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CURRENT CONTROVERSIES IN THROMBOLYTIC USE IN ACUTE PULMONARY EMBOLISM

Brit Long, MD* and Alex Koyfman, MD†

*Department of Emergency Medicine, San Antonio Military Medical Center, Fort Sam Houston, Texas and †Department of Emergency Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas
Reprint Address: Brit Long, MD, 506 Dakota Street, Apartment 1, San Antonio, TX 78203

□ **Abstract—Background: Acute pulmonary embolism (PE) has an annual incidence of 100,000 cases in the United States and is divided into three categories: nonmassive, submassive, and massive. Several studies have evaluated the use of thrombolytics in submassive and massive PE. Objective: Our aim was to provide emergency physicians with an updated review of the controversy about the use of thrombolytics in submassive and massive PE. Discussion: Nonmassive PE is defined as PE in the setting of no signs of right ventricular strain (echocardiogram or biomarker) and hemodynamic stability. Submassive PE is defined as evidence of right ventricular strain with lack of hemodynamic instability. Massive PE occurs with occlusive thromboembolism that causes hemodynamic instability. Thrombolysis is warranted in patients with massive PE. Thrombolytic use in submassive PE with signs of right ventricular strain or damage presents a quandary for physicians. Several recent studies have evaluated the use of thrombolytics in patients with submassive PE. These studies have inconsistent definitions of submassive PE, evaluate differing primary outcomes, and use different treatment protocols with thrombolytics and anticoagulation agents. Although significant study heterogeneity exists, thrombolytics can improve long-term outcomes, with decreased bleeding risk with half-dose thrombolytics and catheter-directed treatments. Major bleeding significantly increases in patients over age 65 years. The risks and benefits of thrombolytic treatment—primarily improved long-term outcomes—should be considered on a case-by-case basis. Shared decision-making with the patient discussing the risks and benefits of treatment is advised. Conclusions: Thrombolytic use in massive PE is warranted, but patients with submassive PE require case-by-case analysis with shared decision making. The risks, including major hemorrhage, and benefits, primarily improved long-term outcomes, should be considered. Half-dose thrombolytics and catheter-directed treatment demonstrate advantages with decreased risk of bleeding and improved long-term functional outcomes. Further studies that assess risk stratification, functional outcomes, and treatment protocols are needed. Published by Elsevier Inc.**

□ **Keywords—acute pulmonary embolism; massive; submassive; thrombolytics; thrombolysis**

INTRODUCTION

Acute pulmonary embolism (PE) is a clinical entity with significant morbidity and mortality, with >100,000 cases in the United States annually. The incidence increases with age, from 1 per 1,500 in early life to 1 in 300 per year after age 80 years (1,2). The clinical presentation varies, with up to one-quarter of patients experiencing sudden death, while other patients with large thrombus burden experiencing few or no symptoms (3).

The American Heart Association and European Society of Cardiology classify acute PE into the following categories: nonmassive, submassive, and massive (4,5). Acute management and treatment is based on the patient, vital signs, and signs of clinical shock/instability. Mortality for PE reaches 17% in the first

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3 months, but rates of mortality in massive PE reach 30% to 50% (6–8). Increased mortality is seen in patients older than 70 years, congestive heart failure, chronic obstructive pulmonary disease, cancer, presence of one lung, hypotension, tachypnea, hypoxia, altered mental status, renal failure, prior cerebrovascular accident, right ventricular (RV) dysfunction, and elevated cardiac biomarkers (9–17).

Thrombolysis is an established therapy for massive PE, but the use of thrombolytics for submassive PE is controversial in the literature due to different definitions of submassive PE, different outcomes and definitions of benefit, and the risk of life-threatening hemorrhage (18). This has created a quandary for physicians in the management of submassive PE. Thrombolytic use may reduce intravascular thrombus size and pulmonary resistance; however, there is risk of major bleeding, including intracerebral hemorrhage (ICH). With the risks and benefits present for thrombolytics, the patient should be involved in the decision-making process.

DISCUSSION

Definitions of PE: Massive vs. Submassive

PE severity can be classified utilizing several systems, with prior classifications using anatomic criteria, including >50% obstruction of pulmonary vasculature or occlusion of two or more lobar arteries on computed tomography (CT). Currently, the definition for massive PE centers on hemodynamic instability. The definitions for massive PE, submassive PE, and nonmassive PE are shown in Table 1 (5,19). Of note, guidelines classify acute PE using different nomenclature. The following are the classifications: nonmassive or low risk, submassive or moderate/intermediate risk, and massive or high risk. This article will use nonmassive, submassive, and massive for classification.

Submassive PE accounts for approximately 20% of all PE, with up to 5% in-hospital mortality rate. Morbidity can also be severe, with increased risk of pulmonary hypertension, impaired quality of life, persistent RV dysfunction, and recurrent thrombus formation (17–19).

Table 1. Pulmonary Embolism Definitions and Criteria (4,5,19,20)

Type of Pulmonary Embolism	Definition
Massive	Pulselessness, persistent bradycardia with rate < 40 beats/min and signs of shock or sustained hypotension Sustained hypotension includes systolic blood pressure (SBP) of < 90 mm Hg for >15 min, a SBP of < 100 mm Hg in a patient with a history of hypertension, or a > 40% reduction in baseline SBP. Decrease in blood pressure must not be due to dysrhythmia, hypovolemia, sepsis, or left ventricular (LV) dysfunction
Submassive	Normal or near-normal SBP (≥90 mm Hg) with evidence of cardiopulmonary stress, including right ventricular (RV) dysfunction or myocardial necrosis Defined by RV dilatation on echocardiography (RV diameter divided by LV diameter > 0.9), RV systolic dysfunction on echocardiography, brain natriuretic peptide (BNP) elevation (>90 pg/mL), N-terminal pro-BNP elevation (>500 pg/mL), or electrocardiogram changes (new right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion). Myocardial necrosis is defined by elevation in troponin I or T over laboratory normal value or above patient baseline.
Nonmassive	No signs of clinical instability, hemodynamic compromise, or RV strain (echocardiogram or biomarker).

Rationale for Treatment

The primary reasons for treating PE include reduction in time to thrombus resolution, earlier reduction in pulmonary vascular hypertension and right heart strain, decreased recurrence of PE (present thrombus acts as a nidus to further increase clot formation), decreased risk of death, improved functional outcomes, and decreased long-term pulmonary hypertension (4,5). In massive PE and in patients requiring cardiopulmonary resuscitation, thrombolytics can reduce RV pressure, pulmonary artery pressure, improve preload, and improve left ventricular function. These benefits, particularly reduction in mortality, are controversial in submassive PE (21–23). However, utilization of thrombolytics may increase the risk of ICH and other hemorrhage (e.g., intra-abdominal, extremity, and renal), as well as cost (4,5).

Current Guidelines

Several society guidelines comment on the use of thrombolytics in PE. These guidelines for thrombolytic use in patients with PE from the American Heart Association (AHA), American College of Chest Physicians (ACCP), European Heart Association (EHA), and American College of Emergency Physicians (ACEP) are shown in Table 2 (4,5,19,20).

Table 2. Thrombolytic Use in Submassive and Massive Pulmonary Embolism (4,5,19,20)

Guideline	Submassive PE	Massive PE
American Heart Association	Fibrinolysis may be considered for patients with submassive 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)	Fibrinolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications. (Class IIa; Level of Evidence B)
The American College of Chest Physicians	In the majority of patients with acute PE and no hypotension, no thrombolytics should be given. (Grade 1B)	In patients with acute PE, systolic BP < 90 mm Hg, and low to moderate risk of bleeding, thrombolytic therapy is recommended. (Grade 2B) Thrombolytic therapy is recommended for patients with acute PE who decompensate after starting anticoagulation and have low bleeding risk. (Grade 2C).
European Heart Association	Routine use of thrombolysis in non–high-risk patients is not recommended, but may be considered in selected patients with intermediate-risk PE and after thorough consideration of conditions increasing the risk of bleeding.	Thrombolytic therapy is the first-line treatment in patients with high-risk PE presenting with cardiogenic shock or persistent arterial hypotension, with very few absolute contraindications.
The American College of Emergency Physicians	At this time, there is insufficient evidence to make any recommendations regarding use of thrombolytics in any subgroup of hemodynamically stable patients. Thrombolytics have been demonstrated to result in faster improvements in right ventricular function and pulmonary perfusion, but these benefits have not translated to improvements in mortality.	Administer thrombolytic therapy in hemodynamically unstable patients with confirmed PE for whom the benefits of treatment outweigh the risks of life-threatening bleeding complications.* (Level B) Consider thrombolytic therapy in hemodynamically unstable patients with a high clinical suspicion for PE for whom the diagnosis of PE cannot be confirmed in a timely manner. (Level C)

PE = pulmonary embolism; RV = right ventricle; BP = blood pressure.
* In centers with the capability for surgical or mechanical thrombectomy, procedural intervention may be used as an alternative therapy.

Treatments

Thrombolytics include alteplase, tenecteplase, and streptokinase. Before providing a thrombolytic medication, heparin should be discontinued during infusion and contraindications should be reviewed (24–27). These contraindications include prior ICH, known structural intracranial cerebrovascular disease, suspected aortic dissection, known malignant intracranial neoplasm, ischemic stroke within 3 months, recent surgery encroaching on the brain or spinal cord, and recent closed-head or facial trauma with fracture or intracerebral injury. Streptokinase has fallen out of favor with the current agents that demonstrate greater safety. Alteplase can be given as a full bolus at 10 mg i.v., followed by 90 mg i.v. over 2 h (for patients > 65 kg). For patients < 65 kg, dosing should be adjusted so the medication does not exceed 1.5 mg/kg. Half-dose treatment can also be used, with alteplase given at 50 mg i.v. bolus. Tenecteplase can be used with bolus dosing, but it is not approved for PE by the Food and Drug Administration. Dosing for tenecteplase is weight-adjusted, with an i.v. bolus of 30 to 50 mg over 5 s with a 5-mg increase every 10 kg from 60 to 90 kg (4,5).

Thrombolysis in Cardiac Arrest due to PE

For patients with cardiac arrest, confirmation with CT angiography is not feasible, but this does provide an opportunity for bedside ultrasound (US). Evaluation of RV size and function is vital in these circumstances using US. If findings on US are consistent with PE, such as RV dysfunction or enlargement, consideration should be given for systemic thrombolysis, catheter-directed thrombolysis, or surgical embolectomy. This will require cooperation with cardiothoracic surgery (4,5,28,29).

Thrombolysis in Massive PE

In massive PE, thrombolysis is recommended, and support exists for patients undergoing cardiopulmonary

resuscitation with echocardiogram evidence of massive PE to receive systemic thrombolytics (30). The majority of clinicians and society guidelines state thrombolysis in patients with hemodynamic instability and massive PE is acceptable (4,5,19,20). Several trials evaluating thrombolysis in unstable patients have found improved mortality. One meta-analysis of trials including 154 patients with massive PE found that thrombolysis decreased the risk of death and recurrent PE from 19% to 9.4%, with an odds ratio (OR) of 0.45 (95% confidence interval 0.22–0.9) (5). For massive PE, a number needed to treat (NNT) to prevent recurrent PE or death with thrombolysis was found to be 10. The number needed to harm (NNH) was 8, however (31). A separate study by Thabut et al. estimated the number needed to harm to be 17 (32).

Thrombolysis in Submassive PE

Several recent studies and meta-analysis have evaluated the use of thrombolytics in submassive PE. Unfortunately, these studies have varying outcomes and definitions for PE (31,32). MAPPET-3 (Management Strategies and Prognosis of Pulmonary Embolism Trial-3) in 2002 was a double-blinded, randomized clinical trial including 256 patients with PE and pulmonary hypertension or RV dysfunction. The patients did not have arterial hypotension or shock. Patients were given heparin with 100 mg of alteplase, or heparin and placebo, with primary endpoint of in-hospital death or clinical deterioration. This was defined as need for vasopressors, surgical embolectomy, cardiopulmonary resuscitation, intubation, or secondary thrombolysis. No difference was found for mortality, but for patients treated with heparin alone, more cases of deterioration were found (24.6% compared to 10.2%; $p = 0.004$). No change in bleeding was found between the groups (33).

The MOPPET (Moderate Pulmonary Embolism Treated with Thrombolysis) trial in 2013 was a single-center, unblinded randomized trial with 121 patients with PE, but this study differs in that it used half-dose thrombolytics. This study is arguably the best supporter of thrombolytic use in PE. These patients had RV dysfunction and were relatively sicker than the patients in MAPPET-3, as these patients demonstrated greater rates of tachypnea, hypoxia, and tachycardia, which are potential signs of clinical decompensation. The moderate-risk PE patients were defined as >70% thrombus in the lobar or main pulmonary arteries (by CT pulmonary angiography), rather than using biomarkers or RV dysfunction. Of note, the investigators use moderate-risk PE, instead of submassive PE. However, these patients had smaller incidence of RV enlargement (21%) and RV dysfunction (6%). The interventional group received thrombolytics at half dose, or 50 mg alteplase, rather than full dose. The investigators used an anatomical definition of submassive PE based on the extent of thrombus. The primary outcome of pulmonary hypertension, as defined by echocardiography at 28 months, was decreased in the thrombolytic group (16% of patients vs. 57%; $p < 0.001$, NNT = 2). No bleeding was found in either group, which brings in to question the quality of data collection. Unfortunately no functional outcome was assessed, and no short-term outcomes were evaluated. This 41% difference in the primary endpoint is suspicious due to use of surrogate outcomes, rather than direct patient outcome. The investigators did not use symptoms plus echocardiographic findings, but echocardiographic findings alone. Evaluating pulmonary hypertension may reflect quality of life and exercise tolerance, but this is not certain (34).

The PEITHO (Pulmonary Embolism Thrombolysis) trial is the largest double-blinded multicenter randomized control trial to date on submassive PE, with 1,006 patients including patients with confirmed PE, abnormal RV on echocardiography or CT, and a positive troponin. Investigators randomized patients to heparin and placebo vs. heparin plus weight-based tenecteplase bolus, with a primary endpoint of death or hemodynamic collapse after 7 days. The primary endpoint was reduced in the thrombolytic group (2.6% vs. 5.6%; OR = 0.44; 95% CI 0.23–0.87; $p = 0.02$), but with an overall difference in hemorrhage of 9% between the thrombolytic and placebo groups. Those given thrombolytics also displayed 2% greater incidence of ICH, with increased minor bleeding in the tenecteplase group. The risk of major bleeding was greatly increased in patients older than 75 years (35).

The TOPCOAT (Treatment of Submassive Pulmonary Embolism with Tenecteplase or Placebo: Cardiopulmonary Outcomes at 3 months) trial in 2014 evaluated 83 patients with submassive PE randomized to tenecteplase with heparin or placebo with heparin. A short-term endpoint of death, need for intubation, or surgical thrombectomy was evaluated at 5 days, and the patients returned at 6 weeks for repeat echocardiogram and 6-min walk test. Patient perception of wellness was measured. Thrombolytic use was associated with higher probability of favorable composite outcome. This trial evaluated patients at 3 months using the composite outcome of recurrent PE, poor functional capacity of *36*-Item Short Form Health Survey (SF-36) score. Unfortunately, the only independent variable in the study statistically significant was self-assessment of health at 90 days using SF-36, which is a survey used for a variety of disease endpoints (36).

Fortunately, several meta-analyses have been completed on thrombolytic use in submassive PE. These meta-analyses have included the prior mentioned studies.

Chatterjee et al. evaluated mortality benefits and bleeding risks in hemodynamically stable patients with RV dysfunction receiving thrombolysis (37). The analysis evaluated 2,115 patients from four trials, finding NNH of 18 for major bleeding, which was not significant for patients younger than 65 years, with NNT of 59 for all-cause mortality benefit. The absolute risk reduction for mortality was 1.12%. Unfortunately, the included studies suffer from significant heterogeneity, with varying definitions of instability, major and minor bleeding, RV dysfunction, and thrombolytic dosing (37). Nakamura et al., in 2014, conducted a meta-analysis of six studies with 1,510 patients, finding a larger absolute risk difference for death of 1.6%, which was not significant (38). The Cochrane database conducted a systematic review of 18 studies with 2,197 patients, but due to significant trial heterogeneity, caution when interpreting results is warranted. The researchers state the low quality of evidence and significant bias limits providers. Thrombolytics were associated with reduced odds of death (OR = 0.57; 95% CI 0.29–0.89) and higher rates of major and minor bleeding (OR = 2.90; 95% CI 1.95–4.31) (39).

A fourth meta-analysis found a significant mortality difference for patients given thrombolytics, but when massive PE was removed, the mortality difference disappeared. A significant increase in rates of major bleeding was found in the thrombolytic group (40). One meta-analysis evaluated thrombolytics vs. anticoagulation in patients with submassive PE, including 15 trials and 1,247 patients. This study found a significant reduction in recurrent PE or death (OR = 0.37; 95% CI 0.21–0.66), with a significant increase in nonmajor bleeding (OR = 4.12; 95% CI 2.37–7.17). Surprisingly, major bleeding was not increased (41). All of these meta-analyses include studies with significant heterogeneity and differing definitions of submassive PE.

Catheter-Directed Treatment

Catheter-directed thrombolysis utilizes a catheter to direct thrombolytics with US assistance at the site of thrombus. One industry-sponsored study in 2014 included 59 patients with acute PE and RV enlargement based on echocardiogram, with patients randomized to US-directed thrombolytic with unfractionated heparin and heparin alone. RV dilatation at 24 h was improved in the catheter-directed thrombolytic group. No bleeding complications were found in the intervention group (28). The recently released SEATTLE II (A Prospective, Single-arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) trial was a multicenter, single-arm trial that evaluated US-facilitated, catheter-directed, low-dose thrombolysis. Investigators included 31 patients with massive PE and 119 patients with submassive PE. Investigators found treatment decreased RV dilatation, reduced pulmonary hypertension, decreased clot burden, and minimized risk of ICH in patients with PE. No patients suffered from ICH, but 1 patient suffered major bleeding with a groin hematoma and transient hypotension (29).

Where Does This Leave the Emergency Physician?

With the patient in cardiac arrest and evidence of PE, thrombolytics are warranted. For the patient with massive PE, the AHA, ACCP, EHA, and ACEP recommend thrombolytics (4,5,19,20). The patient with submassive PE has literature support to reduce long-term pulmonary hypertension with thrombolytic use, but with increased risk of bleeding.

The TOPCOAT and MOPPET trials demonstrate a benefit in long-term outcomes when using thrombolytics in patients with submassive PE. The question is whether the benefits provided to the patient outweigh the risk of major bleeding, specifically ICH at 2%. In addition, studies have utilized different primary outcomes, so how patients can truly benefit is uncertain, except for long-term pulmonary hypertension suggested in MOPPET and TOPCOAT (34,36). Patients with no prior lung disease and pulmonary reserve may show little benefit with thrombolytics, while the patient with conditions, such as heart failure or obstructive lung disease may have greater benefit but at the same time increased risk for bleeding with thrombolytics, as demonstrated in the PEITHO trial (35). The trials also utilize differing protocols and doses for thrombolytics, such as half-dose use in MOPPET. The potential risk of utilizing thrombolytics is major bleeding, particularly ICH. The PEITHO trial reported a bleeding rate of 11.5% with full-dose tenecteplase, compared to 2.4% in the heparin alone group. However, this trial utilized heparin drips targeting activated partial thromboplastin time of 2 to 2.5 times the upper limit of normal with full-dose thrombolytics (35). Chatterjee et al.'s meta-analysis found NNH of 18 for major bleeding, with increased risk in those older than 65 years (37). When patients were younger than the age of 65 years, no increased risk of major bleeding was found (33–41).

Shared Decision Making

In submassive PE, several aspects must be taken into account when considering thrombolytics, and the benefits and risks of bleeding should be discussed in a shared decision-making model with the patient, family, and admitting team. Ultimately, the physician at the bedside is the best judge of the relative merits of thrombolytics on a case-by-case basis after a discussion with the patient. The

AHA, EHA, and ACCP support the consideration of thrombolytics in patients with submassive PE and low risk of bleeding complications (4,5,19). First, patient factors, including comorbidities, age, current medications, and independence/functional ability, are vital. Patients older than 65 years of age or with significant comorbidities, including renal disease, have a significantly increased risk of major bleeding compared to younger patients. The absence of contraindications must be ensured. Second, the clinical picture, including clinical course, ultrasound, biomarkers (troponin and brain natriuretic peptide), and CT results should be evaluated. Signs of clinical decompensation, including hypoxia, worsening tachypnea or tachycardia, and even brief episodes of hypotension, require consideration of thrombolysis.

If the patient is a thrombolytic candidate with low risk of bleeding, using half-dose thrombolytics as a one-time bolus while discontinuing anticoagulation has literature support that demonstrates improved long-term functional outcomes, with lower risk of bleeding compared to full-dose thrombolytics. If thrombolytics at a one-time half dose is not sufficient, a second similar dose can be provided while observing the patient for clinical improvement or decline. Starting anticoagulation after a period of observation for bleeding and decompensation may reduce risk of major bleeding (42).

Catheter-directed treatments provide a separate avenue for patient management. With their extremely low risk of major bleeding, these agents are optimal first-line treatment options. Their use can assist in patients with increased risk of bleeding (such as patients older than 65 years of age), patients with clinical decompensation, and in patients who fail to improve with initial thrombolytic dosing (28,29,43).

Patients with submassive PE will likely require intensive care unit admission due to clot burden and potential clinical decompensation.

CONCLUSIONS

Thrombolytic use in massive PE is warranted, yet submassive PE presents a quandary for physicians. Current literature including meta-analyses have inconsistent definitions of submassive PE, lack functional outcomes, have differing primary outcomes and assessments, and use different treatment protocols with thrombolytics and anticoagulation agents. Literature does support improvement in long-term outcomes with thrombolytics, with increased risk of major bleeding in high-risk patients. The risks and benefits of thrombolytic treatment, primarily improved long-term outcomes, should be considered on a case-by-case basis. Shared decision making with the patient discussing the risks and benefits of treatment is advised. Further studies that assess risk stratification, functional outcomes, and treatment protocols with thrombolytic dosing are needed.

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ARTICLE SUMMARY

1. Why is this topic important?

Acute pulmonary embolism (PE) is a disease with significant morbidity and mortality. The use of thrombolytics is supported in patients with massive PE, but their use in submassive acute PE is controversial.

2. What does this review attempt to show?

This review evaluates the current literature and controversy in thrombolytic use in submassive pulmonary embolism.

3. What are the key findings?

Massive PE warrants thrombolytic use. However, thrombolytic use in submassive PE is controversial, with significant study heterogeneity. Improvement in long-term functional outcomes has been observed with thrombolytic use for submassive PE, though the risk of bleeding significantly increases over age 65 years. Half-dose thrombolytics and catheter-directed treatments are options with significant benefit and lower risk of bleeding.

4. How is patient care impacted?

This review evaluates the current evidence for thrombolytic use in PE. Ultimately, shared decision making with the patient is required for thrombolytic use in submassive PE. Several treatment options exist that display low risk of major bleeding while improving outcomes.