Risk Stratification for Acute Pulmonary Embolism

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Key Words
Risk stratification, acute pulmonary embolism, respiratory failure, anticoagulation, heparin

Abstract
This article discusses state-of-the-art techniques for predicting risk of death after acute pulmonary embolism (PE), with special attention to how underlying malignancy adversely affects survival after an episode. Current methods of risk stratification generally categorize patients with PE as low-, moderate-, and high-risk for in-hospital adverse outcomes of respiratory failure, circulatory shock, and death. Published risk stratification studies find that patients with PE and an underlying malignancy have a worse prognosis, but no validated risk stratification criteria have been published specifically for these patients. Standard treatment is full-dose heparin followed by oral anticoagulation. The term escalated treatment refers to the use of systemic or intrapulmonary fibrinolytic agents, catheter-based treatment, or surgical embolectomy. Most patients with low-risk PE (normal vital signs and normal serum troponin, brain natriuretic peptide, and normal echocardiography) are treated successfully with standard anticoagulation, and many can be treated as outpatients. In contrast, patients with high-risk PE (systolic blood pressure < 90 mm Hg and no contraindications) often benefit from escalated treatment. Treatment decisions for patients with moderate-risk PE (normotension with evidence of right ventricular damage or dysfunction) are most controversial. Most patients in this category of risk recover with standard therapy, but some benefit from escalated treatment. Patients with cancer with an incidentally discovered PE should be risk stratified the same as those who have clinically suspected PE. (JNCCN 2011;9:800–810)

Overview
Victims of a pulmonary embolism (PE) are at risk for short-term complications such as respiratory failure, circulatory shock, or cardiac arrest. In the long term, they may experience cardiopulmonary disability or chronic thromboembolic pulmonary hypertension. A patient's physiologic response to a thromboembolic event depends on the severity of the PE, and the location and type of treatment should vary with severity. This article presents the scientific basis for key variables that predict a bad outcome from PE, and synthesizes a recommendation to stratify patients into low-, moderate-, and high-risk groups, with associated admission locations and treatment options.

Why Risk Stratify?
The process of patient risk stratification helps identify which patients will do well with standard therapy and which ones will likely need more aggressive treatment. According to prospective cohort studies, most patients hospitalized for a PE are admitted to units other than the intensive care unit (ICU). The multicenter EMPORER registry found that 29 of 1880 (1.5%) patients admitted to an emergency department with an acute PE in the United States were transferred within 24 hours of admission from their unmonitored or telemetry bed to an ICU setting. Conversely, 103 of 1880 (5.4%) patients were transferred from the ICU to a ward bed within 24 hours. Initial risk stratification of patients with an acute PE might identify a more appropriate admission location in a small percentage of cases. Risk stratification may be particularly important to oncologists presented with incidentally discovered PE. Systematic risk stratification of patients with acute PE helps predict the need for escalated treatments, including systemic or intrapulmonary fibrinolytic therapy, catheter-based me-
 Risk Stratification for Acute Pulmonary Embolism

Mechanical clot disruption, or surgical embolectomy in moderate-risk patients.

Several risk-stratification scoring systems have been derived and validated for acute PE. All of these systems harness the predictive value of clinical variables to produce a numeric score that predicts risk of bad outcome. Understanding of the value and limitation of these systems requires a brief review of the key elements of these systems that worsen PE prognosis.

**Bedside Evidence of Severe PE**

**Vital Signs**

PE obstructs forward blood flow from the right to left heart leading to right ventricular overload and poor left ventricular filling. Decreased left ventricular filling leads to a smaller ejection volume and a physiologic response similar to hemorrhagic shock, characterized by a high pulse rate and low systolic blood pressure. Frank hypotension, defined as any systolic blood pressure less than 90 mm Hg, indicates massive PE in accordance with definitions agreed on by several expert panels. Hypotension increases the risk of death 5-fold. Hospital mortality rates for these patients is 9% to 15% compared with 1% to 3% in patients who remain normotensive with their PE.

Calculating a patient’s shock index (pulse rate [beats/min]/systolic blood pressure [mm Hg]) is a helpful way to combine pulse rate and blood pressure and thereby grade the severity of an acute PE. Patients with a shock index greater than 1 have a 2-fold increased risk of death. As the shock index increases beyond that, so does the mortality risk. Thrombus obstruction of pulmonary vascular blood flow also causes hypoxemia because of ventilation/perfusion mismatch. Pulse oximetry testing at the bedside can provide information on the integrity of ventilation/perfusion matching. The lower the reading (percentage of oxygen saturation of arterial blood [SaO₂]), the worse the prognosis. A key transition point exists at the single point drop from 95% to 94%, probably because this drop corresponds to the largest decrease in partial pressure of dissolved oxygen. One study found the mortality of PE increased from 2 of 110 (1.8%) for patients with SaO₂ greater than 94%, to 19 of 96 (19.8%) for patients with an SaO₂ less than 95%.

The combination of new altered mental status (either syncope or first-time convulsive spell), respiratory distress, and hypoxemia or shock index greater than 1 represents a particularly lethal combination in PE, with a mortality rate greater than 30%.

**Comorbid Conditions**

Age and past medical history (comorbidity) are powerful indicators of outcome. Data from large epidemiologic databases and carefully performed physiologic studies have shown that advanced age and prior cardiopulmonary disease worsen the hemodynamic response to PE. A medical history including active cancer, prior heart failure, chronic obstructive pulmonary disease or other structural lung disease, prior PE, renal failure, and diagnosis of a PE while the patient is already hospitalized all increase the risk of adverse outcomes (Table 1). In every study of venous thromboembolic disease (VTE; including PE and proximal deep venous thrombosis, down to the calf veins), underlying cancer imparts a 2- to 4-fold increase in mortality.

Prospective registries and PE outcomes studies provide limited specific information about prognosis of PE in patients with cancer. In PE registries, these patients usually constitute only 15% to 20% of the sample population, and few studies provide information about cancer type or stage. The precise cause of death among patients with PE and cancer is often difficult to con-

<table>
<thead>
<tr>
<th>Table 1 Effect of Selected Comorbid Conditions on Risk of Death From Acute Pulmonary Embolism</th>
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<tr>
<td>Factor</td>
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<tr>
<td>Age &gt; 75 y</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Chronic lung disease</td>
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<tr>
<td>Prior PE</td>
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<tr>
<td>Active cancer</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Immobility &gt; 3 d</td>
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<tr>
<td>Inpatient status</td>
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<tr>
<td>Concomitant deep vein thrombosis</td>
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Abbreviation: PE, pulmonary embolism.
firm from chart reviews, death certificates, and peer-reviewed literature because cause of death is often simply advancement of cancer.\textsuperscript{25}

Despite the difficulty in establishing an exact cause of death in many instances, a large body of literature indicates a strong synergistic effect on mortality between PE and cancer. Sadly, PE often strikes patients with cancer when they are most vulnerable. PE may complicate chemotherapy and surgery, and often occurs in patients who have end-organ damage from metastatic disease. The higher rate of VTE recurrence in these patients explains at least part of the worsened prognosis.\textsuperscript{26} Several mechanisms have been proposed for the hypercoagulability that causes patients to be refractory to standard anticoagulation.\textsuperscript{26} One enduring theory implicates the paraneoplastic release of tissue factor, which activates the extrinsic clotting pathway. The tissue factor may be exposed through physical disruption of normal cells or as a consequence of prothrombotic microparticle release from lysing tumor cells.\textsuperscript{27–29} The microparticle hypothesis explains only part of the increased risk of death from PE in patients with cancer, and currently the significance of circulating microparticles and their associated proteins as a biomarker for outcome remains a point of research.\textsuperscript{30} Patients with cancer are also more vulnerable to major bleeding complications from standard anticoagulation therapy for VTE.\textsuperscript{31,32} Bleeding risk is highest in patients with metastatic pancreatic cancer and lowest in those with prostate or breast cancer.\textsuperscript{32} As with all patients, major bleeding risk also rises with increasing age.\textsuperscript{31}

### Clinical Scoring Systems

Several scoring systems for risk stratification of patients with acute PE have been devised based largely on bedside predictor variables. The most extensively studied and validated system is the Pulmonary Embolism Severity Index (PESI).\textsuperscript{3,6,33–36} Another score system was published,\textsuperscript{7} but the PESI score is most likely to be used in clinical practice, especially with respect to home treatment for PE (Table 2). In validation studies, a PESI score of less than 66 predicts a 30-day mortality rate less than 3%.\textsuperscript{11–16} Aujesky et al.\textsuperscript{36} derived and validated the PESI score with the goal of identifying patients at low enough risk for adverse outcomes from PE to allow outpatient management. These investigators recently completed a large, multinational, randomized trial comparing outcomes and cost for inpatient management versus immediate discharge from ambulatory centers when patients with PE have a PESI score of less than 66. Published results are expected within the year.

To the authors’ knowledge, only one other scoring system is available to help decide on home treatment, and as of early 2011 that study was only published in abstract form.\textsuperscript{37} Although studies have clearly examined the role of VTE as a risk factor for death in patients with cancer at all stages of disease, no scoring system has been derived and validated specifically to risk stratify patients with PE and cancer.\textsuperscript{38}

<table>
<thead>
<tr>
<th>Table 2 Two Scoring Systems to Predict Severity of Pulmonary Embolism</th>
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<tbody>
<tr>
<td><strong>PESI Score</strong> \textsuperscript{a}</td>
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<tr>
<td>Age, per year</td>
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<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Heart failure</td>
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<tr>
<td>Chronic lung disease</td>
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<tr>
<td>Pulse &gt; 110 beats/min</td>
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<tr>
<td>Systolic blood pressure &lt; 100 mm Hg</td>
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<tr>
<td>Respiratory rate &gt; 29 breaths/min</td>
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<tr>
<td>Temperature &lt; 36°C</td>
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<tr>
<td>Altered mental status</td>
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<tr>
<td>SaO\textsubscript{2} &lt; 90%</td>
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<tr>
<td>Low-risk score</td>
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<td>High-risk score</td>
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<tr>
<th><strong>Geneva Score</strong> \textsuperscript{b}</th>
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<tbody>
<tr>
<td>Cancer</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Prior deep vein thrombosis</td>
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<tr>
<td>Systolic blood pressure &lt; 100 mm Hg</td>
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<tr>
<td>PaO\textsubscript{2} &lt; 8 kPa</td>
</tr>
<tr>
<td>Concomitant deep vein thrombosis</td>
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<tr>
<td>Low-risk score</td>
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<tr>
<td>High-risk score</td>
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Abbreviations: PaO\textsubscript{2}, arterial partial pressure of oxygen; PESI, Pulmonary Embolism Severity Index; SaO\textsubscript{2}, percentage of oxygen saturation of arterial blood.
Electrocardiography, Biomarkers, Echocardiography, and CT Pulmonary Angiogram Findings

The primary mechanisms of injury to the heart from acute PE stem from development of acute pulmonary hypertension with increased workload on the right side of the heart with a fixed oxygen demand. At the cellular level, acute increase in right ventricular pressure causes contractile failure, mechanical shear injury, and subendocardial ischemia, followed by an intense inflammatory response in the myocardium. These factors result in right ventricular dilation and poor overall contractility, manifested as hypokinesis on echocardiography, electrocardiogram changes, and leakage of proteins from heart muscle. At the bedside, right heart strain can be assessed with a standard 12-lead electrocardiogram. Findings of tachycardia, an S1Q3T3 pattern, incomplete or complete right bundle branch block, and T-wave inversion in leads V1 through V4 are specific but insensitive indicators of right heart strain. More extensive electrocardiogram findings predict higher pulmonary artery pressures. Daniel et al. devised a scoring system for grading the severity of right heart strain caused by PE that has been externally validated.

Right ventricular injury from PE causes the heart muscle to liberate peptides that can help in grading severity of damage. These markers include troponins, brain natriuretic peptide (BNP) and its precursor N-terminal prohormone of BNP (NT-proBNP), fatty acid binding protein, and matrix metalloproteinases. Troponin I and T, BNP, and NT-proBNP are the most extensively studied biomarkers for risk stratifying patients with acute PE.

Several high-quality meta-analyses have quantized biomarkers’ association with adverse outcome. As shown in Table 3, an elevated troponin level predicts a 7-fold increased risk of adverse events associated with acute PE. Elevated troponin seems to be more specifically associated with death directly attributed to PE, independent of other comorbidities. Studies of troponins have used a wide range of cut-off values depending on the platform or the isof orm measured, however. In clinical practice these data can be extrapolated using local laboratory standards for normal, above-normal, and borderline values.

Elevated BNP (< 90 pg/mL) or proBNP concentrations (> 900 pg/mL) in the presence of an acute PE predict a similar 5- to 7-fold increased risk for adverse events. In one prospective study directly comparing multiple biomarkers, BNP provided the highest overall likelihood ratio for predicting short-term in-hospital adverse outcomes and 1-year mortality when compared with echocardiography, troponin, the Daniel electrocardiogram score, and D-dimer concentration. BNP or proBNP seem to offer at least as good or better overall prognostic accuracy as any other single test, including echocardiography.

The natriuretic peptides and troponins can be added together with significant improvement in prognostic value. A 2009 meta-analysis found that 46% of patients with PE had both peptides abnormal, whereas only 4% had a positive troponin in the presence of a normal natriuretic peptide. Among normotensive patients with increased levels of natriuretic peptide, an abnormally elevated troponin level further increased the risk for death directly related to PE (odds ratio [OR], 8.4; 95% CI, 2.1–33.4) and all-cause death (OR, 6.9; 95% CI, 2.3–20.7). When both peptides were normal, the rates of PE-related death, all-cause death, and any serious adverse event were 0% (0/341), 0.2% (1/443), and 1.6% (7/443), respectively.

Two-dimensional echocardiogram with Doppler interrogation can show right ventricular dilation, hypokinesis, and tricuspid regurgitation as manifestations of pulmonary hypertension from PE. Each of these findings worsens prognosis, but hypokinesis is the most specific predictor of shock, respiratory failure, and death. Patients with right ventricular hypokinesis have an approximately 3-fold increased risk for life-threatening complications. Hypokinesis usually starts in the infundibular region or base of the right ventricle. Focal hypokinesis in this region is sometimes referred to as the McConnell’s sign.

Table 3 Mortality With and Without Evidence of Right Ventricular Dysfunction

<table>
<thead>
<tr>
<th>Finding of Right Ventricular Dysfunction</th>
<th>Without</th>
<th>With</th>
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<tbody>
<tr>
<td>Echocardiographic assessment of right ventricular dysfunction</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>Elevated troponin</td>
<td>15%</td>
<td>43%</td>
</tr>
<tr>
<td>Elevated BNP</td>
<td>13%</td>
<td>47%</td>
</tr>
<tr>
<td>Elevated N-terminal prohormone of BNP</td>
<td>5%</td>
<td>32%</td>
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Abbreviation: BNP, brain natriuretic peptide.
In contrast to the thick-walled, resilient left ventricle, the right ventricle adapts poorly to increased afterload. Once it starts to show hypokinesis, unless afterload is reduced, right ventricular function deteriorates rapidly. Ultimately the right ventricular free wall can appear stunned and almost motionless. At this point, the ventricle may be so weak that it cannot even produce a tricuspid regurgitant jet.

Recent investigations have examined the role of CT pulmonary angiography (CTPA) for determining right ventricular dilatation (right ventricular diameter > left ventricular diameter), tricuspid regurgitation causing contrast reflux into the inferior vena cava, or a large percentage of obstructed pulmonary vasculature, particularly in the proximal pulmonary arteries, and a small left atrium. When compared directly, the right:left ratio of the atria and ventricles had the highest correlation with total pulmonary vascular obstruction. The primary clinical efficacy of various CTPA findings currently lies in its ability to predict right ventricular dysfunction and recurrent embolic events, as opposed to survival or quality of life. Most prognostic studies of CTPA findings are retrospective analyses, and their ability to correlate findings with an increased risk for adverse events are inconsistent. No large prospective trial has compared the prognostic value of CTPA with echocardiography, troponins, or natriuretic peptides.

**Hybrid Risk-Prediction Systems**

Many hybrid studies have used a multimarker approach to risk stratify patients, including serum troponin, BNP, or proBNP, echocardiography, and scoring systems. They consistently show that comorbidities (age, cancer, and heart failure) and host-response factors (low systolic blood pressure and low SaO₂, elevated biomarkers, and hypokinesis on echocardiography) represent independent, additive risk factors for an adverse outcome.

**What Should Be Measured**

The shock index, SaO₂, and 12-lead electrocardiography should be measured at least initially on all patients with PE. All patients with hypotension should be admitted to an ICU. A patient without visible respiratory distress, a shock index less than 1, no history of hypotension, a room air SaO₂ always greater than 94%, and a Daniel score of less than 3 within the previous 12 hours, or any patient with a PESI score of less than 66, has a low-risk PE. If any of these screening parameters is abnormal, then a biomarker test should be used to assess the presence or absence of right ventricular dysfunction. A good option would be a proBNP (> 900 pg/mL), BNP (> 90 pg/mL), or troponin measurement. If the chosen biomarker is elevated, the patient has a moderate PE and should be admitted to a telemetry bed. If available, echocardiography would provide more information about the right ventricle. Any normotensive patient with one or more abnormal screening variables and right ventricular hypokinesis should be admitted to a telemetry unit.

**Risk Stratification and Treatment**

Many experts bundle risk stratification data to categorize patients into 3 strata, defined in Table 4. These strata confer different treatment and monitoring needs.

Patients with low-risk PE require heparin anticoagulation with either low-molecular-weight or unfractionated heparin. Based on meta-analysis data showing a lower rate of hemorrhage and recurrent venous thromboembolism in this population, and augmented by clinical experience, the authors recommend low-molecular-weight heparin over unfractionated heparin in patients with PE. Patients with low-risk PE can be admitted to an unmonitored bed. Emerging literature suggests that as many as half of all patients diagnosed with PE and most-risk patients can be discharged home.

Patients with moderate-risk PE require hospitalization and telemetry monitoring during initial heparin anticoagulation. They should be monitored at regular intervals for new evidence of worsening in blood pressure (> 20% reduction or any systolic blood pressure < 90 mm Hg), shock index (> 1.0 for more than 15 minutes), SaO₂ (< 95% breathing room air at sea level), and electrocardiogram (new incomplete right bundle branch block or T-wave inversion in V1–V4). Patients who develop one or more of these new signs of worsening should undergo a repeat biomarker test or echocardiography. If one of these tests is abnormal, the patient has more severe moderate PE.

Patients with more-severe moderate PE, or submassive PE, may require more aggressive care, such as...
fibrinolytic therapy.\(^8\) Controversy surrounds treatment of submassive PE with fibrinolytic therapy, however. Worster et al.\(^7^6\) attempted a meta-analysis of randomized trials that included patients with submassive PE and found inadequate numbers to predict the risk (death from hemorrhage) to benefit (decrease in mortality) ratio of thrombolytic therapy. Even fewer data exist to assess its impact on long-term cardiopulmonary function and quality of life.\(^7^7\) Two studies have suggested that fibrinolysis is associated with improved right ventricular function and exercise tolerance several months after moderate PE.\(^1^,\)\(^7^9\)

Two ongoing studies are being conducted in Europe to test the effect of fibrinolysis with tenecteplase versus placebo on in-hospital and intermediate-term adverse outcomes. The first trial is primarily designed to test the effect of tenecteplase versus placebo, adjunctive to unfractionated heparin, on the rate of short-term hemodynamic collapse (ClinicalTrials.gov identifier NCT00639743). A second trial initiated by one of the authors is testing the effect of tenecteplase versus placebo on the frequency of symptomatic right ventricular dysfunction at 3 months follow-up (ClinicalTrials.gov identifier NCT00680628).

Consistent with recommendations from 3 published clinical guidelines,\(^8\)\(^,\)\(^9\)\(^,\)\(^1^1\) the authors recommend that clinicians strongly consider administering

<table>
<thead>
<tr>
<th>Table 4 Criteria for Categorizing Patients With Acute Pulmonary and Associated Treatment Options</th>
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<tr>
<td>Category</td>
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| Low-risk | Systolic blood pressure > 90 mm Hg at all times and all of the following:  
• Shock index < 1  
• \(\text{SaO}_2\) almost always > 94%  
• Normal electrocardiogram (or Daniel score < 3)  
• Normal troponin and BNP or proBNP  
• PESI score < 66 | • Begin low-molecular-weight heparin  
• Optional admission to unmonitored regular bed  
• Consider outpatient treatment if adequate compliance and follow-up can be assured |
| Moderate-risk | Systolic blood pressure > 90 mm Hg at all times and any one of the following:  
• Shock index \(\geq 1\) at any time  
• \(\text{SaO}_2\) persistently < 94%  
• Electrocardiogram showing any signs of pulmonary hypertension (tachycardia, S1Q3T3, or incomplete RBBB)  
• Elevated troponin or BNP or proBNP  
• PESI score > 65  
• Echocardiography with any degree of right ventricular hypokinesis | • Begin heparin treatment  
• Fibrinolytics in the minority of cases  
• Admission to a telemetry bed |
| More severe (submassive) moderate-risk | Appearance of at least moderate distress AND:  
• Shock index > 1 and severe right ventricular hypokinesis on echocardiography  
• Worsening electrocardiogram, such as S1Q3T3 and a new incomplete RBBB or progression of incomplete to complete RBBB, or development of T-wave inversion in V1–V3  
• \(\text{SaO}_2\) < 90% and the serum troponin clearly elevated or BNP and troponin elevated | • Begin heparin treatment  
• Fibrinolytic treatment in most patients without contraindications in the emergency department  
• Admission to a step-down or intensive care unit |
| High-risk (major) | Any systolic blood pressure < 90 mm Hg or < 20 mm Hg below documented baseline and appearance of distress  
Any persistent systolic blood pressure < 90 mm Hg regardless of appearance | • Begin heparin treatment  
• Fibrinolytic treatment in the emergency department in all patients without contraindications  
• Admission to intensive care unit |

Abbreviations: BNP, brain natriuretic peptide; PESI, Pulmonary Embolism Severity Index; proBNP, prohormone of brain natriuretic peptide; RBBB, right bundle branch block; \(\text{SaO}_2\), percentage of oxygen saturation of arterial blood.
alteplase to patients with submassive PE who have no contraindications to fibrinolysis and any of the following findings: 1) a systolic blood pressure less than 90 mm Hg, even if transient, 2) biomarker evidence of right ventricular dysfunction, including either of 2 biomarkers positive (e.g., BNP > 90 pg/mL or troponin elevated per local threshold), or 3) an echocardiogram with any degree of right ventricular hypokinesis. Unavailability of echocardiography is not a reason to withhold fibrinolysis.

High-risk PE (also known as severe or major PE) occurs in the setting of hypotension. Any patients with high-risk PE require heparin anticoagulation, ICU monitoring, and the strongest consideration for fibrinolysis. Low-molecular-weight heparin has a longer half-life and its anti–factor Xa activity is only approximately 50% reversible with protamine, and therefore many clinicians use unfractionated heparin in these patients as a presumed safety measure. The activated partial thromboplastin time (aPTT) may not be accurate shortly after infusion of a fibrinolytic agent. Anti–factor Xa activity level gives a more accurate measure of heparin’s therapeutic activity under these circumstances. The same is true for low-molecular-weight heparin, which does not affect the aPTT.

Regardless of the choice of heparin product, patients with high-risk or severe PE and no hard contraindications should be treated with fibrinolysis. Absolute contraindications to fibrinolysis include any history of hemorrhagic stroke, a history of ischemic stroke within the previous year, brain metastasis, prior intraocular hemorrhage, head trauma causing loss of consciousness within the past week, recent or active gastrointestinal bleeding, chest or abdominal surgery within the previous 2 weeks, surgery on the brain or spinal canal within the previous month, or allergy to alteplase. Standard of care would allow fibrinolysis to be delayed or omitted if the patient exhibits evidence of marked clinical improvement and has a relative contraindication to fibrinolysis. In the author’s experience, the most common relative contraindications to fibrinolytic therapy include age older than 80 years; advance directives, including a do not resuscitate order; trauma incurred because of recent syncope or seizure-like presentation (facial trauma, epistaxis, and tongue bites); current warfarin use with an International Normalized Ratio greater than 1.7; anemia or thrombocytopenia; metastatic cancer without known brain metastases; current menstruation; recent childbirth; and remote or vague history of stroke or gastrointestinal bleeding.

Fibrinolytic Agents
The most extensively studied fibrinolytic is alteplase, and the FDA-cleared protocol specifies dosing of 100 mg over 2 hours. If unfractionated heparin is used, no controlled clinical data have indicated whether it should be continued or discontinued during alteplase infusion. Based on observations from in vitro experiments, the local action of plasmin on fibrin and fibrinogen in the absence of thrombin inhibition can actually increase clot size. Consequently, the author prefers continued infusion of heparin with a goal aPTT of between 2 and 2.5 times control.

Unsuspected or Incidentally Discovered PE
Incidentally discovered PE has been reported in approximately 1.5% of contrast-enhanced CT scans that include the pulmonary arteries (CTPAs). One large study restricted to patients with cancer estimated the frequency of incidental PE on staging CT scans to be 2.5%. It has been suggested that this finding has increased partly because of enhanced detection of subsegmental PE with multirow detector CT. Although it might seem intuitive that most patients with unsuspected PE would be low-risk, no published data have supported that assertion. However, O’Connell et al. found that in 70 patients with cancer who had unsuspected PE, 53 (75%) had proximal PE. Moreover, 75% of cancer patients with unsuspected PE actually have symptoms of PE, suggesting that the radiological findings were not spurious. The 6-month mortality rate for patients with proximal unsuspected PE was twice that of patients with no PE or with subsegmental PE. These data indicate that not all unsuspected PEs are benign, and that all patients with unsuspected or incidentally discovered PE should be risk stratified the same as those diagnosed with PE based on clinical suspicion.

Other Advanced Treatments
Catheter embolectomy or fragmentation and surgical embolectomy can be considered for patients who have...
proximal PE (lobar or larger arteries) and contraindications to systemic fibrinolysis, or patients whose condition worsens despite administration of fibrinolysis. The primary deterrent to using catheter-based deployment of fibrinolysis versus systemically administered fibrinolysis comes from the only randomized trial comparing the methods and found no differences in hemodynamic or clinical outcomes and a trend toward more adverse events with catheter treatment.\(^8,9\) However, this study was conducted using antiquated catheters. Commercially available catheters use at least 4 methods to recannulate pulmonary arteries: suction, mechanical fragmentation, rheolytic fragmentation, and ultrasonic fragmentation with intrathrombus injection capability. During catheter embolectomy, patients must have a 6F or larger sheath placed in a femoral vein, must be systemically anticoagulated with heparin or bivalirudin, and will receive several hundred milliliters of iodinated contrast; additionally, operators often inject a fibrinolytic agent into the pulmonary artery to assist with clot removal.

The Greenfield suction embolectomy catheter (Medi-tech/Boston Scientific, Natick, Massachusetts) was introduced in 1969 and remains the only FDA-approved device. Thrombus fragmentation has been performed using a pigtail rotational catheter\(^8,9\) and a more recently developed catheter that uses an impeller blade to macerate the thrombus (Amplatzr vascular plug, AGA Medical, Plymouth, Minnesota). Rheolytic thrombectomy catheters inject a high-velocity jet of saline from a central port to disrupt and shear the thrombus into pieces that can be suctioned via the Venturi effect into a separate lumen within the catheter.\(^9\) Commercially available rheolytic catheters include the AngioJet (MEDRAD, Warrendale, Pennsylvania), Hydrolyser (Cordis, Miami, Florida), and Oasis (Medi-tech/Boston Scientific). The fourth category of function is achieved using the Ekos EkoSonic Endovascular System (EKOS Corporation, Bothell, Washington), which has been approved for clinical use in Europe. Advantages of this device may include a reduced dose of intrapulmonary alteplase and less associated bleeding.\(^10\) All catheters have an increased risk of cardiac or great vessel perforation, and a theoretical risk of intrapulmonary hemolysis, which can cause acute pulmonary vasoconstriction. Despite the data from the 1988 randomized trial, many case series have reported more than 90% clinical success with catheter-based treatment, and many experts believe catheter embolectomy should be considered for patients who have contraindications to systemic fibrinolysis or whose condition worsens despite its use.\(^8\)

Fewer data are available regarding surgical embolectomy. The surgical embolectomy was first reported by Trendelenburg in 1908, and since then the literature describing its efficacy is limited to case reports and case series.\(^9\) Surgical embolectomy has requirements that may not be tenable for all patients or hospitals: 1) the patient must be systemically anticoagulated, 2) a thoracic surgeon must be available and willing to do the operation, and 3) an operating theater and anesthesiology team that can provide cardiopulmonary bypass must be available. Pooled data from 46 case series comprising 1300 patients found a mortality rate of 30% associated with surgical embolectomy for PE.\(^9\) Surgical embolectomy should be considered as a rescue therapy for patients with limited comorbidity with hypotension refractory to systemic fibrinolysis.\(^8\)

**Summary**

Risk stratification derives from clinical judgment together with physical examination, biomarkers (BNP, proBNP, and troponin), and echocardiographic features. With these data, patients with PE can be stratified into 1 of 3 risk groups. Patients without respiratory distress, near-normal vital signs, negative biomarkers, and a PESI score of less than 66 are at low risk for complications and can be managed with standard anticoagulation initiated in a nonmonitored bed or at home. Patients without hypotension but with an elevated biomarker or abnormal echocardiogram are at moderate risk and require at least telemetry monitoring with consideration of systemic fibrinolysis. Patients with hypotension and no contraindications should receive fibrinolysis for PE. Patients with cancer and incidentally discovered, unsuspected PE should be risk stratified and treated the same way. Patients with cancer and PE have a particularly poor prognosis, and decisions regarding management of their thromboembolic disease must be consistent with the goals of therapy for their underlying malignancy. Patients being treated with curative intent would benefit more from following the risk stratification guidelines described earlier than those undergoing palliative therapy for metastatic disease.
Kline and Miller

References


Risk Stratification for Acute Pulmonary Embolism


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