# Pulmonary Embolism

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*The natural history of pulmonary embolism (PE) is incompletely characterized, because most episodes of PE go undetected, the clinical presentation mimics so many other common and uncommon diseases, the sensitivity and specificity of the diagnostic tests are poorly defined, and even detection at autopsy is difficult and requires close examination of the pulmonary arteries. Yet PE is a significant cause of morbidity and mortality in the hospitalized patient, and one reason for its extremely high incidence is the failure of physicians to provide adequate prophylaxis to patients who are at risk of developing venous thromboembolism. The mortality rate for PE is less than 8% when the condition is recognized and treated correctly but approximately 30% when untreated. Pulmonary arteriography is still the gold standard in diagnosing pulmonary emboli, but several other imaging modalities have been used to diagnose pulmonary emboli in recent years, including transthoracic and transesophageal echocardiography, magnetic resonance angiography, spiral computerized tomography, and ventilation-perfusion lung scanning. The treatment modality chosen depends directly on the clinical presentation of the patient. Low molecular weight heparin may be equal or superior in efficacy to unfractionated heparin for the treatment of deep venous thrombosis and PE. Thrombolytic therapy can be considered for patients with hemodynamic instability, those with right ventricular dysfunction, and young patients with a massive PE despite a normal right ventricle on echocardiography. In those patients who cannot receive anticoagulation therapy or thrombolysis, or who remain at high risk, an inferior vena cava filter should be placed.*

[Rev Cardiovasc Med. *2002;3(suppl 2):S68–S75*]

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**Key words:** Deep venous thrombosis • Pulmonary embolism • Prophylaxis • Pulmonary arteriography • Thrombolytic therapy

Deep venous thrombosis (DVT) and pulmonary embolism (PE) remain significant causes of morbidity and mortality in the hospitalized patient. It is estimated that approximately 650,000 patients develop PE each year, and in up to 70% of the cases, the diagnosis is not made antemortem. The natural history of PE is incompletely characterized because most episodes of PE go undetected, the clinical presentation mimics so many other common and uncommon diseases, the sensitivity and specificity of the diagnostic tests are poorly defined, and even detection at autopsy is difficult and requires close examination of the pulmonary arteries.

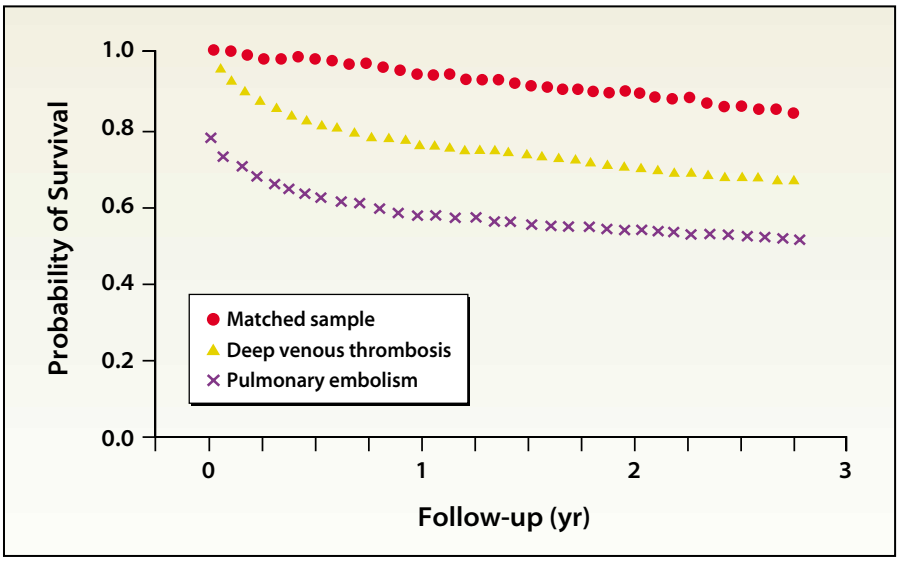


**Figure 1.** *Survival of Medicare enrollees with deep venous thrombosis or pulmonary embolism and a sample of Medicare enrollees matched for age, gender and race. Reproduced, with permission, from Kniffin et al.*[3]

Venous thromboembolic disease is the third most common cardiovascular disease after ischemic coronary heart disease and stroke. The mortality rate for PE is less than 8% when the condition is recognized and treated correctly but approximately 30% when untreated. In 1987, 77% of all of the patients who died at the Malmö General Hospital underwent a postmortem examination. Venous thromboembolism was present in 35% and PE in 26% of all deaths. The PE was the cause of death in 9.4% and contributed to the death in another 9.1% of patients.[1]

Carson and colleagues prospectively studied the natural history of 399 patients with PE, of whom 95 patients (24%) died. The in-hospital mortality was 9.5%, and the 1-year mortality was approximately 24%. The most common causes of death were malignancy, infection, and cardiac or pulmonary disease. PE caused only 10.5% of the deaths.[2] Figure 1 shows a survival curve for patients with DVT and PE compared to aged-matched controls.[3]

*Clinical presentation mimics so many other common and uncommon diseases.*

One of the reasons for this extremely high incidence of PE is the failure of physicians to provide adequate prophylaxis to patients who are at risk of developing venous thromboembolism. Anderson and associates[4] evaluated the pattern of prophylaxis in 16 hospitals. Only 9%–56% of *high-risk* patients received adequate prophylaxis. Appropriate prophylaxis was administered more often in teaching hospitals than nonteaching hospitals (44% vs 19%; $P < .001$). In a recent editorial, Schafer stated emphatically that "the lethal complication of deep-vein thrombosis is pulmonary embolism. Since about 80% of patients who die of pulmonary embolism succumb within 2 hours of the onset of symptoms, intervention must focus on prevention."[5]

Of those patients who develop a PE, 90% have a DVT in the lower extremities as a source. PE may also occur in patients with upper-extremity venous thrombosis secondary to either thoracic outlet syndrome or indwelling central venous catheters. Other less common sites of thrombosis (right heart, inferior vena cava, renal veins, hepatic veins) may also lead to PE.

## Clinical Presentation and Diagnosis of Pulmonary Embolism

The signs and symptoms of PE are nonspecific and may mimic those found in other diseases. Stein and colleagues[6] compared the symptoms and signs in 117 patients who had angiographically documented PE with 248 patients who had no PE on pulmonary angiography (Tables 1 and 2). Based on the signs and symptoms, there is no way to differentiate those patients who had PE from those who did not. The classic triad of dyspnea, pleuritic chest pain, and hemoptysis occurred infrequently. PE presented with syncope approximately 14% of the time. PE must be differentiated from myocardial infarction, exacerbations of chronic obstructive pulmonary

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**Table 1**
**Symptoms of Acute Pulmonary Embolism**
**(No Pre-Existing Cardiac or Pulmonary Disease)**

| Symptom | Pulmonary Embolism (n = 117) | No Pulmonary Embolism (n = 248) |
|---|---|---|
| Pleuritic pain | 77 (66%) | 146 (59%) |
| Cough | 42 (37%) | 89 (36%) |
| Leg swelling | 33 (28%) | 55 (22%) |
| Leg pain | 30 (26%) | 60 (24%) |
| Hemoptysis | 15 (13%) | 20 (8%) |
| Palpitations | 12 (10%) | 44 (18%) |
| Wheezing | 10 (9%) | 28 (11%) |
| Angina-like pain | 5 (4%) | 15 (6%) |
| Pleuritic pain | 77 (66%) | 146 (59%) |

Data from Stein et al.[6]

disease, pneumonia, asthma, congestive heart failure, primary pulmonary hypertension, pneumothorax, malignancy, aortic dissection, anxiety, and musculoskeletal chest pain.[7]

A chest radiograph, electrocardiogram, and arterial blood gases are useful in ruling out other diseases, but these tests may show any number of nonspecific abnormalities or may be completely normal even in the presence of a significant PE. A chest x-ray should be obtained to search for pneumothorax, pneumonia, or malignancy. An electrocardiogram should be obtained to assess the cardiac rhythm and exclude acute myocardial infarction or pericarditis. The arterial blood gases may be especially misleading because it is possible to have a large PE with a completely normal $PO_2$ and/or A-a oxygen gradient on room air. In an editorial entitled "Diagnosis of Pulmonary Embolism (When Will We Ever Learn?)," Robin and McCauley stated: "In the present study in *Chest*, it is demonstrated conclusively that about 20% of patients with angiographically documented pulmonary embolism have a normal $P(A\text{-}a)O_2$ tension difference. Using a normal difference to exclude pulmonary embolism would lead to a large number of false negatives."[8]

These studies underscore the fact that one cannot rely on the arterial blood gases to rule in or rule out PE. Arterial blood gases should be obtained to determine the degree of hypoxemia present and to determine if supplemental oxygen is indicated.[6]

There has been a paradigm shift in how patients with PE are evaluated. In the past, a six-view ventilation and perfusion lung scan (anterior, posterior, right lateral, left lateral, right posterior oblique, and left posterior oblique) would be the imaging study first obtained. The lung scan is particularly helpful if there is completely normal perfusion, thus excluding the diagnosis of PE. Also, if the scan is high probability, then 87% of the time the patient does in fact have an acute PE.[9] The patient should be treated based on a high-probability lung scan as long as there are no contraindications to

**Table 2**
**Signs of Acute Pulmonary Embolism**
**(No Pre-Existing Cardiac or Pulmonary Disease)**

| Sign | Pulmonary Embolism (n = 117) | No Pulmonary Embolism (n = 248) |
|---|---|---|
| Tachypnea (20/min) | 82 (70%) | 169 (68%) |
| Rales | 60 (51%) | 98 (40%)* |
| Tachycardia (> 100/min) | 35 (30%) | 59 (24) |
| $S_3$ or $S_4$ | 31 (27%) | 44 (17%) |
| Increased $PO_2$ | 27 (23%) | 3 (13%)* |
| Deep venous thrombosis | 13 (11%) | 27 (11%) |
| Diaphoresis | 13 (11%) | 20 (8%) |
| Temperature > 38.5°C | 8 (7%) | 29 (12%) |
| Wheezes | 6 (5%) | 21 (8%) |
| Homan's sign | 5 (4%) | 6 (2%) |
| Pleural friction rub | 3 (3%) | 6 (2%) |

*$P$ = .05.
Data from Stein et al.[6]

the use of anticoagulants. In the Prospective Investigation of PE Diagnosis (PIOPED) study, only 42% of patients with a pulmonary embolus had a high-probability scan. It is important to remember that a low-probability or intermediate-probability scan does not exclude the diagnosis of PE. In the PIOPED study, 14% of patients with low-probability scans had pulmonary emboli demonstrated on pulmonary arteriography.[9]

The difficulty lies in patients with a low-probability, indeterminate, or nondiagnostic lung scan. If the lung scan is nondiagnostic, a duplex ultrasound of the leg veins can be obtained. If the duplex is negative, then serial duplex scans can be performed, and treatment can be withheld. However, if there is still a strong clinical suspicion, a pulmonary arteriogram can be performed. Pulmonary arteriography is still the gold standard in diagnosing pulmonary emboli. In the PIOPED study, the death rate associated with pulmonary arteriography in 1101 patients was 0.5%.[10] The overall major complication rate was 1.3%, illustrating that pulmonary arteriography is a safe and effective means to diagnose pulmonary emboli in patients in whom the diagnosis is unclear.

Several imaging modalities have been used to diagnose pulmonary emboli in recent years. Transthoracic echocardiography may demonstrate one or more of the following:

- Right ventricular dilatation and/or hypokinesis;
- Interventricular septal flattening and paradoxical motion;
- Tricuspid valve regurgitation;
- Pulmonary artery dilatation;
- Decrease in inspiratory collapse of the inferior vena cava.

Pruszczyk and colleagues[11] demonstrated that transesophageal echocardiography (TEE) was a highly sensitive and specific test to diagnose pulmonary emboli. TEE showed unequivocal (20 patients) or suspected (3 patients) intraluminal thrombi in 88.5% of 26 patients with pulmonary emboli. The sensitivity of unequivocal pulmonary emboli was 80% and the specificity was 100% (no false positives). TEE is a very useful imaging modality in the critically ill patient with unexplained hypotension or hypoxemia who is too unstable to transport. TEE can be performed rapidly at the bedside with a high degree of accuracy.

Magnetic resonance angiography (MRA) has been used in some centers. However, it may take a long time to perform, and acutely ill patients may find it difficult to hold their breath. We do not routinely use MRA in the diagnosis of PE.

Many centers now perform spiral computerized tomography (CT) scanning as the first diagnostic imaging test. CT scanning requires the administration of a bolus of contrast and some breath-holding. The positive and negative predictive values were quite good when spiral CT scanning was compared with pulmonary arteriography.[12] The sensitivity and specificity range from 60%–100% and 78%–100%, respectively. Several studies have evaluated the clinical outcome in patients suspected of having a PE and a *negative* spiral CT scan who were not treated. If the CT was negative, there was a 99% chance of a favorable clinical outcome.

There are several pitfalls that can occur with CT scanning: interpretive pitfalls can occur with volume averaging of perivascular tissue, in branching points of vessels, and in vessels with nonvertical orientation. Other problems with interpretation can occur due to breathing artifacts in tachypneic patients and extensive parenchymal opacification from pleural fluid. The pulmonary arteries may not be adequately visualized due to inadequate delay before initiation of imaging (technical or pathologic, ie, upper-extremity DVT or SVC obstruction) or if the scanning delay is too long and there is not enough contrast to visualize the vessels.[12]

D-dimer, the breakdown product of crossed linked fibrin, has been studied in patients with deep venous thrombosis and PE.[13–15] The D-dimer can be measured with a

**Table 3**
**Low Molecular Weight Heparin in the Treatment of Patients with Venous Thromboembolism**

| Study | Recurrent Venous Thromboembolism | Major Bleeding | Death |
|---|---|---|---|
| Columbus Investigators[21] | | | |
| Low molecular weight heparin (n = 510) | 27 (5.3%) | 16 (3.1%) | 36 (7.1%) |
| Unfractionated heparin (n = 511) | 25 (4.9%) | 12 (2.3%) | 39 (7.6%) |
| Simonneau et al[22] | | | |
| Low molecular weight heparin (n = 304) | 5 (1.6%) | 6 (2.0%) | 12 (3.9%) |
| Unfractionated heparin (n = 308) | 6 (1.9%) | 8 (2.6%) | 14 (4.5%) |

**Table 4**
**Reasons to Consider Thrombolysis in Pulmonary Embolism**

1) Acute hemodynamic instability
   a) Reverse abnormal hemodynamics
   b) Lower mortality
2) Reverse acute and subacute right ventricular dysfunction
3) Prevent chronic thromboembolic pulmonary hypertension

bedside finger stick. It is useful in excluding deep venous thrombosis or PE and has a negative predictive value of 91%–96%. However, an elevated D-dimer is not very useful. The positive predictive value of a positive D-dimer is only 30%–56%.

## Treatment of Pulmonary Embolism

The treatment modality chosen depends directly on the clinical presentation of the patient. The acuity and severity of the cardiopulmonary hemodynamics will help to determine what therapy is most appropriate in an individual patient. Once the diagnosis of PE is considered, a bolus of heparin or low molecular weight heparin (LMWH) should be administered as long as there are no contraindications to anticoagulation. If the patient is to be treated with unfractionated heparin, a heparin drip should then be started. Both unfractionated heparin (80 U/kg bolus and 18 U/kg/hr)[16] and LMWH (1 mg/kg every 12 hr subcutaneously or 1.5 mg/kg daily subcutaneously for enoxaparin)[17] should be administered based on body weight. After anticoagulant therapy has been started, the patient should then undergo the necessary diagnostic test(s) to rule PE in or out. There should be an overlap of 4–5 days of both heparin (or LMWH) and warfarin.[18] Warfarin should be continued for at least 6 months,[19] and some investigators suggest treating the patient for a longer period of time.[20]

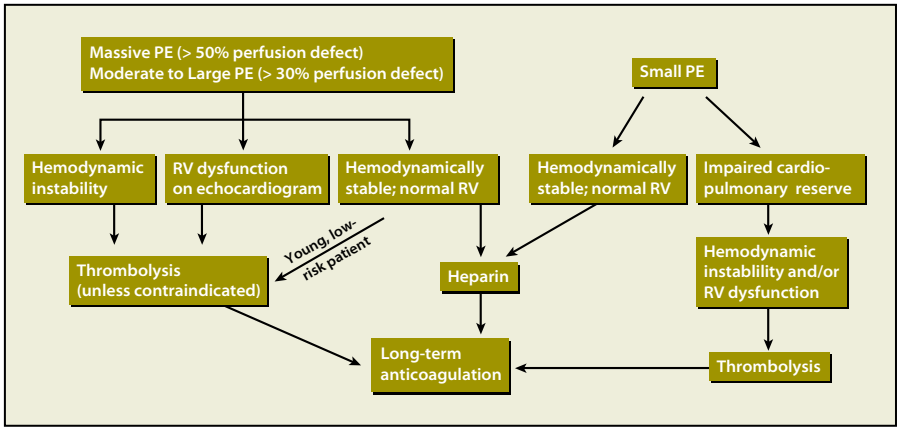
Several studies have demonstrated that LMWH is equal in efficacy to unfractionated heparin for the treatment of DVT and of PE.[17,21,22] Table 3 shows the rate of recurrent venous thromboembolism, bleeding, and death in two studies comparing LMWH to unfractionated heparin. The LMWHs have a more predictable dose–response curve than does unfractionated heparin. In addition, no monitoring is needed in most patients, and therapy can be administered on an outpatient basis in the clinically stable patient. However, the cost of LMWH is significantly higher than unfractionated heparin.

Thrombolytic therapy has proven to be a useful therapeutic modality in patients with pulmonary emboli. There are three major reasons to consider administering thrombolytic therapy (Table 4). We advocate the use of thrombolytic therapy for patients with hemodynamic instability and those with right ventricular dysfunction. Thrombolytic therapy would also be considered in young patients with a massive PE despite a normal right ventricle on echocardiography.[23–25] An algorithm for the treatment of patients with acute PE is shown in Figure 2.

The streptokinase/urokinase PE trials have shown that thrombolytic therapy successfully decreased pulmonary artery pressures acutely and that there was improvement in the lung scan and arteriogram at 12 and 24 hours. There was no overall decrease in mortality in those patients who received thrombolytic agents compared with those who received heparin therapy.[26,27] However, these studies were not powered to assess mortality. Figure 3 shows a representative pulmonary arteriogram prior to the administration of urokinase and 2 and 24 hours after urokinase administration.

Goldhaber and colleagues[28] performed a randomized, controlled trial comparing tissue plasminogen activator with urokinase in the treatment of acute PE. This initial study, which compared 100 mg of recombinant tissue plasminogen activator (rt-PA) with 4400 U/kg/hr of urokinase, determined that rt-PA was more effective in the short term (2 hours) compared with urokinase.

**Figure 2.** *Treatment of acute pulmonary embolism. Data from Wolfe et al,[23] Lualdi et al,[24] Olin JW.[25]*



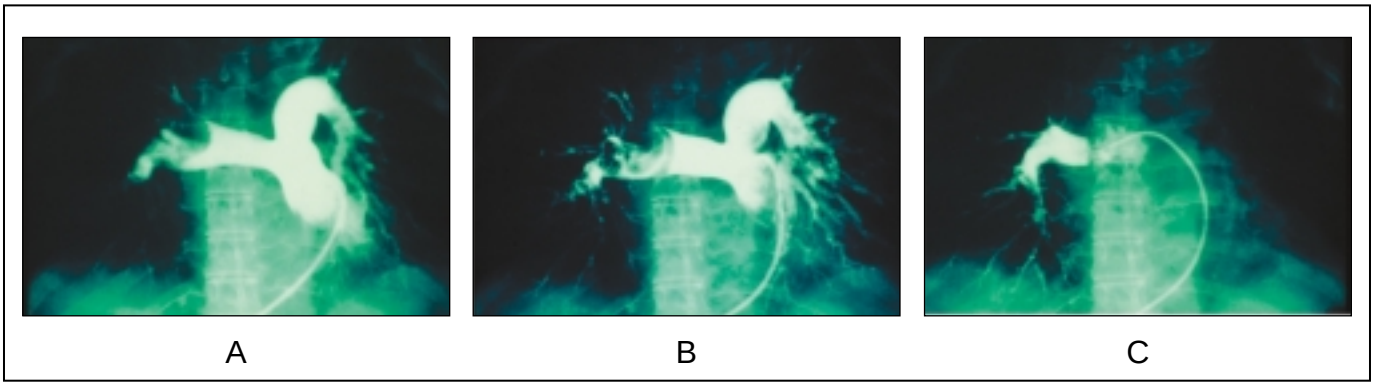



**Figure 3. (A)** *Pulmonary angiogram demonstrating an acute massive pulmonary embolism in the right main pulmonary artery. Urokinase was administered at a dose of 4400 U/kg loading and 4400 U/kg/hr.* **(B)** *The thrombus is beginning to lyse after 2 hours of urokinase administration.* **(C)** *The main pulmonary artery is patent 24 hours later. There is a small amount of residual thrombus in the artery supplying the right lower lobe.*

The dosage between these two drugs was not really comparable. Several years later, Goldhaber and colleagues compared 100 mg of rt-PA with 3 million units of urokinase.[29] One million units of urokinase were given initially as a bolus over 10 minutes, and the remaining 2 million units were given over the next 2 hours. Both drugs were delivered via a peripheral vein. There was no difference in the quantity of thrombolysis at 2 hours or in the improvement in the perfusion lung scan at 24 hours in patients randomized to urokinase or tissue plasminogen activator. Both drugs were equally effective, and the side-effect profile was similar. Several studies have shown that bolus rt-PA therapy (0.6 mg/kg, not to exceed 50 mg) was equally as effective as the standard dose of 100 mg of rt-PA infused over 2 hours.[30,31]

Bleeding is the major complication of thrombolytic therapy, and intracranial bleeding is the most devastating. The incidence of intracranial bleeding in 14 studies using rt-PA was 2.1%. The major bleeding rate is clearly higher in those who underwent pulmonary angiography, ranging from 11% to 20%. The intracranial bleed rate is higher in the elderly and in patients with poorly controlled hypertension. Prior to the initiation of thrombolytic therapy, the blood pressure should be well controlled. Patients should be well informed of this potentially fatal complication. Avoiding invasive procedures prior to the initiation of thrombolysis can lessen bleeding. If a pulmonary angiogram has been obtained, the catheter or sheath should be left in place until thrombolysis is complete.

Echocardiography may be useful in the diagnosis of pulmonary emboli and can help to determine to what degree the pulmonary embolus is causing impairment in right ventricular function. A prospective, randomized trial comparing heparin therapy with intravenous rt-PA (100 mg over 2 hours) demonstrated that rt-PA was superior to heparin in reversing right ventricular dysfunction after an acute pulmonary embolus (Table 5).[32]

The Management and Prognosis of Pulmonary Embolism Registry (MAPPET) studied patients with right heart failure and/or pulmonary hypertension and demonstrated that death and recurrent PE occurred much less frequently in those patients who underwent thrombolysis.[33] However, the major bleeding complication rate was 22% in those receiving thrombolysis and 7.8% in those who received only heparin (Table 6). In addition, intracranial bleeding occurred in 1.2% of patients receiving thrombolysis and 0.4% in those treated with heparin.

In the International Cooperative Pulmonary Embolism Registry (ICOP-

**Table 5**
**rt-PA Versus Heparin in Acute Pulmonary Embolism (Right Ventricular Function at 24 Hours)**

| | Echocardiographic Results | |
|---|---|---|
| | **Improved** | **Worsened** |
| rt-PA (n = 18) | 89%* | 6% |
| Heparin (n = 18) | 44%* | 28% |

*$P$ = .03
rt-PA, recombinant tissue plasminogen activator.
Data from Goldhaber.[32]

ER), 2454 consecutive eligible patients with acute PE were registered from 52 hospitals in 7 countries in Europe and North America.[34] This registry demonstrated that the total mortality at 3 months was 17.4%. The mortality for patients who were hemodynamically stable (n = 2182) was 15.1% at 3 months, and the mortality for the unstable patient (n = 103) was 58.3%. The mortality was 11% at 2 weeks and 15% at 3 months for the 263 patients with a normal right ventricle, whereas the mortality was 21% and 23% at 2 weeks and 3 months, respectively, for the 428 patients with right ventricular dysfunction.

A serious complication of PE is the development of chronic thromboembolic pulmonary hypertension.[35] Thrombolytic therapy can help prevent this complication. A small series showed that at 7 years pulmonary artery pressure and pulmonary vascular resistance were lower at rest and after exercise in patients receiving thrombolysis compared to those treated only with anticoagulation.[36] This may be important, because 25% of patients demonstrate unresolved PE on repeat lung scans, and at least some of these individuals may go on to develop chronic thromboembolic pulmonary hypertension. The subset of patients who do go on to develop chronic thromboembolic pulmonary hypertension may require a pulmonary thromboendarterectomy or else will die of right-sided heart failure. The pulmonary thromboendarterectomy is performed via a median sternotomy and cardiopul-

**Table 6**
**MAPPET Registry: Right Heart Failure and/or Pulmonary Hypertension**

| In-Hospital Event | Thrombolysis (n = 169) | Heparin (n = 550) | *P* Value |
|---|---|---|---|
| Death | 4.7% | 11.0% | .016 |
| Death from PE | 4.1% | 10.0% | – |
| Recurrent PE | 7.7% | 19.0% | <.001 |
| Major bleeding | 22.0% | 7.8% | <.001 |
| Intracranial bleed | 1.2% | 0.4% | – |

PE, pulmonary embolism.

## Main Points

- The mortality rate for pulmonary embolism (PE) is less than 8% when the condition is recognized and treated correctly, but approximately 30% when untreated.
- Thrombolytic therapy has proven to be a useful therapeutic modality in patients with pulmonary emboli.
- Of those patients who develop PE, 90% have a deep venous thrombosis in the lower extremities as a source; PE may also occur in patients with upper-extremity venous thrombosis secondary to either thoracic outlet syndrome or indwelling central venous catheters.
- The streptokinase/urokinase PE trials have shown that thrombolytic therapy successfully decreased pulmonary artery pressures acutely and that there was improvement in the lung scan and arteriogram at 12 and 24 hours.
- Based on signs and symptoms, there is no way to differentiate those patients who have PE from those who do not. The classic triad of dyspnea, pleuritic chest pain, and hemoptysis occur infrequently.
- The Management and Prognosis of Pulmonary Embolism Registry (MAPPET) studied patients with right heart failure and/or pulmonary hypertension and demonstrated that death and recurrent PE occurred much less frequently in those patients who underwent thrombolysis.
- Once a diagnosis of PE is considered, a bolus of heparin or low molecular weight heparin should be administered as long as there are no contraindications to anticoagulation.
- Thrombolytic therapy should be considered for patients with hemodynamic instability, those with right ventricular dysfunction, and young patients with a massive PE despite a normal right ventricle on echocardiography.
- Thrombolytic therapy can help prevent chronic thromboembolic pulmonary hypertension secondary to PE. A small series showed that at 7 years, pulmonary artery pressure and pulmonary vascular resistance were lower at rest and after exercise in patients receiving thrombolysis compared to those treated only with anticoagulation.

monary bypass, hypothermia, and cardioplegia. Pulmonary artery pressures are often decreased after surgery (mean decrease 65%) and the functional class improved. Surgeons from the University of California, San Diego, operated on 457 patients from 1997–2000.[37] The mean pulmonary artery pressure decreased from 877 + 452 dyn·sec·cm–5 preoperatively to 267 + 192 dyn·sec·cm–5 postoperatively. The operative mortality was 7%.

Thrombolytic therapy should not be used in patients with active internal bleeding or a recent stroke (less than 2 months). It also should not be used in patients who have an intracranial process such as neoplasm or abscess. Relative contraindications include recent surgery or organ biopsy (10 days), uncontrolled hypertension, and pregnancy. The major complication associated with thrombolytic therapy is bleeding, and this can be minimized by careful patient selection and avoidance of invasive procedures. Vessels that cannot be directly compressed should not be invaded.

For various reasons, some patients cannot receive anticoagulation therapy or thrombolysis. In these individuals, an inferior vena cava filter should be placed. The indications for inferior vena cava interruption include: prophylaxis against recurrence after a massive PE; contraindication to anticoagulation in a patient with deep venous thrombosis or PE; major complication with anticoagulation; and/or recurrence of PE despite adequate anticoagulation and patients at increased risk of bleeding (elderly, dementia, seizures, alcohol or drug abuse). ■

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