REVIEW ARTICLE

CURRENT CONCEPTS

Acute Pulmonary Embolism

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THE CLINICAL PRESENTATION OF ACUTE PULMONARY EMBOLISM RANGES from shock or sustained hypotension to mild dyspnea. Pulmonary embolism may even be asymptomatic and diagnosed by imaging procedures performed for other purposes. Depending on the clinical presentation, the case fatality rate for acute pulmonary embolism ranges from about 60% to less than 1%.[1] Anticoagulation is the foundation of therapy for pulmonary embolism. Depending on the estimated risk of an adverse outcome, admission to an intensive care unit and treatment with thrombolysis or catheter or surgical embolectomy may be required, but early hospital discharge or even home treatment may be considered. This review focuses on the optimal diagnostic strategy and management, according to the clinical presentation and estimated risk of an adverse outcome.

DIAGNOSIS

Pulmonary embolism should be suspected in all patients who present with new or worsening dyspnea, chest pain, or sustained hypotension without an alternative obvious cause. However, the diagnosis is confirmed by objective testing in only about 20% of patients.[2] This percentage is even lower in some countries, such as the United States, where the threshold to perform a workup for pulmonary embolism is particularly low. The diagnostic workup should be tailored to the severity of the clinical presentation on the basis of whether the patient's condition is hemodynamically stable or unstable.

In patients with hemodynamic stability, the diagnosis of pulmonary embolism should follow a sequential diagnostic workup consisting of clinical probability assessment, D-dimer testing, and (if necessary) multidetector computed tomography (CT) or ventilation–perfusion scanning (Fig. 1).[3,4] The use of the D-dimer assay is of limited value in patients with a high clinical probability of pulmonary embolism.[5] The specificity of an increased D-dimer level is reduced in patients with cancer, pregnant women, and hospitalized and elderly patients.[6] Most hospitalized patients should not undergo D-dimer testing when pulmonary embolism is suspected. The assessment of clinical probability on the basis of the clinical presentation and risk factors, made either implicitly according to clinical judgment or explicitly by means of clinical decision rules, classifies patients with suspected pulmonary embolism into several categories of pretest probability.[3,4] Clinical probability drives the diagnostic workup and facilitates the interpretation of diagnostic tests.

In hemodynamically stable patients with a low or intermediate clinical probability of pulmonary embolism, normal results on D-dimer testing, as measured by a sensitive enzyme-linked immunosorbent assay, avoids unnecessary further investigation. In such patients, if anticoagulant treatment is not given, the estimated 3-month risk of thromboembolism is 0.14% (95% confidence interval [CI], 0.05 to 0.41).[7] Among patients with suspected pulmonary embolism who have normal D-dimer results,

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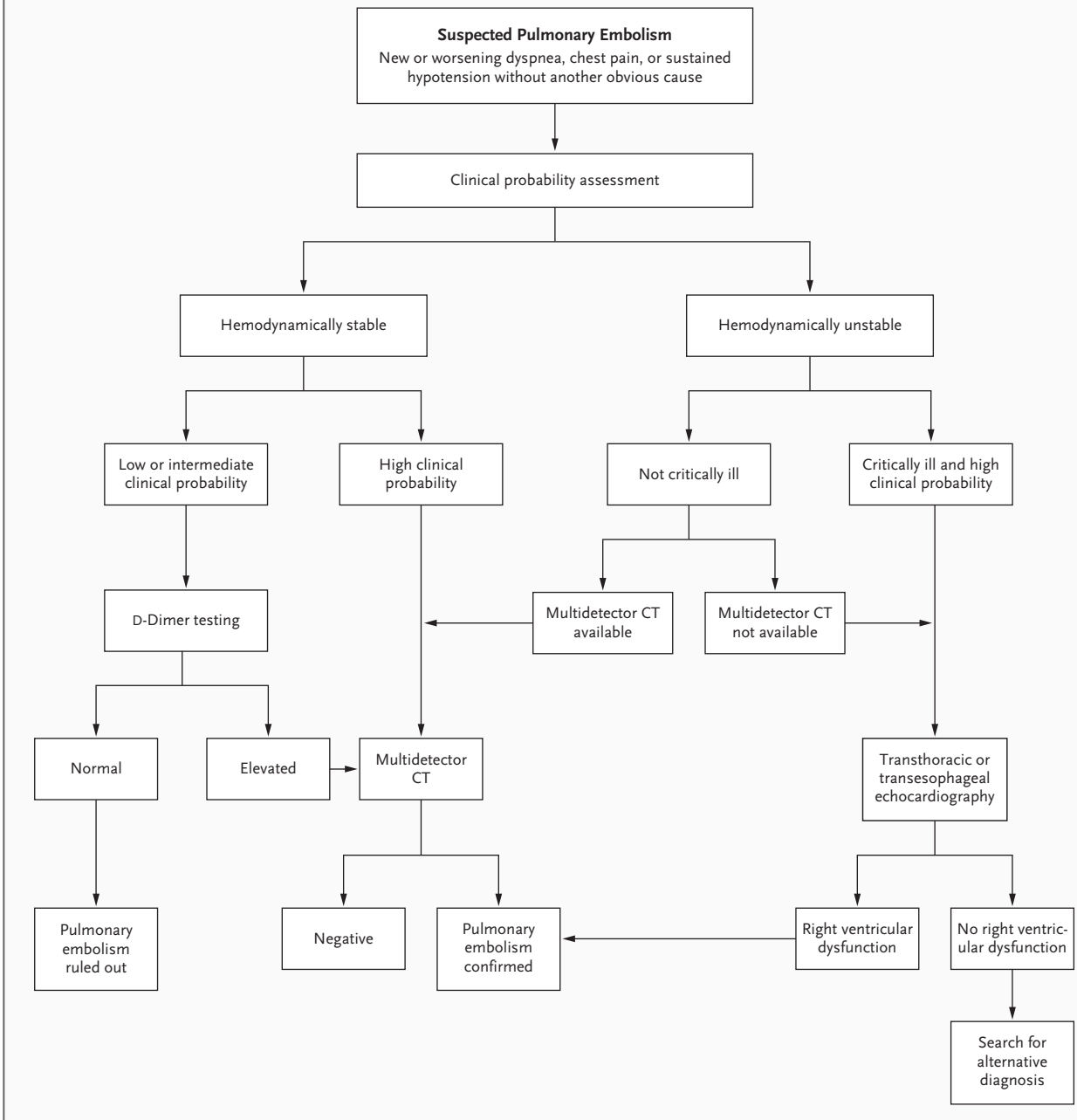

Figure 1. Diagnostic Workup for Pulmonary Embolism.

The initial assessment of the clinical probability of pulmonary embolism is based on either clinical judgment or clinical decision rules (Wells and revised Geneva scores).[3,4] Patients are considered to be hemodynamically unstable if they are in shock or have a systolic blood pressure of less than 90 mm Hg or a drop in pressure of more than 40 mm Hg for more than 15 minutes (in the absence of new-onset arrhythmia, hypovolemia, and sepsis). In cases in which multidetector CT is not available or in patients with renal failure or allergy to contrast dye, the use of ventilation–perfusion scanning is an alternative. In patients with a high clinical probability and an elevated D-dimer level but with negative findings on multidetector CT, venous ultrasonography should be considered. Among critically ill patients with right ventricular dysfunction, thrombolysis is an option; multidetector CT should be performed when the patient's condition has been stabilized if doubts remain about clinical management. In patients who are candidates for percutaneous embolectomy, conventional pulmonary angiography can be performed to confirm the diagnosis of pulmonary embolism immediately before the procedure, after the finding of right ventricular dysfunction.

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further investigation is avoided in about 50% of outpatients and 20% of inpatients.

Hemodynamically stable patients with a high clinical probability of pulmonary embolism or those with a high D-dimer level should undergo multidetector CT. In patients with negative findings on multidetector CT who did not receive anticoagulation therapy, the incidence of thromboembolic events is approximately 1.5% at 3 months[8,9]; the incidence is 1.5% in patients with a high D-dimer level and about 0.5% in patients with a normal D-dimer level.[8] The negative predictive value of CT pulmonary angiography has been marginally improved (from 95 to 97%) by performing concomitant lower-limb CT venography.[10] However, CT venography increases the overall radiation exposure and should therefore be avoided.[11] In patients with a high clinical probability of pulmonary embolism and negative findings on CT, the value of additional testing is controversial. Venous ultrasonography shows a deep-vein thrombosis in less than 1% of such patients.[8,9] In pregnant women with clinical findings suggestive of pulmonary embolism, the concern about radiation is overcome by the hazard of missing a potentially fatal diagnosis or exposing the mother and fetus to unnecessary anticoagulant treatment. Multidetector CT delivers a higher dose of radiation to the mother but a lower dose to the fetus than ventilation–perfusion lung scanning.[12,13] In the Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III) trial (ClinicalTrials.gov number, NCT00241826),[14] magnetic resonance angiography was recently shown to have insufficient sensitivity and a high rate of technically inadequate images when used for the diagnosis of pulmonary embolism.

In cases in which multidetector CT is not available or in patients with renal failure or allergy to contrast dye, ventilation–perfusion scanning is an alternative. A normal ventilation–perfusion scan essentially rules out pulmonary embolism, with a negative predictive value of 97%.[15] A lung scan with findings that suggest a high probability of pulmonary embolism has a positive predictive value of 85 to 90%. However, ventilation–perfusion scanning is diagnostic in only 30 to 50% of patients with suspected pulmonary embolism. In a randomized study enrolling patients in whom pulmonary embolism had been ruled out by imaging, at 3 months venous thromboembolism was diagnosed in 0.4% of patients who had undergone CT and in 1.0% of those who had undergone ventilation–perfusion scanning.[16] Deep-vein thrombosis can be detected by means of ultrasonography in about 4% of patients with a nondiagnostic ventilation–perfusion scan.[16]

If venous ultrasonography of the lower limbs is performed first, lung scanning or multidetector CT can be avoided in about 10% of patients with suspected pulmonary embolism.[17] Hemodynamically stable patients with suspected pulmonary embolism and ultrasonographically confirmed deep-vein thrombosis can be given anticoagulant treatment without further testing. Venous ultrasonography should precede imaging tests in pregnant women with suspected pulmonary embolism and in patients with a contraindication to multidetector CT.[12]

In hemodynamically unstable patients who are hypotensive or in shock, multidetector CT should be performed because of its 97% sensitivity for detecting emboli in the main pulmonary arteries[9] (Fig. 1). If multidetector CT is not available without delay, echocardiography should be performed to confirm the presence of right ventricular dysfunction. In most patients with hemodynamically unstable pulmonary embolism, transesophageal echocardiography may confirm the diagnosis by showing emboli in the main pulmonary arteries. In patients who are so critically ill that transport is unsafe or unfeasible, thrombolytic therapy should be considered if there are unequivocal signs of right ventricular overload on bedside echocardiography. Multidetector CT should be performed when the patient's condition has been stabilized and the patient can be moved safely, if doubts remain about clinical management. The application of validated diagnostic algorithms has led to a decreased use of conventional pulmonary angiography. This procedure is currently reserved for the rare cases in which catheter-based treatment is indicated.

RISK STRATIFICATION

Patients with suspected acute pulmonary embolism should be stratified according to the risk of an adverse outcome during hospitalization. Risk stratification should be done promptly, since fatal pulmonary embolism generally occurs early after hospital admission.[18] Risk stratification is based on clinical features and markers of myocardial dysfunction or injury (Fig. 2).

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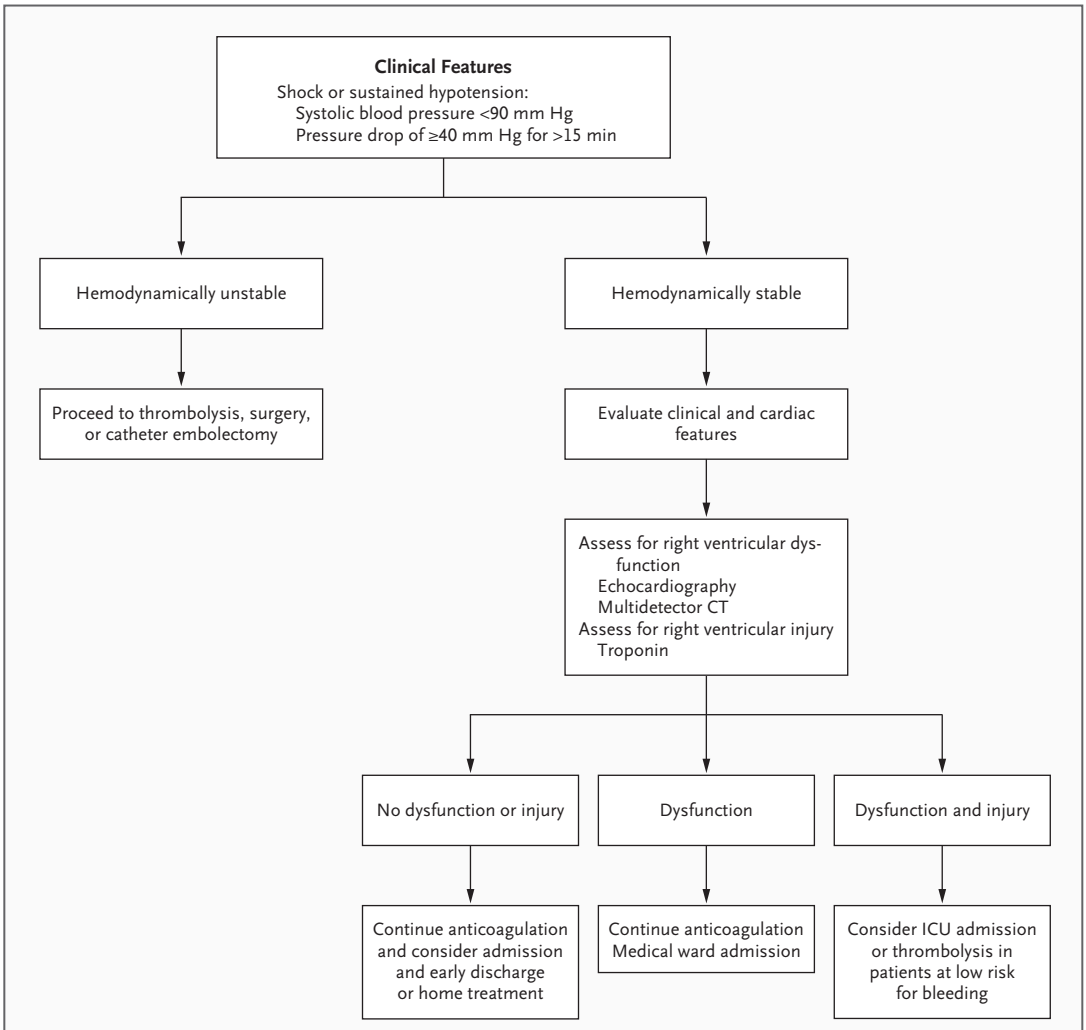

Figure 2. Clinical Management of Confirmed Acute Pulmonary Embolism.
ICU denotes intensive care unit.

Shock and sustained hypotension identify patients at high risk for an adverse outcome. In the International Cooperative Pulmonary Embolism Registry, the death rate was nearly 58% among hemodynamically unstable patients and about 15% among hemodynamically stable patients.[1,19] Immobilization because of a neurologic disease, an age of more than 75 years, cardiac or respiratory disease, and cancer are risk factors for death among patients with acute pulmonary embolism.[20] Prognostic models combining individual risk factors have been derived and seem promising in identifying patients with a favorable prognosis.[21,22]

Markers of myocardial dysfunction or injury may be useful for risk stratification of hemodynamically stable patients. Right ventricular dysfunction on echocardiography has been associated with increased mortality among patients with acute pulmonary embolism.[23-25] Right ventricular hypokinesis and dilatation have been shown to be independent predictors of 30-day mortality among hemodynamically stable patients.[26,27] Right ventricular dysfunction, as assessed by means of multidetector CT, has been suggested to be an independent predictor of 30-day mortality on the basis of retrospective studies.[28] In one study, a value of less than 1.0 for the ratio of the right ventricular diameter to the left ventricular diameter had a 100% negative predictive value for an uneventful outcome (lower limit of the 95% CI,

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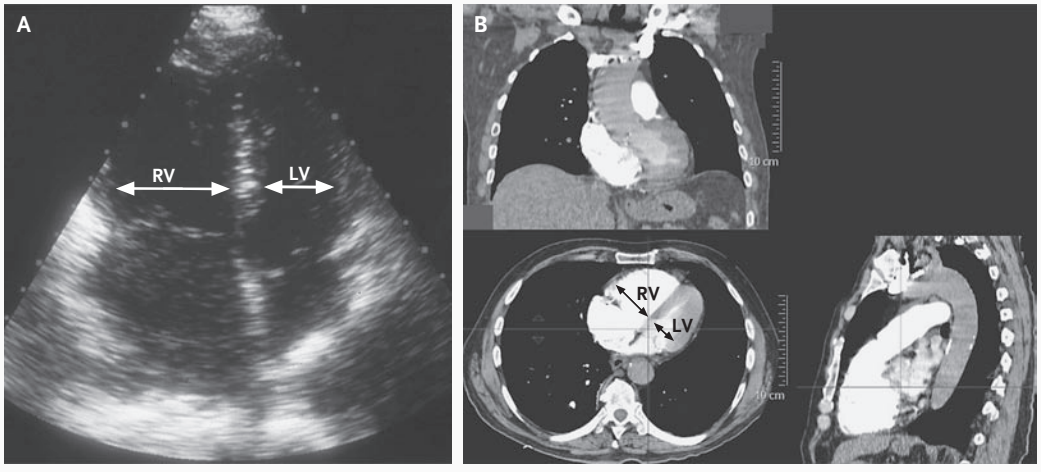

Figure 3. Right Ventricular Dilatation.

Right ventricular hypokinesis and dilatation have been shown to be independent predictors of 30-day mortality among hemodynamically stable patients with pulmonary embolism. In Panel A, right ventricular dilatation is clearly visible on echocardiography. In Panel B, images obtained on multiplanar reconstruction of multidetector CT angiography show the right and left heart chambers in the coronal view (at upper left), in the axial view (at lower left), and in the sagittal view (at lower right). Images obtained on multiplanar reconstruction at the valvular plane in the axial view allow the measurement of the diameter of the right ventricle (RV) and the left ventricle (LV) (at lower left). A ratio of more than 1.0 for the diameter of the right ventricle to that of the left ventricle indicates right ventricular dysfunction.

94.3%). In a large retrospective study, ventricular septal bowing (but not the ratio of the diameter of the right ventricle to that of the left ventricle) was a predictor of death related to pulmonary embolism.[29] In most studies, right ventricular assessment was performed with the use of computerized reformatted images, which are not readily available on an emergency basis in everyday clinical practice (Fig. 3).

One study showed that patients with elevated levels of B-type natriuretic peptide (BNP) and pro-BNP had an increased risk of an adverse in-hospital outcome, as compared with patients with normal levels.[30] Normal levels of BNP and pro-BNP were shown to have a nearly 100% negative predictive value for an adverse outcome in hemodynamically stable patients.

A meta-analysis of several studies has shown the prognostic value of the measurement of troponins in patients with pulmonary embolism.[31] In this analysis, patients with pulmonary embolism and elevated levels of troponin had an increase in the short-term risk of death by a factor of 5.2 (95% CI, 3.3 to 8.4) and an increase in the risk of death from pulmonary embolism by a factor of 9.4 (95% CI, 4.1 to 21.5). The prognostic role of troponin was confirmed in hemodynamically stable patients in another meta-analysis.[32] Among hemodynamically stable patients, the association between an increased troponin level and right ventricular dysfunction on echocardiography identifies a subgroup of patients at particularly high risk for an adverse outcome.[33]

Risk stratification of patients with pulmonary embolism has potential clinical implications. The markers of right ventricular dysfunction and injury have a high negative predictive value. Thus, the absence of right ventricular dysfunction and a normal troponin level can identify patients who are eligible for early discharge or even outpatient treatment. Hemodynamically stable patients with right ventricular dysfunction or injury should be admitted. The positive predictive value of markers of right ventricular dysfunction or increased troponin levels for an adverse outcome ranges from 10 to 20%. This poor predictive value complicates the judgment regarding whether more aggressive treatment is required in patients in whom the markers are positive. An ongoing study is assessing the benefit of thrombolysis as compared with anticoagulation in hemodynamically stable patients with evidence of right ventricu-

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lar dysfunction and an elevated troponin level (NCT00639743).

TREATMENT

Acute pulmonary embolism requires initial short-term therapy with a rapid-onset anticoagulant, followed by therapy with a vitamin K antagonist for at least 3 months; in patients at high risk for recurrence, more extended therapy is required (Fig. 4). In patients with a high clinical probability of pulmonary embolism, anticoagulant treatment should be initiated while diagnostic confirmation is awaited.[34]

The majority of patients with acute pulmonary embolism are candidates for initial anticoagulant treatment with subcutaneous low-molecular-weight heparin or fondaparinux or intravenous unfractionated heparin.[35,36] Enoxaparin (at a dose of 1 mg per kilogram of body weight given twice daily) and tinzaparin (175 U per kilogram given once daily) are low-molecular-weight heparins commonly used for the treatment of pulmonary embolism. Fondaparinux is given once daily at a dose of 5 mg for patients weighing less than 50 kg (110 lb), 7.5 mg for patients weighing 50 to 100 kg (220 lb), and 10 mg for patients weighing more than 100 kg. Intravenous unfractionated heparin is given as an initial bolus dose (80 IU per kilogram or 5000 IU), followed by continuous infusion (usually starting with 18 IU per kilogram per hour) with adjustment to achieve a target activated thromboplastin time that is 1.5 to 2.5 times the normal value, according to validated nomograms.[37]

Low-molecular-weight heparins and fondaparinux are preferred over unfractionated heparin for their ease of use. A meta-analysis of 12 studies showed that treatment with a weight-adjusted low-molecular-weight heparin had an efficacy and safety profile similar to that of intravenous unfractionated heparin.[38] Fondaparinux was shown to be as effective and safe as intravenous unfractionated heparin in a large, open-label study.[39] Since low-molecular-weight heparins and fondaparinux are excreted by the kidneys, unfractionated heparin should be considered in patients with a creatinine clearance of less than 30 ml per minute. The incidence of major bleeding complications with these treatment strategies is about 3% during the hospital stay. A recent systematic review of 11 nonrandomized studies showed that it may be possible to treat low-risk patients effectively and safely at home if proper outpatient care is provided.[40] However, this approach is controversial and should be reserved for selected patients.

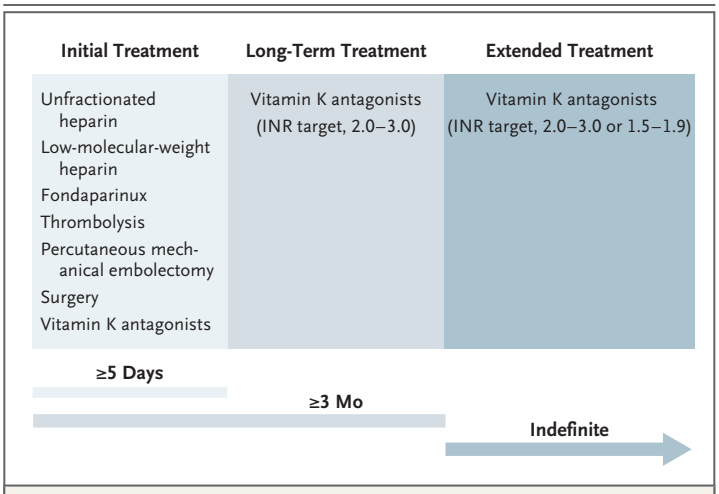

Figure 4. Treatment of Acute Pulmonary Embolism.

Low-molecular-weight heparin (administered either intravenously or subcutaneously) should be the treatment of choice in hemodynamically stable patients. Thrombolysis should be administered to patients whose condition is unstable and should be considered for high-risk, hemodynamically stable patients. Percutaneous mechanical thrombectomy should be restricted to high-risk patients with absolute contraindications to thrombolytic treatment and those in whom thrombolytic treatment has failed to improve hemodynamic status. Low-molecular-weight heparin is preferable to vitamin K antagonists in patients with cancer and in pregnant women. For patients receiving vitamin K antagonists, the international normalized ratio (INR) should be maintained within a therapeutic range (2.0 to 3.0) during long-term therapy (≥3 months); a low-intensity INR target of 1.5 to 1.9 is an option for extended (indefinite) anticoagulant therapy. Extended treatment should be considered for patients with active cancer, unprovoked pulmonary embolism, or recurrent venous thromboembolism. Extended treatment requires a reassessment of the patient's risk–benefit ratio at periodic intervals. Indefinite treatment refers to anticoagulation that is continued without a scheduled stop date but that may be stopped because of an increase in the risk of bleeding or a change in the patient's preference.

In an open study involving hemodynamically stable patients, intravenous thrombolysis reduced the rate of clinical deterioration (mainly, the need for secondary thrombolysis) but not the rate of death, as compared with the use of unfractionated heparin.[41] Intravenous thrombolytic treatment was associated with a more rapid resolution of right ventricular dysfunction; at 1 week, however, the degree of right ventricular dysfunction was similar in the two treatment groups. No clear advantage of catheter-directed thrombolysis, as compared with intravenous thrombolysis, has been shown.

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Hemodynamically unstable patients are candidates for more aggressive treatment, such as pharmacologic or mechanical thrombolysis. This therapeutic option is justified by the high rate of death among such patients and by the faster resolution of thromboembolic obstruction with thrombolysis than with anticoagulant therapy. Mortality can be as high as 60% in untreated patients (and even higher in patients with right heart thrombi) and can be reduced to less than 30% with prompt treatment. The most recent meta-analysis showed that intravenous thrombolysis was associated with a reduction in mortality among hemodynamically unstable patients with pulmonary embolism.[42] Major bleeding was more common with intravenous thrombolysis than with anticoagulant therapy. Major contraindications to thrombolytic therapy include intracranial disease, uncontrolled hypertension, and recent major surgery or trauma (within the past 3 weeks).[35]

There are no conclusive findings from studies comparing different thrombolytic regimens in patients with acute pulmonary embolism. Short infusion times (2 hours or less) are recommended over prolonged infusion times, since they achieve more rapid thrombolysis and are probably associated with less bleeding.[35] Intravenous unfractionated heparin is the only anticoagulant that has been used in conjunction with thrombolytic therapy in patients with pulmonary embolism. Thus, initial anticoagulation with intravenous unfractionated heparin is appropriate if thrombolytic therapy is being considered. Percutaneous mechanical thrombectomy (thrombus fragmentation and aspiration) and surgical embolectomy should be restricted to high-risk patients with an absolute contraindication to thrombolytic treatment and those in whom thrombolytic treatment has not improved hemodynamic status; percutaneous mechanical thrombectomy is an alternative to surgical embolectomy in cases in which immediate access to cardiopulmonary bypass is unavailable. In a recent meta-analysis of case series, catheter-directed therapy had a clinical success rate of 86% and a rate of major procedural complications of 2.4% (95% CI, 1.9 to 4.3).[43]

The use of vena cava filters should be reserved for patients with contraindications to anticoagulant treatment.[35,36] To avoid thrombus extension and recurrence, such patients should receive a conventional course of anticoagulant therapy if and when the risk of bleeding is eliminated. Case series have shown that retrievable vena cava filters may be an option for patients with presumed time-limited contraindications to anticoagulant therapy or for patients requiring procedures that are associated with a risk of bleeding.[35,36] However, the use of retrievable filters has not resulted in increased filter retrieval.

Vitamin K antagonists should be initiated as soon as possible, preferably on the first treatment day, and heparin should be discontinued when the international normalized ratio (INR) has been 2.0 or higher for at least 24 hours.[35,36]

LONG-TERM MANAGEMENT

Patients with acute pulmonary embolism are at risk for recurrent thromboembolic events, mainly a second pulmonary embolism.[44] The risk of recurrent pulmonary embolism is less than 1% per year while patients are receiving anticoagulant therapy, but the risk is 2 to 10% per year after the discontinuation of such therapy.[44] Risk factors for recurrence include male sex, advanced age, and idiopathic or unprovoked pulmonary embolism (i.e., occurring in the absence of any identifiable risk factor for venous thromboembolism). The frequency of unprovoked pulmonary embolism can be as high as 50% among patients with pulmonary embolism. The risk of recurrence is particularly high among patients with cancer. The risk of recurrence is about 3% per year among patients in whom the first pulmonary embolism was associated with a temporary risk factor, such as major surgery, immobilization because of an acute medical illness, or trauma.

The duration of long-term anticoagulation should be based on the risk of recurrence after cessation of treatment with vitamin K antagonists, the risk of bleeding during treatment, and the patient's preference. In patients with pulmonary embolism secondary to a temporary (reversible) risk factor, therapy with vitamin K antagonists should be given for 3 months. Patients with unprovoked pulmonary embolism, those with cancer, and those with recurrent unprovoked pulmonary embolism are candidates for indefinite anticoagulation with periodic reassessment of the risk–benefit ratio.[34] Conventional-intensity warfarin therapy (INR target, 2.0 to 3.0) is recommended during the first 3 to 6 months after the acute event; after an initial course of conventional-intensity warfarin therapy, low-intensity warfa-

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rin therapy (INR target, 1.5 to 1.9) may be an option.[45] Low-molecular-weight heparins should be chosen over warfarin for long-term therapy in patients with cancer[46] and pregnant women.[12] New anticoagulant agents with a more predictable anticoagulant effect and reduced drug–drug interactions, as compared with warfarin, are currently under investigation for the treatment of venous thromboembolism[47] (NCT00643201, NCT00633893, NCT00986154, NCT00439777, NCT00440193, NCT00439725, and NCT00680186). These agents do not require laboratory monitoring. Dabigatran, an oral antithrombin agent administered at fixed doses, has been shown to be as effective and safe as warfarin for the treatment of venous thromboembolism.[48]

After an acute pulmonary embolism, patients should be monitored for chronic thromboembolic pulmonary hypertension. The incidence of chronic thromboembolic pulmonary hypertension 2 years after the acute event ranges from 0.8 to 3.8%.[49,50]

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