2197-9.
69. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143-50.
70. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-9.
71. Tapson VF, Gurbel PA, Witty LA, Pieper KS, Stack RS. Pharmacomechanical thrombolysis of experimental pulmonary emboli: rapid low-dose intraembolic therapy. Chest 1994;106:1558-62.
72. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg 2005;129:1018-23.
73. Meyer G, Tamisier D, Sors H, et al. Pulmonary embolectomy: a 20-year experience at one center. Ann Thorac Surg 1991;51:232-6.
74. Alpert JS, Smith R, Carlson J, Ockene IS, Dexter L, Dalen JE. Mortality in patients treated for pulmonary embolism. JAMA 1976;236:1477-80.
75. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:Suppl:338S-400S.
76. Bratzler DW, Raskob GE, Murray CK, Bumpus LJ, Piatt DS. Underuse of venous thromboembolism prophylaxis for general surgery patients: physician practices in the community hospital setting. Arch Intern Med 1998;158:1909-12.
77. Goldhaber SZ, Tapson VF. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. Am J Cardiol 2004;93:259-62.
78. Tapson VF, Decousus H, Pini M, et al. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. Chest 2007;132:936-45.
79. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371:387-94.
80. Nicolaides AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism: International consensus statement. Int Angiol 2006;25:101-61.
81. Colwell CW Jr, Spiro TE, Trowbridge AA, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement: a clinical trial comparing efficacy and safety. J Bone Joint Surg Am 1994;76:3-14. [Erratum, J Bone Joint Surg Am 1994;76:4741.]
82. Brookenthal KR, Freedman KB, Lotke PA, Fitzgerald RH, Lonner JH. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. J Arthroplasty 2001;16:293-300.
83. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med 1996;335:701-7.
84. Green D, Lee MY, Lim AC, et al. Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. Ann Intern Med 1990;113:571-4.
85. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999;341:793-800.
86. Leizorovicz A, Cohen AT, Turpie AGG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874-9.
87. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332:325-9.
88. Kleber F-X, Witt C, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J 2003;145:614-21.
89. Sherman DG, Albers GW, Bladin C, et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. Lancet 2007;369:1347-55.
90. Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. J Clin Epidemiol 2001;54:810-6.
91. Hull RD, Schellong S, Tapson V, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recent reduced mobility: the EXCLAIM study. In: Program and abstracts of the XXI Congress of the International Society on Thrombosis and Haemostasis, Geneva, July 6–12, 2007:O-S-001. abstract.
92. Rogers FB, Shackford SR, Ricci MA, Wilson JT, Parsons S. Routine prophylactic vena cava filter insertion in severely injured trauma patients decreases the incidence of pulmonary embolism. J Am Coll Surg 1995;180:641-7.

93. American Public Health Association. Deep-vein thrombosis: advancing awareness to protect patient lives. White paper. Public Health Leadership Conference on Deep-Vein Thrombosis, Washington, DC, February 26, 2003. (Accessed February 4, 2008, at http://www.apha.org/NR/rdonlyres/A209F84A-7C0E-4761-9ECF-61D22E1E11F7/0/DVT_White_Paper.pdf.)
94. Surgical Care Improvement Project. SCIP process and outcome measures. (Accessed February 4, 2008, at http://www.medqic.org/scip 2005.)
95. National Quality Forum. NQF project brief: national voluntary consensus standards for the prevention and care of venous thromboembolism (including deep-vein thrombosis and pulmonary embolism). January 2006. (Accessed February 4, 2008, at http://www.qualityforum.org/projects/ongoing/vte/index.asp.)
96. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ III. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005;143:697-706.
97. Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. Arterioscler Thromb Vasc Biol 2002;22:201-10.
98. Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. Ann Intern Med 2000;132:689-96.

Hama, Syria

Christian Müller, M.D.