

# Thrombolytic Therapy for Acute Pulmonary Embolism\*

### A Critical Appraisal

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Pulmonary embolism (PE) is a prevalent condition that may account for > 300,000 deaths annually in the United States alone. Although thrombolytics have been studied as a treatment for acute PE since the 1960s, to date there have been only 11 randomized controlled trials comparing thrombolytic therapy to conventional anticoagulation, and the numbers of patients included in these trials has been small. Many studies confirm that thrombolytic therapy leads to rapid improvement in hemodynamic aberrations associated with PE, and this approach to massive PE with cardiogenic shock is a guideline-based practice. It is widely accepted that acute PE without associated right ventricular (RV) dysfunction or hemodynamic instability can be readily managed with standard anticoagulation. The appropriate therapy for submassive PE (PE associated with RV dysfunction but preserved systemic arterial BP) remains an area of contention, and definitive data proving mortality benefit in this setting are lacking. Further efforts at risk stratification may better determine who is in need of aggressive therapy. This article reviews historical aspects of and current evidence for thrombolytic therapy in acute PE with specific attention to bleeding risk, and data regarding hemodynamic parameters and mortality. We also discuss risk stratification techniques and propose a clinical algorithm for the incorporation of thrombolytic therapy. (CHEST 2009; 135:1321-1329)

**Abbreviations:** ACCP = American College of Chest Physicians; BNP = brain natriuretic peptide; CI = confidence interval; CTA = CT angiography; LMWH = low-molecular-weight heparin; OR = odds ratio; PE = pulmonary embolism; rt-PA = recombinant tissue plasminogen activator; RV = right ventricular

A 77-year-old woman with a history of hypertension and left ventricular diastolic dysfunction presented to the emergency department with 1 week of unilateral calf swelling and dyspnea. She denied chest pain, palpitations, hemoptysis, syncope, or known risk factors for venous thromboembolism,

except for her age. Examination revealed a slightly anxious elderly woman who was comfortable at rest but dyspneic with minimal movement. She was afebrile, the pulse was 66 beats/min while receiving  $\beta$ -blocker therapy, the respiratory rate was 22 breaths/min, and the BP, 140/86 mm Hg. The oxygen saturation was 88% on room air. There was no elevated jugular venous pressure, loud S2, or precordial lift. The right lower extremity was swollen from the ankle to the knee. Laboratory evaluation findings were notable for an elevated d-dimer level, a negative troponin T level, and a pro-brain natriuretic peptide (BNP) level that was elevated at 1,608 pg/mL (reference range, < 600 pg/mL). Arterial blood gas measurement revealed a pH of 7.45, PCO<sub>2</sub> of 30 mm Hg, and PO<sub>2</sub> of 59 mm Hg on room air, at rest. The ECG did not show right ventricular (RV) strain. She was placed on oxygen at 2 L/min, and subcutaneous enoxaparin was initiated. A CT angiog-

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raphy (CTA) scan of the chest revealed extensive pulmonary embolism (PE) in the left and right pulmonary arteries with extension into the right upper, right lower, and left lower lobe segmental and subsegmental pulmonary arteries. Ultrasound of the right leg revealed nonocclusive thrombus in the proximal femoral vein. Transthoracic echocardiography demonstrated moderate RV enlargement with hypokinesis. The patient was admitted to the hospital ward where discussions of thrombolytic therapy ensued. As one might anticipate, highly divergent opinions emerged, and there was difficulty reaching a consensus.

This case illustrates the inadequate evidence base and the varied opinions regarding the use of thrombolytic therapy for acute PE. Although PE may be responsible for as many as 300,000 deaths per year in the United States, the number of patients included in randomized controlled trials evaluating thrombolytics has been very small.<sup>1,2</sup> To date, only 11 such studies<sup>3–13</sup> have compared thrombolytic therapy to conventional anticoagulation in the treatment of PE. Unfortunately, 1 of these studies did not include mortality data, and only 1 of the 11 was designed and powered to detect a mortality end point.

In stark contrast, thrombolytic therapy was studied in thousands of patients with acute myocardial infarction prior to its acceptance into standard clinical practice.<sup>14</sup> The objectives of this article are to review historical aspects of and current evidence for thrombolytic therapy in patients with acute PE with specific attention to bleeding risk, and to review data regarding hemodynamic parameters and mortality. In addition, attention is given to risk stratification in order to identify patients in danger of deterioration, and a clinical algorithm for the incorporation of thrombolytic therapy into the management of PE is proposed.

#### HISTORICAL ASPECTS

Academic interest in <u>thrombolytic</u> therapy began in the <u>1930s</u> when it was discovered that certain species of  $\beta$ -hemolytic streptococci produce streptokinase and lyse fibrin clots.<sup>15</sup> These properties of streptokinase were further explored in the 1950s when it was infused into rabbits with vascular thrombosis and noted to decrease or eliminate clot burden.<sup>16</sup> This same decade brought the discovery of urokinase by Maurice Guest, a physiologist at the University of Texas. In 1957, Lederle Laboratories manufactured streptokinase, and its first successful use in treating acute myocardial infarction was documented.<sup>15</sup> Throughout the 1960s, several case series reported successful use of both streptokinase and urokinase in canines and, later, in humans with massive PE. In some case series,<sup>17–20</sup> remarkable improvement in pulmonary angiography was noted after the administration of thrombolytics. A study conducted by Hirsh and colleagues<sup>21</sup> in Australia in 1968 involved 21 patients with major PE proven by pulmonary arteriography. Eighteen of the patients were subsequently treated with an IV infusion of streptokinase. Marked angiographic improvement was noted only 24 h after streptokinase infusion with a discernable increase in peripheral pulmonary vascular perfusion. For comparison, three patients were treated with heparin alone. Pulmonary arteriography findings after 24 h of heparin therapy were unchanged from baseline, demonstrating persistent high-grade obstruction of the main, right, and left pulmonary arteries.<sup>21</sup>

By the late 1960s, thrombolytics were established as clinically feasible, and the National Heart and Lung Institute funded the first multicenter randomized controlled trial comparing urokinase therapy to therapy with heparin alone in patients with acute PE. In 1970, this landmark trial, known as the Urokinase in Pulmonary Embolism Trial (or **UPET**), reported an increased PE resolution rate in the thrombolytic group when compared to the group that received heparin alone. Although no survival benefit was noted, patients were not stratified based on the severity of the event.<sup>22</sup> In the late 1970s, recombinant tissue plasminogen activator (rt-PA) was discovered, and from the 1980s to the present day there has been ongoing research into the use of thrombolytic therapy in patients presenting with acute venous thromboembolism VTE.

#### THROMBOLYTIC AGENTS

Thrombolytic agents are IV plasminogen activators that set the fibrinolytic system into motion. They have a high affinity for binding plasminogen, which is bound to plasmin either in the circulation or on the clot surface. When thrombolytic agents bind the plasminogen/plasmin complex, they activate plasminogen and hydrolyze a peptide bond to form free plasmin. Free plasmin in the circulation is rapidly neutralized by the inhibitor  $\alpha$ -antiplasmin; however, fibrin-bound plasmin is protected from this rapid inhibition and hydrolyzes several key bonds within the clot matrix, promoting clot lysis. Agents that preferentially activate plasminogen on the clot surface, such as rt-PA, are considered *fibrin specific*, whereas agents that have no preference, such as streptokinase and urokinase, are appropriately referred to as *nonselective*.<sup>23</sup> In theory, this difference might appear to be advantageous, but no clear clinical benefit has been proven.

Table 1—Thrombolytic Regimens for Acute Pulmonary Embolism

Drugs	Dosing Regimens
Streptokinase	250,000 units over 30 min, then 100,000 units/h over 24 h
Urokinase	4,400 units/kg over 10 min, then 4,400 units/kg/h over 12 h $$
rt-PA	10 mg bolus, then 90 mg over 2 h

Three thrombolytic agents are currently approved by the US Food and Drug Administration for use in patients with acute PE: streptokinase, urokinase, and rt-PA. Early experiences with streptokinase and urokinase indicated efficacy based on rapid thrombolysis. Although streptokinase is cheaper than other agents, it is antigenic, and so recent streptococcal infection and previous exposure to streptokinase place the patient at risk for allergic reactions that may be severe. Table 1 outlines the approved dosing regimens.<sup>24</sup> Tenecteplase is a newer thrombolytic agent, typically given as a single IV bolus, currently being studied for use in PE; however, it is not yet approved for this indication.<sup>25</sup> It is important to note that of the three approved drugs, no definitive studies have proved the superiority of one regimen over another. A 2005 metaanalysis<sup>26</sup> aimed at identifying differences among thrombolytic regimens failed to exhibit any statistically significant differences related to efficacy. Furthermore, the authors<sup>26</sup> concluded that the "paucity of published randomizedcontrolled trials is still too great to enable adequately powered statistical tests to be performed in order to produce definitive conclusions." Despite the lack of data proving superiority, the American College of Chest Physicians (ACCP) guidelines suggest using the thrombolytic regimen with the shortest infusion time, which is currently rt-PA.<sup>27</sup> Reports<sup>5,28</sup> have indicated that thrombolytic therapy for PE may offer the most benefit when given within 48 h of symptom onset, although enhanced clot lysis may be seen when administered up to 2 weeks after the event.

#### <mark>Bleeding</mark> Risk

Certainly, because thrombolytics are IV agents with systemic action they possess the ability to lyse clots anywhere within the vasculature, and thus complications from bleeding, with intracranial hemorrhage being the most feared, become relevant. A number of absolute and relative contraindications to thrombolytic therapy have been proposed to minimize the bleeding risk (Table 2); however, in dire clinical circumstances even absolute contraindica-

Table 2—Proposed	Absolute and Relative
<b>Contraindications</b> to	o Thrombolytic Therapy

Absolute contraindications*	
History of intracranial hemorrhage	
Known intracranial neoplasm, arteriovenous malformation, or	
Significant head trauma	
Active internal bleeding	
Known bleeding diathesis	
Intracranial or intraspinal surgery within 3 mo	
Cerebrovascular accident within 2 mo	
Relative contraindications	
Recent internal bleeding	
Recent surgery or organ biopsy	
Recent trauma, including cardiopulmonary resuscitation	
Venipuncture at noncompressible site	
Uncontrolled hypertension	
High risk of left heart thrombosis	
Diabetic retinopathy	
Pregnancy	
Age > 75 yr	

\*Although absolute contraindications should be carefully assessed, some of these (except concurrent intracranial hemorrhage) might not be "absolute" in the most extreme circumstances of massive PE.

tions may not preclude the use of thrombolytics in the eyes of some clinicians. Pooled data from the 11 randomized trials<sup>3–13</sup> of thrombolytics for acute PE have shown a trend toward increased major hemorrhagic events in the thrombolytic group vs the group that received heparin alone, although this did not reach statistical significance at 9.1% for thrombolytic therapy vs 6.1% for heparin therapy (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.40 to 1.12). Minor bleeding events were significantly increased in the thrombolytic group (22.7% vs 10%, respectively; OR, 2.63; 95% CI, 1.53 to 4.54).<sup>29</sup>

Generalizing the significance of bleeding data beyond the confines of the clinical research setting is limited because clinical trials frequently have strict exclusion criteria, and investigators may be more reluctant to enroll patients with relative contraindications or with significant comorbid illness. <u>Registry</u> data from the International Cooperative Pulmonary Embolism Registry reported<sup>2</sup> that 21.9% of patients who received thrombolytics for the treatment of PE had a major bleeding complication, with 3% demonstrating intracranial hemorrhage, compared with 0.3% in the <u>heparin</u>-treated group. However, the baseline characteristics were not similar between these patient groups.<sup>2</sup> Similarly, Fiumara and colleagues<sup>30</sup> reported a major bleeding rate of 19.2% among patients who received rt-PA for the treatment of acute PE between 1996 and 2004 at Brigham and Women's Hospital. Of these, one patient (5%) had proven intracranial hemorrhage. Thus, it is feasible that the risk of bleeding is higher in such "real-world"

settings than it is in randomized trials that have more strict inclusion criteria involving bleeding risk.

#### Hemodynamic Parameters

After acute PE, a series of ensuing hemodynamic events may occur, including an abrupt increase in pulmonary artery pressure that can precipitate acute RV failure, decreased left ventricular stroke volume, decreased cardiac output, hypotension, decreased organ perfusion, and ultimately cardiac arrest and death. In isolated studies, thrombolytics are associated with rapid and statistically significant improvement in hemodynamic parameters. The Urokinase in Pulmonary Embolism Trial study,<sup>3</sup> for example, demonstrated a significant reduction in pulmonary arterial systolic pressure 24 h after urokinase infusion. Various other studies<sup>3,4,9</sup> have shown that, when compared to heparin alone for the treatment of PE, thrombolytics resulted in significantly reduced mean pulmonary arterial pressures, total pulmonary resistance, and RV end-diastolic pressure as well as a significant increase in cardiac index. One study<sup>11</sup> used echocardiography to evaluate RV wall motion and tricuspid regurgitation in patients with confirmed PE who then received either rt-PA in addition to heparin or heparin alone. The study<sup>11</sup> revealed a rapid, statistically significant improvement in RV wall movement and tricuspid regurgitation at 3 and 24 h after thrombolytic therapy.

It should be noted that many trials<sup>31</sup> have demonstrated a catch-up phenomena in the heparin group, with hemodynamic parameters similar to the thrombolytic group at 1 week of follow-up and beyond. This would indicate that, although thrombolytics may be beneficial for patients at risk for early hemodynamic deterioration, others, particularly those who present for clinical evaluation  $\geq 1$  week after symptom onset, may receive no benefit. Although these findings are provocative, it remains unclear whether improvement in such surrogate, short-term end points is clinically meaningful. Indeed, the medical literature is replete with examples of improvement in a surrogate marker by a given treatment that later, in larger scale trials, fails to translate into improvement in clinically meaningful hard end points.<sup>32</sup> Furthermore, determining which patients are at risk for early hemodynamic deterioration poses an important clinical challenge, as discussed in further detail later.

#### MORTALITY DATA FOR THROMBOLYTIC THERAPY IN ACUTE PE

To date, only 11 randomized controlled trials<sup>3–13</sup> have compared thrombolytic therapy to conventional

unfractionated heparin in the treatment of acute PE. Together, these studies account for < 800 patients. Unfortunately, only 10 of these studies3-5,7-13 include mortality data, and only 1 study<sup>13</sup> was designed and powered to detect clinical end points. Certainly, the most objective clinical end point and the end point most relevant to patient care is mortality. When addressing mortality data from studies examining the administration of thrombolytics for PE, it is fair to divide the relevant data as it applies to three fundamentally different subgroups, as follows: (1) an unselected patient population including both those presenting with shock and those who are hemodynamically stable at the time of presentation; (2) only those presenting with shock; and (3) those who are hemodynamically stable at the time of presentation but have evidence of RV dysfunction (submassive PE). Since the most recent randomized trial comparing thrombolytic therapy with heparin alone, published in 2002 by Konstantanides and colleagues,<sup>13</sup> there has been one metaanalysis<sup>29</sup> and one systematic review<sup>33</sup> aimed at combining data from the various randomized trials in an attempt to better power mortality statistics.

#### Mortality (Unselected PE Patients)

This single metaanalysis<sup>29</sup> included all 11 randomized controlled trials<sup>3–13</sup> published to date (n = 748). Length of follow-up ranged between 72 h and 30 days or "in-hospital." In this unselected PE patient population, pooled data suggested there was no statistically significant difference in survival; the mortality rate was 4.3% in the thrombolytic group and 5.9% in the heparin-only group (OR, 0.70; 95% CI, 0.37 to 1.30).<sup>29</sup> The single Cochrane systematic review<sup>33</sup> included only 8 of the 11 randomized controlled trials published to date (n = 679), citing poor methodological quality, lack of confirmed diagnosis of PE prior to enrollment, and comparison of two thrombolytic dosing regimens as reasons for excluding the remaining three studies.

In an unselected patient population, there were 15 deaths (4.5%) in the thrombolytic group compared with 16 deaths (4.7%) in the heparin group (OR, 0.89; 95% CI, 0.45 to 1.78).<sup>33</sup> Notably, the number of patients randomized and the event rate in both groups were low. Based on current data, administration of thrombolytics to an unselected patient population has not demonstrated a mortality benefit. However, it has been suggested<sup>34</sup> that based on these low adverse event rates, a future trial should include at least 1,000 patients in order to have sufficient power to detect clinical end points.

#### Mortality (Massive PE)

Although it appears that administration of thrombolytics to an unselected patient population presenting with acute PE offers no mortality benefit, certainly those presenting with hemodynamic instability and cardiogenic shock (defined as a systolic  $BP \leq 90$ mm Hg) would, in theory, stand to benefit from the rapid improvement in hemodynamics offered by prompt thrombolysis. The ACCP currently carries a grade 1B level of evidence recommendation in support of thrombolytic administration to hemodynamically unstable patients with acute PE.27 Thus far, only one randomized trial<sup>12</sup> of thrombolytic therapy vs heparin alone included only patients with hemodynamic instability. In this study, eight patients were randomized to a one-time bolus of streptokinase followed by a heparin infusion or heparin infusion alone. The four patients who received streptokinase all survived to 2 years of follow-up; all four patients who received heparin alone died within a few hours of presentation. It should be mentioned that patients in this study<sup>12</sup> did not have a confirmed diagnosis of PE but were only considered to have a high clinical suspicion of the disease.

A subgroup analysis of five randomized trials<sup>29</sup> that included, but was not limited to, patients presenting with cardiogenic shock reported a 6.2% death rate in the thrombolytic group compared to 12.7% in the group that received heparin alone (OR, 0.47; 95%) CI, 0.20 to 1.10). Although there seemed to be a trend toward decreased mortality in the thrombolytic group, this did not reach statistical significance.<sup>29</sup> Was this lack of statistical significance due to an overall low event rate, or is there, in fact, no difference? That question remains to be answered; however, it is highly unlikely that there will ever be another randomized clinical trial performed to answer this question. Despite the lack of a verifiable mortality benefit associated with thrombolytic therapy in patients with massive PE resulting in hemodynamic instability, most clinicians accept this clinical scenario as an indication for thrombolytics and it is guideline based. In this situation, this approach may be lifesaving, and it is considered the standard of care in most institutions. The presence of intracranial bleeding remains the most absolute contraindication.

#### Mortality (Submassive PE)

Although thrombolytics are accepted as the standard of care for patients with hemodynamic instability, a great deal of controversy remains about the benefits of thrombolytic therapy for patients who present with acute PE, are hemodynamically stable, but have echocardiographic or other evidence of RV failure or strain. It is estimated that this clinical scenario describes 40 to 50% of patients presenting with acute PE, and current literature<sup>2,35,36</sup> suggests that these patients may have a higher mortality than those with normal RV function. For example, registry data from the International Cooperative Pulmonary Embolism Registry<sup>2</sup> indicated that patients with RV hypokinesis on echocardiography even in the presence of a normal systemic arterial BP were at a twofold increased risk of death compared to those patients who had normal RV wall motion. Another series<sup>35</sup> of 162 consecutive patients presenting with acute PE reported that 31% had concomitant RV dysfunction that was associated with a 5% mortality rate compared to a 0% mortality rate in those with preserved RV function.

Based on early data suggesting that patients with RV dysfunction are at an increased risk of PEassociated death, Konstantinides and colleagues<sup>13</sup> designed a study that enrolled 256 hemodynamically stable patients (systolic BP > 90 mm Hg) with proven acute PE and evidence of RV dysfunction or pulmonary hypertension. Patients were randomized to receive rt-PA plus heparin or placebo plus heparin with a follow-up period of 30 days. The main outcome measure was a combined end point that included in-hospital death and clinical deterioration requiring escalation of care. Clinical deterioration was defined as worsening symptoms, respiratory failure, hypotension, or shock, and escalation of care was defined as the need for vasopressors, rescue thrombolysis, embolectomy, intubation, or cardiopulmonary resuscitation.

The study results indicated that patients who received rt-PA were significantly less likely to deteriorate clinically and reach the combined clinical end point than those who received placebo (11% vs 25%, respectively; relative risk reduction, 55%; 95% CI, 21 to 75%; number needed to treat, eight). However, the groups did not differ in all-cause mortality with a 3.4% mortality rate in the rt-PA group compared to 2.2% in the placebo group (relative risk increase, 56%; 95% CI, 60 to 513%).<sup>13</sup> The study has been criticized because it allowed treating physicians to break protocol and administer "rescue" thrombolysis if they judged that a patient's clinical condition was deteriorating. The high rate of rescue thrombolysis may have driven the composite end point to statistical significance. As of yet, there is no definitive trial proving the utility or the ineffectiveness of thrombolytics in patients with preserved systemic arterial BP. In the recently published 2008 ACCP recommendations, it is suggested that all PE patients undergo rapid risk stratification (grade 1C). It is suggested that selected high-risk patients without hypotension, judged to have a low risk of bleeding, receive thrombolytic therapy; however, it is given a less

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## Table 3—Selected Thrombolytic Therapy Recommendations From the 2008 American College of Chest Physicians Evidence-Based Guidelines<sup>27</sup>

- 1. All PE patients should undergo rapid risk stratification (grade 1C).\*
- For patients with hemodynamic compromise, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk (grade 1B). Thrombolysis in these patients should not be delayed because irreversible cardiogenic shock may ensue.
- 3. In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy (grade 2B).
- 4. The decision to use thrombolytic therapy depends on the clinician's assessment of PE severity, prognosis, and risk of bleeding.
- 5. In patients with acute PE, when a thrombolytic agent is used, we recommend that treatment be administered via a <u>peripheral</u> <u>vein</u> rather than placing a pulmonary artery catheter to administer treatment (grade 1B).
- 6. In selected highly compromised patients who are unable to receive thrombolytic therapy because of bleeding risk, or whose critical status does not allow sufficient time for systemic thrombolytic therapy to be effective, we suggest use of interventional catheterization techniques if appropriate expertise is available (grade 2C).

\*Grade 1 = strong recommendation; grade 2 = weak recommendation; B = moderate-quality evidence; C = low-quality or very low-quality evidence.

rigorous grade (2B) than that for the hemodynamically unstable patient.<sup>27</sup> Table 3 shows these ACCP thrombolytic recommendations and the grading scheme. Although data using CTA to evaluate RV enlargement suggest that RV size-reconstructed, four-chamber views predict adverse clinical events in patients with acute PE,<sup>37</sup> more thrombolytic trials to date have utilized echocardiography.

#### **RISK STRATIFICATION**

Due to the lack of a definitive trial giving clinicians a clear sense of the management of patients with acute PE in association with RV dysfunction and preserved systemic arterial BP, many have proposed that this patient population be further risk stratified to determine which subgroups may be at the highest risk of clinical deterioration and therefore may benefit the most from more intense monitoring or perhaps even the administration of thrombolytic therapy. One approach, not yet well studied, would be to better delineate degrees of RV enlargement and dysfunction. Another approach has been to utilize biomarkers, including cardiac troponins and BNP. These have emerged as useful prognostic indicators in patients with acute PE.

Cardiac troponins are biomarkers with high sensitivity for myocardial cellular injury.<sup>38</sup> In PE patients, an abrupt rise in pulmonary artery and RV pressures and consequent RV dilation may cause local myocardial ischemic injury, precipitating the release of cardiac troponins into the circulation. Cardiac troponin levels have been found to correlate directly with the extent of RV dysfunction in patients with acute PE, and many studies<sup>39-42</sup> have demonstrated that troponins have a high negative predictive value for in-hospital death associated with acute PE. Thus, a normal cardiac troponin level supports a relatively low risk of clinical deterioration and advocates against more aggressive therapy, such as thrombolytic therapy, in a hemodynamically stable patient. It should be noted that an increase in cardiac troponin concentrations may not occur for 6 to 12 h after symptom onset. Thus, although serial measurements troponin levels may appear to be a useful approach to risk stratification,<sup>40</sup> this practice can be difficult, based on the potential delay.

**BNP** elevation also correlates with degree of RV dysfunction in patients with acute PE and has a high negative predictive value for in-hospital death.<sup>43–46</sup> This hormone is released into the circulation in response to cardiomyocyte stretch. Unlike atrial natriuretic peptide, BNP is produced to a greater degree by ventricular myocytes, thus increasing serum levels of BNP are indicative of increasing ventricular stretch.<sup>38</sup> Unfortunately, the positive predictive value of BNP for PE is quite low, in the range of 12 to 23%.<sup>43–46</sup> Therefore, an elevated BNP level, by itself, is not enough to warrant more aggressive therapy in a hemodynamically stable patient. Additionally, many available studies<sup>43–46</sup> evaluating BNP as a prognostic indicator in patients with acute PE have defined relevant cutoff concentrations in a retrospective fashion, and these concentrations have varied significantly between studies. Thus, pending a prospectively validated cutoff concentration for BNP, cardiac troponin is the preferred biomarker for risk stratification in patients with acute PE.

#### Other Potential Scenarios for Thrombolytic Therapy

There are other clinical situations in which thrombolytic therapy may be beneficial, but these have been inadequately studied. Hemodynamically stable patients with severe hypoxemia sometimes have normal RV function, but very little data exist in these patients with regard to outcome with or without thrombolytic therapy. A survey<sup>47</sup> performed fifteen years ago indicated that a significant proportion (73%) of pulmonologists would, in fact, strongly consider thrombolytics in patients with PE associated with severe hypoxemia. Similarly, the presence of extensive residual thrombus in the lower extremities could be a risk for higher mortality in patients with acute PE, particularly in those patients who already have RV dysfunction, and perhaps thrombolytic therapy would be beneficial in this setting. However, this also remains unstudied and unproven. Future investigations should address these issues.

#### Mode of Delivery of Thrombolytic Therapy

In patients with acute PE, thrombolytic therapy appears to be no more beneficial when administered directly into the pulmonary arteries than when given by peripheral IV administration.<sup>48</sup> It is feasible, however, that direct, intraembolic infusion of thrombolytics into large proximal emboli might be more beneficial than the peripheral route.<sup>49</sup> Again, we are limited by inadequate data. The ACCP has suggested the use of interventional catheterization techniques (if appropriate expertise is available) in selected highly compromised patients who are unable to receive systemic thrombolytic therapy (grade 2C). Finally, bolus delivery of rt-PA has been studied.<sup>50</sup> Goldhaber and associates<sup>50</sup> compared rt-PA administered at 0.6 mg/kg/15 min (maximum, 50 mg) to 100 mg of rt-PA administered as a continuous infusion over 2 h among hemodynamically stable patients with PE in a double-blind, double-dummy, randomized, controlled trial, and 90 patients were randomized. There were no significant differences detected between the two groups with respect to mortality, bleeding complications, adverse clinical events, or imaging studies. At present, the standard dosing regimen of rt-PA delivered > 2 h is recommended, although in settings deemed clinically urgent, more rapid delivery can be considered.

#### A MANAGEMENT ALGORITHM

In light of the available data regarding thrombolytic therapy for acute PE, the following algorithm can be proposed (Fig 1). In patients with massive PE with shock, thrombolytic therapy should immediately be considered; this is a widely accepted recommendation. The diagnosis of cardiogenic shock due to PE and failure of the RV can sometimes be made at the bedside by observing not only hypotension but also clinical signs of poor tissue perfusion, including oliguria, cyanosis, cool extremities, and altered mentation. Acute PE accompanied by hypotension but without evidence of shock is still considered an indication for thrombolytics by many clinicians.<sup>47</sup> Conversely, a hemodynamically stable patient with



FIGURE 1. A proposed algorithm for the consideration of thrombolytic therapy in acute PE. \* = massive PE with shock is the clearest indication for thrombolysis. To some clinicians, "hemodynamically unstable" refers to the presence of hypotension. To many clinicians, hypotension in the setting of acute PE is an indication for thrombolytic therapy. With hypotension, fluids should be administered in this setting and vasopressor therapy initiated when indicated.  $\dagger$  = there is not a universal definition for "RV dysfunction," but in clinical trials in general, any degree of RV dysfunction has sufficed for inclusion. Severe RV enlargement and dysfunction may portend a worse prognosis than mild dysfunction, but few data are available. Although the presence of positive biomarkers should be considered together with other criteria, these tests have not allowed for stratification of groups who will benefit from thrombolysis.  $\ddagger$  = when hypoxemia is severe, requiring very high-flow oxygen, thrombolytic therapy can be considered, although no studies have proved beneficial in this setting. Very extensive clot burden by CTA or ventilation/ perfusion scan, without hypotension or RV dysfunction may also suggest the need for thrombolytic therapy, but no proven mortality benefit has been demonstrated. Finally, extensive residual venous thrombosis in the setting of acute PE may also suggest the potential for increased mortality, but this has not been proven either. In such settings, patients should be carefully individualized. DVT = deep venous thrombosis.

normal RV function or lack of other high-risk features, such as positive cardiac troponin levels, should be readily managed with standard anticoagulation. The management of patients with submassive PE remains an area of controversy; however, steps should be taken to further stratify risk in these patients. Patients with multiple poor prognostic indicators warrant, at the very least, closer monitoring given the increased risk of clinical deterioration, and perhaps, in certain circumstances, consideration should be given to thrombolytic therapy. More definitive data are essential in this area. Issues such as the extent of RV dysfunction, the severity of hypoxemia, or the degree of residual venous clot burden have not been explored and merit further study. A large-scale European multinational randomized controlled trial aimed at enrolling > 1,000 patients with acute PE associated with positive cardiac biomarkers and RV dysfunction is underway. While clinicians around the world anticipate the results of the largest study ever to examine the role of thrombolytics in the management of PE, our current practice must be guided by the data available, despite its limitations.

In the case presented, the patient had been started on therapy with low-molecular-weight heparin (LMWH), which, in general, is favored over unfractionated heparin (ACCP grade 1A) in the setting of nonmassive PE.<sup>27</sup> Anticoagulation had been initiated even before the diagnosis was proven because the level of suspicion for PE was high (ACCP grade 1C).<sup>27</sup> Clinicians supporting thrombolytics stressed the size of the embolus seen on CTA, the elevated pro-BNP level, and the status of the RV. The dissenting view emphasized the patient's advanced age and the risk of bleeding from thrombolytic therapy, as well as the lack of clear mortality data favoring thrombolysis based on PE size or RV size and function. When lytics are being considered, standard unfractionated heparin is suggested by the ACCP,<sup>27</sup> based on a shorter half-life than LMWH and more effective reversal with protamine, although it is a weak grade 2C recommendation. Thus, LMWH was a logical initial choice, and the evidence base does not unequivocally favor either, even once lytics are being considered as therapy.

Several hours after hospital admission, the patient deteriorated with hypotension (systolic BP, 70/44) unresponsive to IV fluids. The oxygen requirement increased to 100% by nonrebreather mask with an oxygen saturation that was still only 82%. Vasopressor therapy was initiated, and the clinical team all agreed that thrombolytics should now be administered. IV rt-PA (100 mg) was administered over 15 min, and no further enoxaparin was administered. The more rapid infusion was chosen based on the rapidity and severity of the deterioration. Over the subsequent hour, the BP improved and the patient was weaned from pressors over 3 h. Intubation was avoided. A large right neck hematoma developed at the site of the central venous catheter. Melena developed with a decrease in hematocrit from 35 to 28%. An inferior vena caval filter was placed. Upper endoscopy revealed a duodenal ulcer. (Had the bleed not occurred, heparin therapy would have been initiated after the rt-PA infusion when the patient's partial thromboplastin time or thrombin time returned to twice normal or less.) The patient was discharged after 12 days in the hospital. At the follow-up at 1 month, she remained somewhat weak, but her breathing and oxygenation had returned to the pre-PE baseline. Although no firm evidence base exists for imaging or echocardiographic follow-up of massive PE, an echocardiogram was repeated at 1 month, revealing normal RV size and function. Therapy with LMWH and warfarin was ultimately initiated, and enoxaparin therapy had been discontinued when the international normalized ratio was therapeutic. The filter was not removed.

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