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Systemic Thrombolysis for Pulmonary Embolism: Who and How

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Anticoagulation has been shown to improve mortality in acute pulmonary embolism (PE). Initiation of anticoagulation should be considered when PE is strongly suspected and the bleeding risk is perceived to be low, even if acute PE has not yet been proven. Low-risk patients with acute PE are simply continued on anticoagulation. Severely ill patients with high-risk (massive) PE require aggressive therapy, and if the bleeding risk is acceptable, systemic thrombolysis should be considered. However, despite clear evidence that parenteral thrombolytic therapy leads to more rapid clot resolution than anticoagulation alone, the risk of major bleeding including intracranial bleeding is significantly higher when systemic thrombolytic therapy is administered. It has been demonstrated that right ventricular dysfunction, as well as abnormal biomarkers (troponin and brain natriuretic peptide) are associated with increased mortality in acute PE. In spite of this, intermediate-risk (submassive) PE comprises a fairly broad clinical spectrum. For several decades, clinicians and clinical trialists have worked toward a more aggressive, yet safe solution for patients with intermediate-risk PE. Standard-dose thrombolysis, low-dose systemic thrombolysis, and catheter-based therapy which includes a number of devices and techniques, with or without low-dose thrombolytic therapy, have offered potential solutions and this area has continued to evolve. On the basis of heterogeneity within the category of intermediate-risk as well as within the high-risk group of patients, we will focus on the use of systemic thrombolysis in carefully selected high- and intermediate-risk patients. In certain circumstances when the need for aggressive therapy is urgent and the bleeding risk is acceptable, this is an appropriate approach, and often the best one.
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Introduction

Pulmonary embolism (PE) is a major cause of death worldwide and is the leading preventable cause of death in hospitalized patients.[1-3] A timely diagnosis remains critical but can be hindered by the often silent nature of deep venous thrombosis and the unavoidable, unpredictable sudden death that occurs from PE in some patients.

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The clear benefit of anticoagulation for acute venous thromboembolism has been realized for decades.[4] Therapy that is more aggressive than anticoagulation has generated both substantial research efforts as well as controversy for more than 40 years.[5] Systemic thrombolytic therapy is highly effective at rapidly lysing thrombi and emboli, and patients with overt right ventricular (RV) failure causing persistent hypotension or cardiogenic shock at presentation (acute high-risk PE) are in immediate need of effective reperfusion.[6] Systemic thrombolysis is often the fastest approach, generally being delivered over 2 hours or, in more urgent situations, over a much shorter period. Catheter-directed and surgical techniques require expertise and specific resources, and in urgent clinical settings of shock or severe hypotension, the success of these approaches requires not only available personnel, but the immediate availability of a catheterization laboratory or operating room. Based on the latter limitations, and the minimal available randomized clinical trial data for

catheter-directed or surgical therapy, and in view of the relatively rapid delivery possible with systemic thrombolysis, the latter still plays a major role in the treatment of high-risk (massive) acute PE.[7,8] However, clinicians continue to justifiably fear the potential for major and especially intracranial hemorrhage (ICH). This has kept systemic thrombolysis from being used routinely, even in high-risk (massive) PE. Hypotension with shock is the clearest indication for systemic thrombolysis. When the patient is not hypotensive, clinical trends and other parameters become crucial. There is no clear agreement among experts as to whether intermediate-risk PE patients should be considered for systemic thrombolysis; one large study indicates no change in mortality in this group,[9] although meta-analytic data suggest improved mortality.[10] We will present the available data and our suggestions regarding the use of systemic thrombolysis. The 2 drugs most commonly studied in the modern era have been tissue-type plasminogen activator (tPA), and tenecteplase. Of these, only tPA is approved for use for acute PE in the United States. There have been no valid head-to-head comparisons.

Severity of Acute Pulmonary Embolism: Definitions

Severity of acute PE is judged using a number of parameters and guidelines that have generally been consistent but not identical. Acute PE is commonly divided into 3 general groups based upon severity. These include low-risk, intermediate-risk ("submassive"), and high-risk ("massive") PE[11-13] (Table 1). The clinical classification of acute PE severity is based on the estimated early death risk.[13] Based on prior consensus statements by the American College of Chest Physicians (ACCP),[11] American Heart Association (AHA),[12] and the European Society of Cardiology (ESC),[13] the following definitions apply. Low-risk acute PE indicates that the patient is normotensive, has normal RV function, and is not excessively tachycardic or hypoxemic. Intermediate-risk PE patients have evidence of RV dysfunction, but are normotensive. High-risk PE is characterized by hypotension, most often defined as a systolic blood pressure <90 mm Hg for ≥ 15 minutes, or a drop of 40 mm Hg or more in systolic blood pressure.[11-13] It is impossible, however, to always base therapeutic decisions on this simple classification. Clearly, within these classifications, there is heterogeneity regarding severity and thus, prognosis. The Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) were introduced by the ESC in 2014 as an additional key feature in risk stratification.[13] Patients with an sPESI >0 are considered intermediate-risk; this category is further divided depending on RV function and biomarker results (Table 1). Based on the ESC guidelines, it may help to further classify patients into an intermediate-high- and an intermediate-low-risk category.[13] The PESI has been extensively validated and the simplified version (sPESI) is easier to use and includes 3 key physiological parameters (heart rate, blood pressure, and oxygen saturation) (Table 2).[14,15] The sPESI has been shown to possess a high negative predictive value for ruling out an adverse early outcome.[15] When the sPESI is 0, the 30-day mortality has been estimated at 1.0% with a 95% CI of 0.0%-2.1%, whereas an sPESI of ≥ 1 has been associated with a 30-day mortality of 10.9%; 95% CI of 8.5%-13.2%.[15] In spite of the prognostic value of the sPESI, categorizing a patient based on this score alone does not necessarily dictate a clear treatment approach. Both brain natriuretic peptide and troponin are included in the ESC designation of high-intermediate or low-intermediate-risk PE, and both have been shown to predict mortality in acute PE.[16-19] Nonetheless, elevated values of these tests are not used independently to make therapeutic decisions.

Clinical Evaluation and Risk Stratification of Acute PE

Although patients should be classified as suggested in Table 1, these definitions are not always adequate to permit straightforward therapeutic decisions in all clinical scenarios. Blood pressure and RV function are key determinants, but a more inclusive list of parameters may facilitate risk-stratification and thus, therapeutic decisions (Table 3). Although dyspnea is the most common symp-

Table 1 Categories of Acute Pulmonary Embolism Based Upon Severity

Severity	Low-Risk	Intermediate-Risk* (Submassive)	High-Risk (Massive)
Criteria†	Hemodynamic stability (normotensive) RV function normal Troponin/BNP normal sPESI = 0	Hemodynamic stability (normotensive) RV function abnormal Troponin/BNP may be abnormal sPESI > 0	SBP <90 mm Hg ≥15 min (or drop of 40 mm Hg from baseline) RV function abnormal causing the sustained hypotension.

BNP, brain natriuretic peptide (may be elevated from causes other than pulmonary embolism); SBP, systolic blood pressure.

* European Society of Cardiology consensus has divided intermediate-risk PE (sPESI > 0) into intermediate-high risk (RV dysfunction and positive biomarkers) and intermediate-low risk (either RV dysfunction or positive biomarker, or neither).[2]

† Heart rate, severity of hypoxemia, anatomic extent of PE, residual leg clot, and rate of deterioration, should also be considered during risk stratification.

Table 2 The Simplified Pulmonary Embolism Index

Parameter	Points
Age > 80	1
History of cancer	1
History of heart failure	1
History of chronic lung disease	1
Pulse ≥ 110/minute	1
Systolic blood pressure < 100 mm Hg	1

tom in acute PE, dizziness, lightheadedness, or presyncope suggest hypotension.[20] When syncope has occurred, this is clearer evidence that hypotension has been present even if the blood pressure has since recovered. Other nonspecific symptoms suggesting a more extensive clot burden include chest pressure, as well as nausea and abdominal pain which while nonspecific, may signal hepatic congestion. Tachypnea, diaphoresis and anxiety or sense of impending doom are concerning. Heart rate is an indirect indicator of RV reserve. Based on the ESC consensus,[13] a heart rate ≥110 per minute (PESI and sPESI) in a normotensive patient qualifies a patient as intermediate risk. However, there is no specific heart rate threshold that defines high-risk PE or a heart rate that suggests that systemic thrombolytic therapy or other aggressive therapy will be beneficial in a normotensive patient. A patient with a heart rate of 130 per minute would appear be a more appropriate candidate for systemic thrombolysis than a patient with a heart rate of 80 per minute although this has not been validated. In the acute PE setting, an elevated troponin indicates RV damage and an elevated brain natriuretic peptide denotes RV dilation; these are used together with echocardiography to assess RV status. Key echocardiographic parameters are RV size and function, and evidence of clot-in-transit. Although treatment decisions are rarely, if ever, made solely based on biomarker results, these should be included in the risk-stratification process. Hypoxemia is included in the sPESI, but only includes a simple cutoff of 90% O_2 saturation. *Extent* of hypoxemia should be taken into consideration, although there is no degree of hypoxemia that differentiates intermediate-risk from high-risk status. Although patients with very extensive acute PE and RV dysfunction sometimes have minimally abnormal oxygenation, severe hypoxemia (eg, requiring oxygen by nonrebreather) generally indicates a substantial clot burden and high mortality whether or not there is underlying lung disease present. An elevated lactate level in the setting of acute PE is a poor prognostic sign.[21] The serum creatinine is sometimes elevated in high-risk acute PE, or certain intermediate-risk PE patients and may represent significantly reduced cardiac output. Similarly, elevated liver function tests or computed tomographic (CT) findings of reflux of contrast into the inferior vena cava may signify hepatic congestion from severe RV failure.[22]

Table 3 Risk Stratification of Acute Pulmonary Embolism: Data to Consider

- History (syncope/lightheadedness/severe dyspnea)
- Clinical appearance (diaphoresis, anxiety)
- Vital signs (hypotension, tachypnea, tachycardia)
- Other examination findings, for example, elevated neck veins
- Oxygenation (O_2 saturation/arterial blood gas/FIO_2 requirement)
- Extent of emboli (marked obstruction/extensive proximal main PA involvement)*
- Echocardiography (RV size and function, clot-in-transit)
- Brain natriuretic peptide/troponin
- Liver function testing (hepatic congestion due to RV failure)
- Serum lactate
- Serum creatinine (Poor renal perfusion due to poor cardiac output)
- Cardiopulmonary reserve (concomitant cardiopulmonary disease)
- Residual deep venous thrombosis
- Bleeding risk
- Clinical trends
- Simplified pulmonary embolism severity score (sPESI)
- Shock index
- Resources available

FIO_2, fraction of inspired oxygen; O_2 = oxygen; PA = pulmonary artery.

* Some saddle emboli are thin and nonobstructive so that this finding *alone* is not an indication for aggressive therapy.

Clot burden has been shown to predict mortality in acute PE.[23] One retrospective study suggests that the mortality may be increased 11-fold when the obstruction index is >40%.[23] However, although extensive clot burden is often associated with severe RV dysfunction, it may be present in the setting of normal or mildly abnormal RV dysfunction. One retrospective study of 82 patients with "severe PE" evaluated pulmonary artery clot burden scores and CT cardiovascular parameters as predictors of mortality.[24] Two blinded independent readers quantified pulmonary arterial (PA) clot burden by using 4 scoring systems. Twelve patients died within 14 days. RV and left ventricular (LV) short axis, RV/LV ratio, as well as azygos vein, superior vena cava, and aorta diameters; and contrast medium reflux into the inferior vena cava were significantly different between survivors and nonsurvivors ($P < 0.05$). In this study, no significant relationship was found between PA clot burden and mortality rate. RV/LV ratio and azygos vein diameter allowed correct prediction of survival in 89% of patients ($P < 0.001$).[24] This suggests that extent of clot as estimated by CT does not always correlate with extent of lung perfusion. However, at some point when clot burden reaches a certain limit it *will* predict mortality; at the extremes, it *has* to! But for most patients, clot burden alone, does not appear to. The key point is that not only clot burden should be assessed—all aspects of the CT together with other data should be carefully reviewed. In the future, by allowing visualization of both emboli and perfusion, use of dual-energy CT could offer improved risk stratification.[25]

Trends are very important to follow and deterioration can suggest a clearer indication for systemic thrombolysis.[11-13]

In summary, the definitions in Table 1 should be considered along with the parameters in Tables 2 and 3, with blood pressure or evidence of shock being the clearest indication for systemic thrombolysis. Finally, contraindications to anticoagulation and thrombolysis (stated later) should be considered during the risk-stratification process. Naturally, in patients who are alert and more stable, therapeutic options can be discussed in detail and decisions made taking into account patient preferences. All PE patients are anticoagulated unless contraindicated, regardless of whether or not thrombolysis is being considered. Those deemed intermediate- or high-risk are carefully assessed for additional therapy. High-risk patients stable for transport are transferred to the intensive care unit and intermediate-risk PE patients should be considered for a monitored bed or possible intensive care unit admission.

Contraindications to Systemic Thrombolysis

Contraindications to thrombolytic therapy should be considered early in the evaluation of a PE patient being considered for aggressive therapy beyond anticoagulation. There are some clear, absolute contraindications to systemic thrombolysis, including established ICH or very recent spinal or intracranial surgery. Many contraindications, however, are relative (Table 4).[10,26,27] The absolute or relative designation of contraindications depends not only on the specifics of the contraindication but also the urgency of the clinical scenario. Certain surgeries or a gastrointestinal bleed might potentially be only a relative contraindication if the patient is in shock with impending cardiac arrest. In patients with contraindications to thrombolytic therapy, surgical embolectomy or mechanical embolectomy may be considered.[26,27]

Table 4 Contraindications to Systemic Thrombolysis

Absolute*
Active bleeding
Previous intracranial hemorrhage
Structural intracranial/spinal cord disease
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Relative†
Systolic blood pressure > 180 mm Hg
Diastolic blood pressure > 100 mm Hg
Recent bleeding
Recent surgery or invasive procedure
Ischemic stroke within 3 mo
Ischemic stroke > 3 mo previously
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age > 75 y
Low body weight (eg, <60 kg)

* Thrombolysis likely to result in a life-threatening deterioration.
† Thrombolysis is acceptable if the benefits outweigh the risks.

How Should Heparin Be Managed When Thrombolysis Is Undertaken?

When there is a high clinical suspicion of PE, and in the absence of contraindications, anticoagulation should be initiated while the diagnostic workup is being completed. Generally, when thrombolysis is planned, unfractionated heparin (UFH) is utilized based upon its shorter half-life and reversibility and the clinician must consider how best to handle the intravenous (IV) heparin infusion. The American Heart Association consensus has stated that the decision to coadminister thrombolytic agents with heparin anticoagulation requires a strict risk-benefit assessment.[12] The ESC recommends withholding parenteral anticoagulation when first-generation thrombolytics are administered, but states that UFH may be given in conjunction with tPA infusions.[13] In Europe, the latter approach is more often considered. Generally, in the United States, anticoagulation is withheld during delivery of the thrombolytic agent and reinstituted without a bolus once the activated partial thromboplastin time (aPTT) has returned to less than twice the upper limit of the normal therapeutic range. If the aPTT exceeds this value, the test is repeated every 3-4 hours until it is safe to proceed with heparin. Laboratory turn around for the aPTT should be short enough that the risk of subtherapeutic anticoagulation is minimized. It appears reasonable to continue with anticoagulation after the thrombolytic infusion, using UFH until the bleeding risk is deemed low enough to change to a longer acting drug. Every effort should be made to maintain a therapeutic PTT (or heparin level) subsequently, in the absence of bleeding. In patients receiving therapeutic low-molecular-weight heparin (LMWH) every 12 hours (1 mg/kg dosing) at the time thrombolysis is initiated, initiation of another anticoagulant should be delayed until 12 hours after the last LMWH injection, and delayed 24 hours if the LMWH is dosed once daily. Although few data exist with the direct-acting oral anticoagulants, it appears reasonable to follow a similar schedule. In the MOPPETT study discussed later, heparin was given for a total of 24 hours after completion of thrombolysis and rivaroxaban started at 2 hours after termination of the heparin infusion.[28] There are no randomized trials comparing continuing anticoagulation during systemic thrombolysis vs stopping during the infusion.

Systemic Thrombolytic Therapy For High-Risk Acute Pulmonary Embolism

When patients with PE present with hypotension, initial support should focus on restoring perfusion with cautious IV fluid resuscitation, vasopressor support, and addressing hypoxemia. Intubation and mechanical ventilation should be avoided unless essential since the introduction of positive pressure may worsen RV function. Anticoagulation should be

quickly initiated. There are no large, randomized controlled trials of systemic thrombolysis in high-risk PE. In an epidemiological study, in-hospital mortality attributable to PE was lower in high-risk patients who received thrombolytic therapy, compared with those who did not (relative risk = 0.20; 95% CI: 0.19-0.22; $P < 0.0001$).[8] In spite of the lack of high level supportive evidence demonstrating benefit compared with systemic anticoagulation alone, most would now consider such a trial unethical. Patients presenting in shock from PE who have not yet arrested, that is, those who still have a measurable blood pressure, are the most ideal high-risk candidates for systemic thrombolysis. In more critically ill patients who have already arrested, there is inadequate blood flow for systemic thrombolytic therapy to be effective. In such cases, if extracorporeal membrane oxygenation can be instituted quickly enough, a patient may be salvageable.[29]

This high-risk PE group of patients is heterogeneous. A patient with acute PE resulting in severe hypotension who remains in shock despite high-dose pressor therapy as well as being severely hypoxemic and tachycardic may not have the same outcome as a patient whose systolic blood pressure has been stable at 85-90 mm Hg over several hours but who is awake and alert, and only requiring 2 L of oxygen. Both are high-risk (massive PE) patients. The first patient requires rapid action and assuming a low bleeding risk, systemic thrombolysis would be very reasonable. The second high-risk patient, while more stable, could still be considered for systemic lysis, but catheter-based therapy might also be a consideration. Could an aggressive catheter-based approach be employed in the first patient also? It would depend on local expertise and resources and how rapidly these resources could be mobilized. At present, guidelines recommend systemic thrombolysis over catheter-based techniques except in certain specific circumstances,[11-13] but this area is evolving. Patients who receive systemic thrombolytic therapy and fail, that is, worsen or remain hypotensive, can be considered for catheter-directed thrombolysis or other mechanical interventions.[11-13] Thrombolytics are administered as soon as possible when indicated, as they are likely to offer the optimal benefit with fresh clot. However, patients with acute PE and recent deterioration with symptoms that have been present for weeks may have an acute component to the clot burden. In summary, in the setting of high-risk PE, the severity of hypotension and other parameters should be carefully examined, and particularly when the scenario dictates extreme urgency and contraindications have been considered, systemic thrombolysis should be considered. Once cardiac arrest has occurred, the efficacy of this approach is dramatically reduced.

Thrombolysis for Acute Pulmonary Embolism After Cardiac Arrest

Case reports and series have reported occasional success from systemic thrombolysis during cardiopulmonary resuscitation after massive PE.[30,31] One retrospective study reported a 5% incidence of PE (diagnosed by autopsy, clinically, or echocardiography) in 1246 cardiac arrest victims.[31] Subgroup analysis suggested that thrombolysis was associated with a higher rate of return to spontaneous circulation compared to those who were not thrombolysed. However, another randomized study of 233 patients who presented with pulseless electrical activity arrest of unknown etiology reported that compared to placebo, thrombolysis did not improve survival or return of spontaneous circulation.[32] There are insufficient data to argue for or against the routine use of thrombolytic therapy during cardiac arrest caused by PE or presumed PE so that the decision should be considered on a case-by-case basis. It would appear likely that publication bias particularly regarding retrospective studies might affect the literature, so that only successful thrombolysis after PE-induced cardiac arrest is generally reported. It would appear that when cardiac arrest occurs secondary to PE, that while the chance of success may be low, the potential benefit outweighs the risk. A bolus of between 50 and 100 mg IV of tPA is recommended.

Systemic Thrombolytic Therapy For Intermediate-Risk Acute Pulmonary Embolism

Consensus guidelines are less supportive of systemic thrombolysis in intermediate-risk PE, although a number of clinical trials have been conducted. In view of the potentially life-threatening bleeding risk associated with systemic thrombolysis, its use in intermediate-risk is not recommended by consensus statements, unless hemodynamic decompensation or collapse subsequently develops.[11-13] Over the last 15 years, a number of randomized thrombolytic trials have been conducted. The MAPPET-3 trial, conducted in 2002, evaluated the use of heparin plus IV tPA 100 mg over 2 hours in 118 patients vs 138 receiving heparin plus placebo.[33] The primary endpoint was met with in-hospital death or clinical deterioration being significantly higher in the heparin or placebo group than in the tPA or heparin group ($P = 0.006$), and the probability of 30-day event-free survival was higher in the tPA or heparin group ($P = 0.005$). However, there was no difference in in-hospital deaths which were low in both groups (3.4% for tPA or heparin and 2.2% in the heparin or placebo group, $P = 0.71$).[33] The bleeding rate was higher with tPA, but no fatal bleeding or ICH occurred in patients receiving tPA. Based on these data, and in spite of the low mortality in both groups, it was concluded at that time that the indications for thrombolysis could be extended to include intermediate-risk acute PE in hemodynamically stable patients.[33] Additional studies followed, including the TIPES and TOPCOAT trials.[34,35] which studied bolus tenecteplase, but the PEITHO results rendered these previous randomized trials much less relevant.[9]

The randomized, double-blind PEITHO trial was a pivotal trial in acute PE.[9] This trial compared a single IV bolus of tenecteplase plus heparin with placebo plus heparin in 1006 patients with intermediate-risk PE. To be included, patients had to have RV dysfunction by echocardiogram or computed tomography angiography and a positive troponin. The study's primary outcome (all-cause death or hemodynamic decompensation or collapse within 7 days of randomization) occurred in 13 of 506 patients (2.6%) in the tenecteplase group compared with 28 of 499 patients (5.6%) in the placebo group ($P = 0.02$). However, there was no difference in the (exceedingly low) all-cause mortality between the groups. Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and in 6 patients (1.2%) in the placebo group ($P < 0.001$). ICH occurred in 10 patients (2.0%) in the tenecteplase group and in only one patient (0.2%) in the placebo group. Thus, thrombolytic therapy was shown to prevent hemodynamic decompensation, but at an increased risk of major hemorrhage and stroke, and with no difference in mortality. This result has influenced guidelines which do not endorse systemic thrombolysis for patients with intermediate-risk PE except when there is evidence of clear deterioration.[11-13]

The question still remains, however, as to whether a subset of intermediate-risk PE patients exists who have abnormal enough RV function or possess other specific criteria that would lead to a mortality benefit from systemic thrombolysis. One potential concern with PEITHO is that although the patients were required to have RV dysfunction by echocardiography and an elevated troponin, even these criteria do not necessarily imply a severe ill enough intermediate-risk PE population.[9] Intermediate-risk PE is a heterogeneous category and perhaps the study could have been enriched by "higher-risk" intermediate-risk patients, for example, with very extensive clot burdens, very severe RV dysfunction, and marked tachycardia or hypoxemia but who remained normotensive. The PEITHO's very low mortality, indicate that RV dysfunction plus an elevated troponin (patients who by ESC criteria would likely be "high-intermediate risk,") does *not* identify a population of patients with a mortality benefit from systemic thrombolysis. The author's current belief is that intermediate-risk patients require individualized evaluation regarding the potential risks and benefits of therapy beyond anticoagulation. An understanding of the available evidence base is essential as is an experienced and systematic approach. A patient with intermediate-risk PE is presented in the Figure. Therapy was determined in this case based upon the earlier discussion.

Meta-Analyses of Systemic Thrombolysis in Acute Pulmonary Embolism

Meta-analyses of thrombolytic therapy trials have been conducted in an attempt to increase patient numbers in hopes of forming firmer conclusions. Published meta-analyses of thrombolytic therapy trials overlap, and also suffer from the same drawbacks found in other areas of medicine; the clinical trials conducted often have differences in a number of parameters including overall study size and design, drug(s) utilized, primary and secondary efficacy and safety endpoints, follow-up duration, and statistical methods, mandating extreme caution when interpreting the results. These analyses include both high-risk and intermediate-risk patients which also hamper interpretation. Chatterjee et al,[10] meta-analyzed the survival benefit of thrombolysis compared with that of anticoagulation in patients with acute PE. The analysis included 16 studies, which enrolled a total of 2115 patients. Eight of these trials involved 1775 patients with intermediate-risk PE. Thrombolytic therapy was found to be associated with lower all-cause mortality compared with anticoagulation alone (2.17% vs 3.89%), but major bleeding was increased (9.24% vs 3.42%) as was ICH (1.46% vs 0.19%). Major bleeding was not significantly increased in patients 65 years of age or younger. In the intermediate-risk population, mortality was also shown to be improved ($P = 0.03$). The results of this analysis have been challenged because of purported flaws in the statistical methods; specifically, limitations of the Peto method have been emphasized.[6]

In another meta-analysis, Xu et al,[36] analyzed data from 7 studies involving a total of 1631 patients with intermediate-risk PE treated with thrombolytics or anticoagulation alone. The 2 treatment groups were not significantly different regarding 30-day, all-cause mortality ($P = 0.08$). The patients treated with thrombolytic agents, however, had significantly lower rates of clinical deterioration ($P < 0.01$) and recurrent PE ($P = 0.01$). Surprisingly, there was no difference in the rates of major bleeding events between the 2 groups ($P = 0.25$), which represents an unexpected finding, not consistent with the bulk of the thrombolysis literature.

In a meta-analysis of 15 randomized trials involving a total of 2057 patients,[37] thrombolysis appeared to reduce overall mortality (odds ratio [OR] = 0.59, 95% CI: 0.36-0.96) and showed a significant reduction in the combined endpoint of death or treatment escalation (OR = 0.34, 95% CI: 0.22-0.53). As usual, this favorable effect came at the cost of an increased risk of major hemorrhage (OR = 2.91, 95% CI: 1.95-4.36) and fatal or ICH (OR = 3.18, 95% CI: 1.25-8.11). These 3 meta-analyses are different but naturally overlap significantly regarding studies included, and suggest that systemic thrombolysis is likely beneficial in some settings. The major bleeding and ICH rates that are documented in these analyses indicate that bleeding risk should be analyzed carefully, but that this risk is not always predictable.

Meyer et al,[38] recently reviewed the main advances and recommendations involving recent data on the use of thrombolytic therapy. The authors concluded (as in PEITHO) that thrombolytics are associated with a reduction in the combined endpoint of mortality and hemodynamic decompensation in patients with intermediate-risk

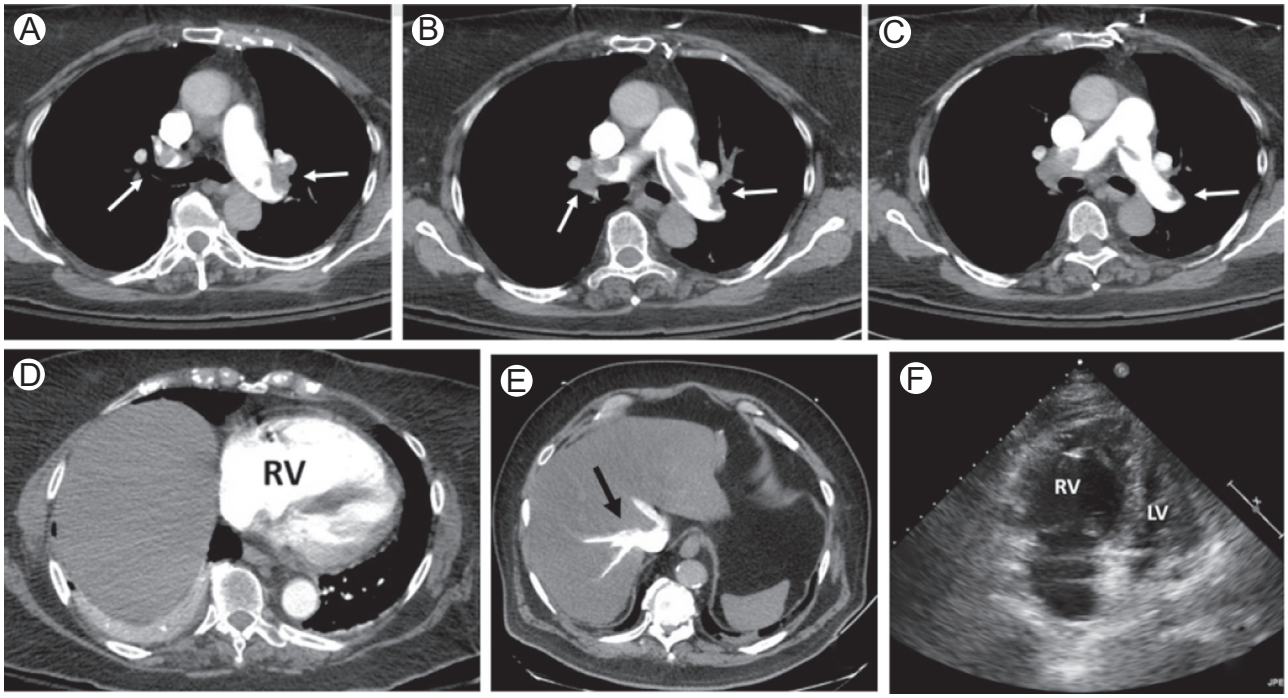

Figure A 46 year-old man presented with acute dyspnea and extensive acute pulmonary embolism (PE) (A-C). Heart rate was 120/minute, blood pressure 136/72 mm Hg, and oxygen saturation 94% on 4 L by nasal cannula. The right ventricle was dilated on chest computed tomographic angiography (D) and there was reflux of contrast into the inferior vena cava and hepatic veins (E). The right ventricle was severely dilated (and hypokinetic) by echocardiography (F). The patient was thus, intermediate-risk PE. There was extensive residual right leg deep venous thrombosis. He was anticoagulated and considered for catheter-based therapy. However, in the emergency department, he developed near syncope, with blood pressure dropping to 92/48, and tachypnea at 30 breaths/minute. The heart rate increased to 140/minute and oxygen requirement increased to 4 L and then to 60% by facemask. He received 1 L of intravenous fluid with no blood pressure improvement. The rate of progressive deterioration was believed too rapid for the standard 2-hour regimen. Based this (*although still intermediate-risk based on his blood pressure)*, his young age, and perceived low risk for bleeding, he was given intravenous tissue-type plasminogen activator (30 mg over 10 minutes and remaining 70 mg over the subsequent 20 minutes). Over the next 4 hours, the heart rate slowed to 92/minute, blood pressure increased, and O_2 requirement decreased to 2 L/min. No major bleeding occurred. If there had been rapid access to catheter-based therapy, it is feasible that approach would have also been successful also.

PE, but this benefit is obtained without a decrease in overall mortality and with a significant increase in major extracranial and intracranial bleeding. In these investigator's opinions, thrombolytic therapy should be administered in cases in patients with "high-intermediate risk" PE when there is hemodynamic worsening.[38]

Systemic Thrombolysis in the Absence of Proven Pulmonary Embolism

When acute PE is highly suspected but not proven, thrombolytic therapy can be carefully considered but every effort should be made to secure a diagnosis if at all possible. A hypotensive and severely hypoxemic young patient, for example, with a clear chest radiograph, McConnell's sign on echocardiography and a very high D dimer and troponin level might appear very likely to have acute PE and merit rapid therapy. Careful clinical judgment should be employed in such settings. A rapid bedside leg ultrasound showing acute deep venous thrombosis will increase the level of suspicion for acute PE. No guidelines exist for this clinical scenario.

Drug, Dose and Infusion Duration

First-generation thrombolytic agents (strepotokinase and urokinase) are only very rarely used now. They are not contraindicated, they are simply less convenient because the approved regimens are prolonged (12-24 hour infusions) which is impractical, particularly for patients with high-risk PE and shock. Clinical trials conducted over the past 15 years have utilized tPA or tenecteplase. The former is food and drug administration–approved in the United States for acute PE, the latter is not. Variable doses and infusion durations have been studied. Tenecteplase is infused by IV bolus, while tPA is recommended as a 2-hour infusion. ESC guidelines specifically recommend tPA

100 mg infused IV peripherally over 2 hours in place of first-generation thrombolytics.[13] The ACCP suggests short infusion times (eg, 2-hour infusion).[11]

Bolus Injections

Bolus infusion of thrombolytics may be effective without excessive bleeding complications.[34,39] However, this approach has not been directly compared to a 2-hour infusion of tPA. Trials comparing the regimens are necessary before routine bolus infusion replaces the more conventional 2-hour regimen. An exception is the use of bolus thrombolytic therapy for patients with imminent or actual cardiac arrest. The effect of bolus infusion was illustrated by a double-blind trial in which 58 patients with acute PE were randomly assigned to receive tPA (0.6 mg/kg over 2 minutes) plus heparin or placebo plus heparin.[34] Patients who received tPA were more likely to have >50% clot resolution and increased perfusion within 24 hours, although there were no detectable differences by the seventh day. There was no major bleeding in either group. In PEITHO, tenecteplase was administered as an IV push with weight-based dosing (30 mg for ≤60 kg; 35 mg for 61-69 kg; 40 mg for 70-79 kg; 45 mg for 80-89; 50 mg for ≥90 kg) and heparin was either unfractionated or LMWH.[9]

Low-Dose Systemic Thrombolysis

Based upon the fear of bleeding, particularly regarding ICH,[15] efforts have been made to study lower than conventional doses of IV thrombolytics in hopes of maintaining efficacy but reducing the risk of major bleeding. Lower doses of thrombolytics may be of particular interest in elderly, frail, small, and pregnant patients as well as those with relative contraindications such as recent minor surgery or trauma.[40] A randomized clinical trial of 118 patients conducted in China with either high- or intermediate-risk PE found that that half-dose recombinant tPA resulted in fewer hemorrhagic complications than full-dose tPA and was noninferior in terms of improving pulmonary vascular obstruction.[41] There were some limitations of this study including the fact that the severity of the intermediate-risk patients was not clear. Furthermore, the trial had to be terminated prematurely and thus, technically remained inconclusive. Nonetheless, the study offered strong evidence of efficacy with a lower major bleeding rate, suggesting that lower-dose tPA is a potential option.[41]

Subsequently, the prospective, randomized, unblinded MOPPETT study was published examining 121 patients classified as "moderate-risk PE," who were allocated to either anticoagulation plus tPA or anticoagulation alone.[28] Moderate PE was defined as the presence of symptoms and signs of PE plus chest computed tomography angiography demonstrating >70% involvement with embolism in ≥2 lobar arteries or main pulmonary arteries or by a high probability ventilation-perfusion scan showing ventilation-perfusion mismatch in ≥2 lobes. These inclusion criteria do not correspond to a standardized definition of clinical severity of PE. The tPA was administered as low-dose tPA at 0.5 mg/kg with maximum of 50 mg (10 mg bolus administered over 1 minute, with the remainder of the dose administered over 2 hours).[28] Compared with conventional therapy, this lower-dose regimen of tPA resulted in the following:

The rate of death plus recurrent PE was 1.6% for the heparin or tPA group compared with 10.0% for the heparin group ($P = 0.049$), although there was no difference in all-cause mortality.[28] "Pulmonary hypertension" (PH) was said to occur in 16% (9 of 58) of the tPA group compared with 57% (32 of 56) of the anticoagulation only group ($P < 0.001$). Pulmonary artery pressures were higher at 28 ± 5 months of follow-up in the anticoagulation alone group, however, the PH diagnosis was based on echocardiography which is inaccurate and does not prove PH. There was no proof that chronic thromboembolic pulmonary hypertension (CTEPH) occurred. The average duration of hospitalization was 2.2 days for heparin or tPA vs 4.9 days for heparin alone ($P < 0.001$). Thus, the study suggests that lower doses of tPA can be delivered safely, and that length of stay may be shorter but there is no proof that the patients receiving tPA truly had better outcomes. The study reported no major or minor bleeding episodes which is extremely unusual in a study of this size in patients receiving anticoagulation and exceedingly unusual in a study in which 61 patients received systemic thrombolysis.

Finally, a meta-analysis of trials using low-dose recombinant tPA in patients with acute PE found that a low dose (50 mg infusion over 2 hours) was as effective as the standard dose (100 mg IV over 2 hours), with fewer major bleeding events.[42] In summary, based on the available data, half-dose systemic thrombolysis may be as effective and safer than full-dose thrombolysis but the data still do not permit an evidence-based change in treatment algorithms. Our suggestion is that patients deemed good candidates for systemic thrombolysis could be considered for the half-dose approach, particularly if they are elderly, small, frail, or have relative contraindications to systemic thrombolysis. The evidence base is inadequate and that more data are needed. Catheter-directed reperfusion techniques employ even lower doses of thrombolytic agents, and may be an alternative to systemic thrombolysis or surgical embolectomy.[24] This form of therapy will be covered elsewhere in this volume.

Bleeding Complications and Management of Bleeding

Unfortunately, the rates of major bleeding complications associated with systemic thrombolysis have remained high since the early studies conducted in the late 1960s and early 1970s.[6,10] Clinicians have respected the potential for life-threatening bleeding, but unfortunately this fear has even extended to patients who may benefit the most, that is, those with massive PE and shock.[6] Prospective trials

evaluating systemic thrombolytic therapy for acute PE from more than 4 decades ago up to modern times have reported major bleeding rates between 0% and 33%, and ICH rates between 0% and 7.4%.[26,39,43-46] The variable bleeding rates reported are due to (1) differences in study inclusion or exclusion criteria (2) differences in reporting criteria and (3) small study sample sizes. In 4 meta-analyses by Chatterjee et al,[10] Nakamura et al,[47] Marti et al,[37] and Riera-Maestre et al,[48] the rates of major bleeding with fibrinolytic treatment for PE were 9.2%, 6.6%, 9.9%, and 5.9%, respectively. Intracranial bleeding rates were 1.5%, 1.7%, 1.7%, and 1.7%, respectively, and were significantly increased compared with anticoagulation. In the subgroup of those older than 65 years in one meta-analysis,[10] the risk of thrombolysis-associated bleeding was 3-times greater (12.9 vs 4.1%; OR = 3.10, 95% CI: 2.10-4.56). Older patients also did not derive a mortality benefit from thrombolysis in this same analysis.

Independent predictors of major bleeding with thrombolysis in one study included administration of catecholamines for hypotension (OR = 115, 95% CI: 9.4-1410, $P < 0.001$), cancer (OR = 16.0, 95% CI: 3.2-80, $P = 0.004$), diabetes mellitus (OR = 9.6, 95% CI: 1.7-54, $P = 0.010$), and elevated international normalized ratio before fibrinolysis (OR = 5.8, 95% CI: 1.5-22, $P = 0.012$).[26] One recent study[46] identified major surgery within the prior 3 weeks (OR = 9, 95% CI: 1-80), international normalized ratio > 1.7 (OR = 13.2, 95% CI: 1.54-113), weight < 100 kg (OR = 1.18 for each 10 kg less than 100 kg, 95% CI: 1.01-1.37), and at least one of the following characteristics (OR = 5.02, 95% CI: 1.78-18.6): internal bleeding in previous 4 weeks, hypertension, acute myocardial infarction, stool occult positive, presence of intra-aortic balloon pump, African-American race, gastrointestinal bleeding in prior 3 months, aortic dissection, acute pancreatitis, CPR > 10 minutes, bilirubin > 3 mg/dL, or dementia. Advanced age greater than 75 years (OR = 2.8; 95% CI: 1-7.9) and female sex (OR = 11.5; 95% CI: 2.67-49.5) were independently associated with rates of major extracranial bleeding, with rates of 11.1% and 8%, respectively.[49] In summary, although studies vary, and CIs are wide, thrombolysis imparts a significant bleeding risk. The severity of PE and risk of bleeding must be weighed carefully. Bleeding during thrombolytic therapy occurs most commonly at sites of invasive procedures such as pulmonary arteriography or arterial puncture but these tend to be the least consequential.

When severe bleeding occurs, the anticoagulation and thrombolytic infusions are discontinued. Neurology or neurosurgery consultation should be secured for ICH.[50-53] Supportive therapy, including application of pressure when appropriate, volume repletion with blood products and fluid, and emergency embolization or surgery are considered.[50,51] Reversing heparin with protamine sulfate can be used to reverse heparin; generally at 1 mg of protamine for every 100 units of heparin, for a maximum of 50 mg.[50] Aminocaproic acid has been utilized to encourage hemostasis after thrombolysis-induced hemorrhage. There are no clear guidelines for reversing, and the extent of bleeding as well as the severity of the thromboembolic event must be considered. Cryoprecipitate may be administered in patients with massive bleeding. IV tranexamic acid has also been used in patients with post-tPA bleeding.[54] Fortunately, the short half-life of thrombolytic agents often means that by the time the hemorrhage occurs, the biological effect of the drug may have already abated. Finally, thrombolytic agents may affect a number of processes independent of their effects on clot disruption, including extracellular matrix degradation and cell signaling.[55] Interventions targeted at reversing these noncoagulopathic effects may lead to promising avenues of research.

Long-Term Outcomes: What are the Data?

Long-term outcome studies in acute PE patients suggest that a significant minority of patients who have survived an acute PE episode report persistent functional limitation or reduced quality of life for months to several years after the acute PE event.[35,56,57] Some degree of persistent PH or RV dysfunction has been observed in as many as 40% of survivors followed over 6-12 months after acute PE.[57-59] Although the MOPPETT study[28] suggests lower pulmonary artery pressure in patients receiving thrombolysis at long-term follow up, these data rely on echocardiographic data which do not prove PH per se. True CTEPH has been reported to develop in 0.1%-9.1% of the patients within the first 2 years after a symptomatic PE event.[60] It is feasible that early thrombolysis might exert favorable prolonged effects on clinical and hemodynamic outcomes. But to date, we have no proof of reduced incidence of CTEPH or improved long-term quality of life. Larger randomized studies with long-term outcome data would be needed.

The long-term follow-up data are now available from PEITHO.[61] Long-term (median = 37.8 months) survival was assessed in 98.3% of patients in the thrombolysis arm and in 98.0% of the placebo arm. The overall mortality rate was no different at 20.3% and 18.0%, respectively ($P = 0.43$). Between day 30 and long-term follow-up, 65 deaths occurred in the thrombolysis group and 53 in the placebo arm. Although persistent dyspnea or functional limitation was reported by 36.0% vs 30.1% of the survivors ($P = 0.23$) it was mostly mild. Echocardiography was available at follow up in more than half the patients in each group and it did not reveal significant differences in PH or RV dysfunction. CTEPH was confirmed in 4 (2.1%) vs 6 (3.2%) subjects ($P = 0.79$). Thus, although approximately 33% of patients reported some degree of persistent functional limitation after intermediate-risk PE, CTEPH was rare. Thrombolytic treatment did not affect long-term mortality rates, and it did not appear to reduce residual dyspnea or RV dysfunction in these patients.

Table 5 Consensus Statement Summaries: Systemic Thrombolysis for Acute Pulmonary Embolism

American College of Chest Physicians 2016[11]

- In patients with acute PE associated with hypotension (eg, systolic BP $<$ 90 mm Hg) who do not have a high bleeding risk, systemically administered thrombolytic therapy is suggested over no such therapy (grade 2B).
- In most patients with acute PE not associated with hypotension, systemically administered thrombolytic therapy is not recommended (grade 1B).
- In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, systemically administered thrombolytic therapy is suggested (grade 2C).
- In patients with acute PE, when a thrombolytic agent is used, short infusion times (eg, a 2-hour infusion) are suggested over prolonged infusion times (eg, 24 hours) (grade 2C).
- When thrombolytics are utilized, the systemic route is suggested over catheter-directed approaches (grade 2C).

American Heart Association 2011[12]

- Systemic thrombolysis is reasonable for patients with massive (high-risk) acute PE and acceptable risk of bleeding complications (class IIa; Level of Evidence B)
- Thrombolysis may be considered for patients with submassive (intermediate-risk) acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications (class IIb; Level of Evidence C).
- Thrombolysis is not recommended for patients with low-risk PE (class III; Level of Evidence B) or submassive PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening (class III; Level of Evidence B).
- Thrombolysis is not recommended for undifferentiated cardiac arrest (class III; Level of Evidence B).

European Society of Cardiology 2014[13]

- Systemic thrombolytic therapy is recommended for PE with shock or hypotension (class I, Level B).
- Systemic thrombolytic therapy should be considered for patients with intermediate-high risk PE and clinical signs of hemodynamic decompensation (class IIa, Level B).
- Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension (class III, Level B).

BP, blood pressure.

* See specific guidelines for recommendations on catheter-directed therapy.

Guidelines and Consensus Statements

The AHA,[11] ACCP,[12] and ESC,[13] all offer recommendations for the use of systemic thrombolysis in acute PE (Table 5). Unfortunately, evidence-based guidelines are limited by the available data. The ESC[13] classifies thrombolytic administration in patients with acute high-risk PE as a 1B recommendation, and the 2016 updated CHEST guidelines list it as a grade 2B recommendation. (The ACCP grading of 1 is deemed a "recommendation" while 2 is a "suggestion.") The ACCP[11] has recommended that patients with acute PE without hypotension who have severe symptoms or marked cardiopulmonary impairment should be monitored closely for deterioration. If hypotension does develop, thrombolytic therapy is suggested (2B recommendation). In general, these recent guidelines agree with a strategy of therapeutic anticoagulation and cautious observation in intermediate-risk PE, with a recommendation of rescue thrombolysis if signs of hemodynamic decompensation develop. Recommendations for catheter-directed thrombolysis or clot extraction procedures are discussed in the earlier guidelines but these will be discussed in another chapter of this treatise. The 2016 ACCP guidelines[11] do not go into detail regarding the coadministration of anticoagulants and thrombolytics, but they do state that patients with acute PE whose condition worsens after parenteral anticoagulation may receive systemic thrombolytic therapy (grade 2C recommendation).

Future Thrombolytic Drug Options

Thrombin activatable fibrinolysis inhibitor (TAFI) appears to inhibit fibrinolysis by catalyzing the removal of C-terminal lysines of fibrin partially degraded by plasmin. TAFI plays an important role in connecting the coagulation and fibrinolytic cascades, and therefore, this inhibitor and its activation by thrombin-thrombomodulin and plasmin constitute an antifibrinolytic pathway analogous to the anticoagulant protein C pathway. A phase 1b, double-blind placebo-controlled, randomized, multicenter trial is underway to assess a TAFIa inhibitor in subjects with acute intermediate-risk acute PE.[62] It is possible that through a mechanism such as this, effective thrombolysis would occur but with a lower bleeding risk than with current thrombolytic agents.

Design of a modified recombinant microplasminogen has been recently reported.[63] This has combined features of previously developed thrombolytic agents into one fusion molecule. The microplasminogen has been altered so it is activated by thrombin fused to an activation-specific anti-glycoprotein IIb/IIIa single-chain antibody, thereby "hijacking the coagulation system to initiate thrombolysis." Efficient thrombolytic capacities were demonstrated in 2 different mouse models of thrombosis at a dose of this novel fusion molecule "SCE5-HtPlg" that was associated with no bleeding time prolongation. The activation of this fusion molecule or fibrinolytic construct

by thrombin *generated within the clot itself* rather than by a drug (plasminogen activator), which needs to be delivered systemically, provides a novel targeted approach to improve thrombolysis.[63] The in vitro permeability assay conducted revealed that the SCE5-HtPlg affects primary human brain microvascular endothelial cells, but only when activated with thrombin. This result suggests that no undesired adverse effect would be observed on the endothelium remote from thrombosis sites. Another recent approach by the same investigators involves development of layer-by-layer nanocapsules that release urokinase upon degradation by thrombin.[64] Other studies have suggested synergism between novel agents.[65] These recent advances could ultimately represent a promising alternative to the to current therapies potentially changing the risk-benefit profile for systemic thrombolysis.

Conclusions

Systemic thrombolysis is very effective at rapidly improving lung perfusion compared with anticoagulation alone. However, the risk of major bleeding, particularly intracranial bleeding warrants extremely cautious risk-benefit analysis. The most obvious clinical scenario in which systemic thrombolysis would appear indicated is with a younger patient with high-risk PE with severe pressor-dependent hypotension or shock, but not cardiopulmonary arrest, and no evident bleeding risk. Catheter-based interventions or surgical embolectomy may be feasible in such settings but require expertise and specific resources, and importantly would need to be applied without delay.

The high-risk and intermediate-risk acute PE categories are heterogeneous. There are "mild" and "severe" ends of the spectrum for each group. Clinical trials have never differentiated patients *within* these classifications. Patients with intermediate-risk PE should be carefully individualized. Although meta-analytic data suggest improved all-cause mortality with systemic thrombolysis, the largest single trial conducted to date indicates a low overall mortality and an increased risk of major bleeding including ICH. Those with mild RV dysfunction will generally recover well on anticoagulation alone. We believe that those on the severe end of the spectrum (eg, severe RV dysfunction, severe hypoxemia, significant tachycardia, but who (by definition) are normotensive, can be considered for systemic thrombolysis, particularly when the trend appears to be worsening. Although catheter-directed techniques with a lower bleeding risk are being utilized more frequently in this setting, mortality data are still lacking. The available data for half-dose systemic thrombolysis are intriguing and may be applicable in some clinical settings, particularly when patients have relative contraindications to thrombolysis or are elderly, small, or frail. Use of systemic thrombolysis continues to have an important role in acute PE, although in a distinct minority of patients. Unfortunately, while overall CTEPH rates after PE appear to be lower, there is no proof that thrombolysis lowers the rate further.

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