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Submassive Pulmonary Embolism: Risk Evaluation and Role of Fibrinolysis

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Abstract Submassive pulmonary embolism (PE) is characterized by hemodynamic stability with evidence of right ventricular dysfunction or myocardial necrosis, and represents a heterogeneous population at risk for adverse outcomes. Although patients with this subtype of PE are at higher risk of death, it is unclear whether escalation of care with fibrinolytic therapy mitigates this risk. The controversial role of fibrinolytic therapy for submassive PE is driven by a paucity of data, conflicting results from clinical trials, and lack of reliable positive predictive markers of mortality in this population. When compared with anticoagulation therapy alone, systemic fibrinolytic therapy leads to a more rapid improvement in pulmonary artery hemodynamics, restoration of right ventricular function, improved lung perfusion, and fewer episodes of clinical deterioration. The clinical significance of these findings remains uncertain because fibrinolytic therapy has not been demonstrated to improve mortality or reduce recurrent PE in patients with submassive PE. However, it is unclear whether this reflects methodological limitations such as small sample size and rescue fibrinolytic therapy in those assigned placebo, the absence of benefit in all patients with submassive PE, or the benefit is limited to an undefined, high-risk subset. The decision to administer adjunctive fibrinolytics in patients with submassive PE should be made on an individual basis, with serious consideration given to those with severe PE-related clinical manifestations and an acceptable risk of bleeding.

Keywords Thrombolytics · Fibrinolytics · Pulmonary embolism · Submassive · Massive

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Introduction

In the US, venous thromboembolic (VTE) disease affects an estimated 300,000–600,000 individuals each year, and approximately one-third of patients seeking medical care for VTE are diagnosed with pulmonary embolism (PE) [1]. The prognosis and outcomes associated with PE are diverse. Patients with PE are at risk for morbid outcomes such as recurrent VTE and chronic thromboembolic pulmonary hypertension (CTEPH); moreover, PE is the primary cause of mortality associated with VTE, the leading cause of preventable hospital death, and a common cause of sudden death [1]. Acute PE has a correspondingly wide range of clinical manifestations, many of which are nonspecific and sometimes asymptomatic, making a rapid diagnosis difficult to establish. Despite advances in the tools used to identify PE, it is often undetected and continues to be a challenging diagnosis [2].

Therapeutic anticoagulation reduces the incidence of recurrent VTE by inhibiting the growth and propagation of formed thrombi. It is a proven treatment modality recommended for all patients with highly suspected or confirmed acute PE without contraindications [3••, 4••]. Anticoagulation therapy does not, however, accelerate lysis of existing thrombi and is not effective for prompt restoration of perfusion in patients with cardiovascular collapse; the adjunctive use of fibrinolytics would be needed to yield these effects. When compared with anticoagulation therapy alone, systemic fibrinolytic therapy leads to a more rapid improvement in pulmonary artery hemodynamics, restoration of right ventricular (RV) function, and improved lung perfusion [3••, 4••]. However, fibrinolytic therapy has not been demonstrated to improve mortality or prevent recurrent VTE in non-massive PE and is associated with a higher risk of serious bleeding [3••, 4••]. Therefore, the net clinical benefit of fibrinolytic therapy in patients with acute PE appears to have the greatest potential when it is given early to patients with clinical characteristics associated with a high risk of death.

The considerable risk of early mortality as well as the serious adverse effects associated with treatment of acute PE highlights the need for prompt risk stratification to identify candidates who may require escalation of care, including fibrinolytic therapy. Outcomes from multicenter, international registry data derived from patients with acute PE consistently identified sustained hypotension and circulatory arrest as indicators of substantially higher mortality [5, 6]. Accordingly, massive PE is defined as sustained hypotension, pulselessness, or persistent bradycardia attributable to acute PE [3••, 4••]. It is associated with a high mortality rate but accounts for fewer than 5 % of all patients with acute PE [4••, 5]. Patients with massive PE are widely accepted as eligible for more aggressive interventions such as systemic or catheter-directed fibrinolytic therapy or surgical embolectomy [3••, 4••].

In contrast with massive PE, patients with neither hypotension nor evidence of RV dysfunction (RVD) account for the majority of patients with acute PE, have a more favorable prognosis, and are considered low risk for adverse outcomes when treated with anticoagulation therapy alone [3••, 4••]. In fact, preserved RV function and normal cardiac biomarkers portend excellent negative predictive value and may be useful for identifying patients suitable for early discharge and outpatient therapy [7]. Among patients with acute PE, this subtype is the least likely to benefit from fibrinolytic therapy.

Submassive PE is characterized by the presence of hemodynamic stability with evidence of RVD or myocardial necrosis and represents a heterogeneous population that accounts for approximately 20–25 % of patients with acute PE [4••, 8]. However, unlike massive and low-risk PE subtypes, fibrinolytic therapy for submassive PE is an area of significant therapeutic controversy complicated by a paucity of data and difficulty in early recognition of patients most likely to benefit. The purpose of this article is to evaluate the risks and review the fibrinolysis-related clinical trial outcomes associated with submassive PE.

Submassive Pulmonary Embolism: Definition and Risk Evaluation

In normotensive patients with acute PE, evidence of RVD or myocardial necrosis is associated with heightened risk for early mortality and adverse outcomes; these patients are considered to have submassive PE. Several common diagnostic tools (electrocardiography, echocardiography, computed tomography) and laboratory tests [brain natriuretic peptide (BNP), *N*-terminal pro-BNP (NT-proBNP)] can be employed to determine if RVD exists, and troponin levels can be obtained to assess for myocardial necrosis.

Right Ventricular Dysfunction

In a prospective study conducted in hemodynamically stable PE patients, 9.2 % of those with RVD developed PE-related shock and 4.6 % died; in contrast, these complications were absent in patients without RVD [9]. The available data, which include the MAPPET-3 and ICOPER registries, prospective studies, and meta-analyses, have related echocardiographic- or computed tomography-determined RVD with a 2- to 2.57-fold excess risk of mortality within 30 days and a high negative predictive value approaching 100 % for ruling out an adverse outcome in normotensive PE patients [10–14]. However, use of RVD alone has been shown to be insufficient for predicting PE-related mortality (positive predictive value of ~5–12 %) and the composite of PE-related death or clinical deterioration [12, 14–16].

Elevated levels of BNP or NT-proBNP are significantly associated with RVD [7, 17]. In a systematic review of hemodynamically stable PE patients, high BNP and NT-proBNP concentrations corresponded with a 9.5- and 5.7-fold increased risk of in-hospital or 30-day mortality, respectively [13]. Although both markers were modestly accurate at ruling out an adverse outcome (BNP's negative predictive value =76 %; NT-proBNP's negative predictive value =81 %), they were not reliable for predicting in-hospital or 30-day survival or the composite of in-hospital PE-related death or clinical deterioration [13, 15].

Myocardial Necrosis

In a study of normotensive patients with acute PE, all in-hospital deaths (12.5 %) occurred in those with elevated

troponin T levels, among which the in-hospital mortality rate was 25 % [18]. Results of prospective studies and meta-analyses performed in hemodynamically stable PE patients have correlated troponin I or T elevation with a 2.66- to 21-fold increased risk of PE-related mortality and 4.12- to 24.1-fold excess risk of adverse clinical events [13, 14, 18, 19]. The use of these cardiac biomarkers may be helpful for ruling out (negative predictive value 95.8 %) the development of PE-related death; however, they are unreliable for ruling it in (positive predictive value 10.5 %) [14]. In a multicenter, prospective study by Bova et al., troponin I was not a reliable predictor of the composite of in-hospital PE-related death or clinical deterioration [15].

Right Ventricular Dysfunction Combined with Myocardial Necrosis

The presence of both RVD and elevated troponin has been associated with a 5.6-fold increased risk of 30-day mortality in normotensive PE patients [20]. Their combined use, however, is still inadequate (negative predictive 94.7 %; positive predictive value 15.2 %) for predicting PE-related mortality [14].

The American College of Chest Physicians (ACCP) and American Heart Association (AHA) recommend assessment of hemodynamics and RV function to distinguish between massive, submassive, and low-risk subtypes (Table 1) [4••].

Table 1 Acute pulmonary embolism subgroup definitions [4••]

Subgroup	Definition
Massive	Sustained hypotension not due to a cause other than PE
	SBP <90 mmHg for at least 15 min or requiring inotropic support
	Persistent profound bradycardia
	HR <40 bpm with signs or symptoms of shock
	Pulselessness
Submassive	RVD without hypotension
	RV dilation (LV:RV diameter >0.9 on computed tomography or echocardiography)
	RV systolic dysfunction on echocardiography
	Elevation of BNP (>90 pg/ml)
	Elevation of NT-proBNP (>500 pg/ml)
	Electrocardiographic changes
	Myocardial necrosis without hypotension
	Elevation of troponin I (>0.04 ng/ml)
	Elevation of troponin T (>0.1 ng/ml)
Low risk	No evidence of RVD, myocardial necrosis, or hypotension

BNP brain natriuretic peptide, *HR* heart rate, *LV* left ventricle, *NT-proBNP* N-terminal pro-BNP, *PE* pulmonary embolism, *RV* right ventricle, *RVD* right ventricular dysfunction, *SBP* systolic blood pressure

Fibrinolytics: Mechanism of Action

Fibrinolytic agents work by enhancing the conversion of inactive plasminogen within the circulation to active plasmin [21]. Both circulating and fibrin-bound plasminogen have the potential to be converted to the protease plasmin depending on the fibrin specificity of the fibrinolytic used. Once generated, plasmin acts on fibrin clots by cleaving both fibrinogen and fibrin crosslinks [22]. Degradation of coagulation factors V and VIII may also be possible with nonspecific plasmin. These processes of plasminogen activation and fibrinolysis continue until plasminogen activator inhibitor type-1 (PAI-1) or alpha-2 antiplasmin form a stable complex with free plasmin, which results in inactivation of this enzyme and cessation of the degradation phase. The older generation plasminogen activators such as streptokinase and urokinase are classified as nonspecific fibrinolytics due to their ability to lyse thrombus without fibrin specificity [23, 24]. The newer generation fibrinolytics, which include alteplase, reteplase, and tenecteplase, are classified as fibrin-specific and are more efficient at dissolving thrombi without depleting systemic coagulation factors, in contrast to non-fibrin specific agents [22, 25–27]. Dissolution of physiologic thrombi in addition to enhanced systemic activity of the nonspecific plasmin contributes to the bleeding complications associated with administration of fibrinolytics. Furthermore, agents that do not induce a significant depletion in circulating alpha-2 antiplasmin demonstrate less of a systemic fibrinolytic effect [27]. Pharmacokinetic and pharmacodynamic properties of fibrinolytics are summarized in Table 2.

Efficacy Outcomes Associated with Fibrinolysis in Submassive Pulmonary Embolism

The results of double-blind, randomized, controlled clinical trials evaluating fibrinolytics in submassive PE are presented in Table 3.

Right Ventricular Function and Lung Perfusion

The adjunctive use of fibrinolytics in normotensive patients with acute PE and RVD results in quicker resolution of RV impairment and perfusion lung defect compared to treatment with anticoagulation alone [28, 29]. Evidence from two small randomized trials [TIPES ($n = 58$), Fasullo et al. ($n = 72$)] demonstrated superior RV function improvements at 24 h ($p = 0.04$ and $p < 0.0001$) with fibrinolytic therapy compared to placebo [28, 29]. It is unclear, however, if this effect is maintained over time. TIPES indicated RVD reduction may not differ between

Table 2 Properties of fibrinolytics [22–24, 26, 27]

	1st Generation		2nd Generation	3rd Generation	
Compounds	Streptokinase	Urokinase	Alteplase (t-PA)	Reteplase (r-PA)	Tenecteplase (t-PA)
Source	Group C beta hemolytic strep	Human neonatal kidney cell tissue	Recombinant DNA	Recombinant DNA	Recombinant DNA
MW	47	30	70	39	70
Plasma half-life (min)	18–80	6–18	2–8	13–16	20–24
Plasminogen Activation	Indirect	Indirect	Direct	Direct	Direct
Fibrin specificity	–	–	++	+	+++
Fibrinogen depletion	N/A	N/A	16–36 %	63–75 %	4–15 %
Inhibited by PAI-1	N/A	N/A	Yes	Yes	No
FDA approval for PE	Yes	Yes	Yes	No	No
Fibrinolytic dose	250,000 IU IV bolus followed by 100,000 IU/h infusion for 24 h	4,400 IU/kg bolus, followed by 4,400 IU/kg/h for 12 h	100 mg IV infusion over 2 h	Double 10 U IV bolus 30 min apart	Weight-adjusted IV bolus over 5 s <60 kg: 30 mg ≥60–<70 kg: 35 mg ≥70–<80 kg: 40 mg ≥80–<90 kg: 45 mg ≥90 kg: 50 mg

FDA Food and Drug Administration, *IU* international units, *MW* molecular weight in 1,000 of Daltons, *N/A* not applicable, *PAI-1* plasminogen activator inhibitor-1, *PE* pulmonary embolism

Table 3 Randomized clinical trials

Study	Participants	Interventions	Efficacy				Safety			
MAPPET-3 (2002) [32•]	$n = 256$	Alteplase 100 mg over 2 h		*Alteplase*	*Placebo*	*Statistics*		*Alteplase*	*Placebo*	*Statistics*
	Hemodynamically stable PE	Placebo	All-cause mortality	3.4 %	2.2 %	$p = 0.71$	Major bleeding	0.8 %	3.6 %	$p = 0.29$
	Symptom onset ≤96 h	*** Both groups received unfractionated heparin IV	Recurrent PE	3.4 %	2.9 %	$p = 0.89$	Fatal bleeding	None	0.7 %	$p = 1.0$
	Evidence of RVD and/or pulmonary HTN		Treatment escalation	10.2 %	24.6 %	$p = 0.004$	Hemorrhagic stroke	None	None	$p = \text{NR}$
			Rescue fibrinolysis	7.6 %	23.2 %	$p = 0.001$				
			Catecholamine infusion	2.5 %	5.8 %	$p = 0.33$				
			Intubation	2.5 %	2.2 %	$p = 0.85$				
			CPR	None	0.7 %	$p = 1.0$				
TIPES (2010) [28]	$n = 58$	Tenecteplase (weight-based)		*Tenecteplase*	*Placebo*	*Statistics*		*Tenecteplase*	*Placebo*	*Statistics*
	Hemodynamically stable PE	Placebo	All-cause mortality	None	3.3 %	$p = \text{NR}$	Major bleeding	7.1 %	3.3 %	$p = \text{NR}$
	Symptom onset ≤10 days	*** Both groups received unfractionated heparin IV	Recurrent PE	3.6 %	3.3 %	$p = \text{NR}$	Minor bleeding	46.4 %	3.3 %	$p = \text{NR}$
	Evidence of RVD		Clinical deterioration	None	3.3 %	$p = \text{NR}$				
Fasullo et al. (2011) [29]	$n = 72$	Alteplase 100 mg over 2 h		*Alteplase*	*Placebo*	*Statistics*		*Alteplase*	*Placebo*	*Statistics*
	Hemodynamically stable PE	Placebo	All-cause mortality	None	14.2 %	$p = 0.055$	Major bleeding	5.4 %	2.85 %	$p = \text{NS}$
	Symptom onset ≤6 h	*** Both groups received unfractionated heparin IV					Minor bleeding	29.7 %	11.4 %	$p = 0.20$
	Evidence of RVD + dyspnea, chest pain, tachypnea, hypoxemia ($PO_2 \leq 75$ mm Hg), $PCO_2 < 40$ mm Hg, $SaO_2 < 90$ % in room air, D-dimer elevation, ECG with S1-Q3-T3 pattern or T wave inversion in V1 to V4 or RBBB or right axis deviation									

Table 3 continued

Study	Participants	Interventions	Efficacy	*Tenecteplase*	*Placebo*	*Statistics*	Safety	*Tenecteplase*	*Placebo*	*Statistics*
PEITHO (2013) [33••]	$n = 1006$	Tenecteplase (weight-based)	All-cause mortality	1.2 %	1.8 %	$p = 0.43$	Non-intracranial major bleeding	6.3 %	1.5 %	$p < 0.001$
	Hemodynamically stable PE	Placebo	Recurrent PE	0.2 %	1.0 %	$p = 0.12$	Fatal bleeding	0.4 %.	None	$p = \text{NR}$
	Symptom onset ≤15 days	*** Both groups received unfractionated heparin IV	Hemodynamic collapse	1.6 %	5.0 %	$p = 0.002$	Intracranial bleeding	2.0 %	0.2 %	$p = \text{NR}$
	Evidence of RVD + elevated troponin		Rescue fibrinolysis	0.8 %	4.6 %	$p < 0.001$				
			Catecholamine infusion	0.6 %	2.8 %	$p = \text{NR}$				
			Intubation	1.6 %	3.0 %	$p = 0.13$				
			CPR	0.2 %	1.0 %	$p = \text{NR}$				

CPR cardiopulmonary resuscitation, *ECG* electrocardiography, *HTN* hypertension, *IV* intravenously, *NR* not reported, *NS* not significant, *PE* pulmonary embolism, PCO_2 partial pressure of carbon dioxide, PO_2 partial pressure of oxygen, *RBBB* right bundle-branch block, *RVD* right ventricular dysfunction, SaO_2 oxygen saturation

fibrinolysis and placebo at 7 days ($p =$ not significant), while Fasullo et al. suggested the benefit may persist throughout hospitalization ($p < 0.0001$) and also at 6 months ($p < 0.0001$) [28, 29]. In one retrospective cohort study ($n = 128$), fibrinolytic therapy yielded a larger relative improvement in perfusion lung defect compared to heparin monotherapy at 1 week (54 vs. 42 %; $p = 0.01$); additionally, a greater proportion of fibrinolysis-treated individuals attained >50 % relative improvement in perfusion lung defect (57 vs. 37 %; $p =$ not reported) [30].

Mortality

Despite more rapidly resolving RVD, use of fibrinolysis in hemodynamically stable PE patients who have RVD does not appear to be effective for improving short-term survival. The initial evidence from early non-randomized studies provided conflicting results; one retrospective investigation suggested fibrinolysis might not affect in-hospital PE-related death, whereas subgroup analyses of a randomized trial and the MAPPET-3 registry alluded to reduced 30-day mortality with fibrinolysis [10, 30, 31]. Since these publications, the findings of four randomized studies (MAPPET-3, TIPES, Fasullo et al., PEITHO) exploring the role of fibrinolytics in normotensive PE patients who have RVD have been reported. MAPPET-3, the first randomized and second largest trial to date, concluded fibrinolysis does not reduce in-hospital all-cause mortality ($p = 0.71$) in hemodynamically stable PE patients with RVD and/or pulmonary hypertension [32•]. TIPES did not show any differences or reveal any trends, while Fasullo et al. suggested fibrinolysis may favorably impact short-term survival; both studies were small, however, and not adequately powered to detect differences in clinical outcomes [28, 29]. In the more recent PEITHO trial (not yet published), the largest study to date that included normotensive PE with RVD patients who also had evidence of myocardial necrosis, there were no differences in 7-day ($p = 0.43$) and 30-day mortality ($p = 0.42$) between those randomized to fibrinolysis and placebo [33••]. Several factors may be predictive of mortality risk and adverse outcomes. In MAPPET-3, age >70 years, female gender, and arterial hypoxemia were each associated with a significant 2.29-, 2.68-, and 3.57-fold increased risk of in-hospital death or treatment escalation, respectively [32•].

Recurrent Pulmonary Embolism

Current evidence suggests adjunctive fibrinolysis may not be useful for preventing recurrent PE in acute PE patients who are hemodynamically stable and have RVD. While

one subgroup analysis provided hope of a benefit and a positive trend was noted in one small randomized trial with fibrinolysis, results of other studies indicate a lack of effect [29, 31]. A retrospective cohort study and meta-analysis found comparable rates of recurrent PE between individuals receiving adjunctive fibrinolysis and heparin monotherapy [30, 34]. The MAPPET-3 and PEITHO trials confirmed these findings, with no observed differences between fibrinolysis and placebo for in-hospital ($p = 0.89$) and 7-day recurrent PE ($p = 0.12$), respectively [32•, 33••].

Hemodynamic Collapse and Escalation of Therapy

In spite of a lack of benefit on early mortality and recurrent PE, adjunctive fibrinolysis significantly decreases the risk of clinical deterioration and the need for additional interventions in hemodynamically stable PE patients with RVD. In MAPPET-3 and PEITHO, rates of in-hospital treatment escalation [composite of catecholamine infusion, rescue fibrinolysis, endotracheal intubation, cardiopulmonary resuscitation (CPR), embolectomy, or thrombus fragmentation] and 7-day hemodynamic collapse (composite of CPR, hypotension or drop in blood pressure, or catecholamine infusion) were significantly lower in patients receiving fibrinolysis compared to placebo ($p = 0.004$ and $p = 0.002$), respectively [32•, 33••]. The use of rescue fibrinolysis was the main driver of reduced in-hospital treatment escalation with fibrinolytic therapy in MAPPET-3 ($p = 0.001$), a benefit also evident in PEITHO ($p < 0.001$) [32•, 33••]. A review of secondary outcomes indicates fibrinolysis may not lead to reduced catecholamine initiation (MAPPET-3: $p = 0.33$; PEITHO: $p =$ not reported), intubation (MAPPET-3: $p = 0.85$; PEITHO: $p = 0.13$), and CPR (MAPPET-3: $p = 1.0$; PEITHO: $p =$ not reported). [32•, 33••] The benefits of fibrinolysis on clinical deterioration seen in MAPPET-3 and PEITHO may extend beyond the index hospitalization; in TIPES, more patients in the placebo group tended to be hospitalized for clinical worsening due to RVD at 6 months' follow-up (8.6 vs. 0 %; $p =$ not significant) [29].

Quality of Life

Use of fibrinolysis in hemodynamically stable patients with RVD may confer an improved quality of life at long-term follow-up. In an analysis of normotensive PE patients ($n = 162$) treated with adjunctive fibrinolysis or heparin alone, no patients treated with fibrinolytics had an RV systolic pressure (RVSP) at 6 months' follow-up that was greater than that at diagnosis [35]. In contrast, 27 % of heparin-only patients had worsened RVSP at 6 months, 46 % of which had dyspnea with limited activity or at rest (New York Heart Association $\geq$3) or exercise intolerance (6-min walking distance <330 m) [35]. These findings suggest fibrinolysis may reduce the development of CTEPH. When the analysis was limited to those who had RVSP >30 mmHg at baseline, however, only 9 % of heparin-monotherapy patients had an RVSP increase at 6 months [35].

Complications of Fibrinolysis

Table 3 also summarizes key safety results, including total major, intracranial, fatal, and minor bleedings, from randomized clinical trials evaluating the use of fibrinolysis in submassive PE.

The occurrence of serious bleeding complications is the main concern associated with fibrinolytic therapy. The available data, however, have not consistently demonstrated higher rates of total major or severe bleeding with adjunctive fibrinolysis in hemodynamically stable PE patients with RVD. There were more severe hemorrhagic episodes in those receiving fibrinolysis compared to heparin monotherapy in one retrospective cohort study (9.4 vs. 0 %; $p = 0.028$), while similar rates of major bleeding were observed between fibrinolysis and control groups in a meta-analysis (RR 0.86; CI 0.18–4.03) [30, 34]. The results of randomized trials have also been conflicting. In MAPPET-3 and Fasullo et al., there were no differences in major bleeding between fibrinolysis and placebo groups [29, 32•]. The larger PEITHO trial, in contrast, saw higher rates of non-intracranial major bleeding within 7 days in the fibrinolytic group ($p < 0.001$) [33••]. The reasons for these discordant findings are unclear, but one possible explanation could be differing patient populations. The mean age in MAPPET-3 and Fasullo et al. was 62 years and 56 years, respectively. Since patients enrolled in PEITHO were older (mean age 66 years) and 32 % were age >75 years, a relative contraindication to use of fibrinolytics, they may have been at a higher risk of bleeding. There is currently no validated tool for predicting bleeding risk with fibrinolytics in PE [3••]. Table 4 lists contraindications and warnings regarding fibrinolytics [3••].

The administration of fibrinolytics in hemodynamically stable PE patients with RVD may produce higher rates of intracranial bleeding or hemorrhagic strokes and similar rates of fatal bleeding compared to treatment with anticoagulation alone. A retrospective cohort study showed that in-hospital intracranial bleeding tended to occur more commonly in those receiving adjunctive fibrinolysis (4.7 vs. 0 %; $p = 0.24$), and the PEITHO trial yielded similar findings (2.0 vs. 0.2 %; $p =$ not reported) [30, 33••]. Interestingly, there were no hemorrhagic strokes in either treatment group in MAPPET-3 [32•]. Several factors may be associated with increased risk of intracranial hemorrhage. One retrospective analysis that utilized a national database of 49,500 PE

Table 4 Major and relative contraindications to fibrinolytics [3••]

Major contraindications	Relative contraindications
Structural intracranial disease	SBP >180 mmHg
Previous intracranial hemorrhage	DBP >110 mmHg
Ischemic stroke within 3 months	Recent bleeding (nonintracranial)
Active bleeding	Recent surgery or invasive procedure
Recent brain or spinal surgery	Ischemic stroke more than 3 months previously
Recent head trauma with fracture or brain injury	Anticoagulation
Bleeding diathesis	Traumatic cardiopulmonary resuscitation
	Pericarditis or pericardial fluid
	Diabetic retinopathy
	Pregnancy
	Age >75 years
	Low body weight (e.g., <60 kg)
	Female sex
	African-American race

DBP diastolic blood pressure, *SBP* systolic blood pressure

patients treated with fibrinolysis found a higher rate of intracerebral hemorrhage in patients age >65 years or with kidney disease compared to those age ≤65 years without kidney disease (1.4 vs. 0.5 %; $p < 0.0001$) [36]. The prevalence of intracerebral hemorrhage was also increased in patients for whom PE was a secondary diagnosis compared to those in whom it was a primary diagnosis (1.7 vs. 0.6 %; $p < 0.0001$) [36]. An elevated diastolic blood pressure has additionally been linked to excess intracranial bleed risk [37]. The incidence of fatal bleeding with fibrinolytics in hemodynamically stable PE patients with RVD appears to be low (<1.0 %) based on findings from MAPPET-3 and PEITHO and no different than when treated with anticoagulation alone [32•, 33••].

The available data consistently hint at increased risk of minor bleedings with adjunctive fibrinolytics in normotensive PE patients with RVD. In TIPES, minor bleedings occurred more frequently (14-fold) with fibrinolysis compared to placebo at 30 days (p = not reported) [28]. Fasullo et al. presented similar findings, with fibrinolytic use associated with a 2.6- and 2-fold excess risk of in-hospital ($p = 0.20$) and 6 months' minor bleedings (43.2 vs. 22 %; $p = 0.005$), respectively [29].

Who Should Be Considered for Fibrinolytics?

Given the lack of established benefit on early mortality and recurrent PE and increased risk of serious bleeding complications, caution is warranted when deciding whether to pursue this course of therapy in a particular patient with submassive PE. A review of current guideline recommendations as well as patient-specific characteristics may facilitate the decision process.

The most recent ACCP guidelines state that most patients who do not meet criteria for massive PE should not receive fibrinolytic therapy (grade 1C), with the exception of a select group of normotensive patients who are characterized as having a high risk of death or hypotension (i.e., submassive PE) but a low risk of bleeding (Grade 2C) [3••]. The guidelines further outline that radiographic imaging and laboratory measures, in combination with evidence of clinical instability, may be used to identify this population. Radiographic and laboratory evidence includes RVD on electrocardiogram, echocardiography, or computed tomography, as well as biomarkers, such as elevated troponin and BNP; furthermore, clinical instability markers include a decrease in systolic blood pressure that is still greater than 90 mmHg, tachycardia, elevated jugular venous pressure, poor tissue perfusion, and hypoxemia [3••]. Similarly, AHA proposed a treatment algorithm for use of fibrinolytics in submassive PE based upon analogous evidence of RVD and risk for hemodynamic instability [4••]. Although both recommending bodies stress the need to assess for PE severity based on RV function and evidence of clinical instability as well as to evaluate the risk of bleeding, there remains a lack of data to determine for which specific normotensive patients fibrinolysis is not only most effective but also reasonably safe.

In addition to the recommendations set forth by ACCP and AHA, current evidence suggests that several characteristics may be useful when evaluating whether fibrinolytics will be effective for submassive PE. These include patient age, extent of PE, and duration of symptoms. In PEITHO, patients ≤75 years old who received fibrinolysis had a significantly reduced risk of the primary end point of all-cause death or hemodynamic collapse within 7 days (OR 0.33; CI 0.12–0.85), while those >75 years old did not derive the same benefit (OR 0.63; CI 0.23–1.66) [33••]. Parker et al. [38] determined that more extensive pulmonary perfusion defects prior to fibrinolytic therapy were correlated with more significant improvements in pulmonary function following fibrinolysis. This study, in addition to that of Daniels et al., confirmed there is an inverse relationship between duration of PE symptoms and improvement in lung reperfusion post-fibrinolysis; therefore, patients are likely to derive the most benefit from fibrinolytics if they are initiated soon after symptom onset [38, 39]. The latter study, however, also determined that benefits from fibrinolysis may be observed if initiated within 14 days after symptom onset [39].

Consideration of a patient's risk of bleeding with fibrinolytic therapy must be assessed prior to initiation (see section on "Complications of Fibrinolysis" and Table 4).

Fibrinolytic Choices

Currently, the only two agents available on the US market that have been approved by the Food and Drug Administration (FDA) for use in patients with acute PE are urokinase and alteplase. Despite having an FDA indication for treating acute PE, streptokinase is no longer available for use. Both urokinase and alteplase only have indications for treating acute massive or hemodynamically unstable PE. Drug-specific characteristics may be considered when selecting an agent for fibrinolysis. Newer generation plasminogen activators have enhanced fibrin specificity to allow preferential activation of clot-bound plasminogen and limitation of systemic side effects. Unfortunately, since there are no definitive studies that have proved the superiority of one regimen over another, cost and hospital formulary availability might be the deciding factors on which agent is available for administration. Of note, the fibrinolytic agent evaluated in MAPPET-3 and Fasullo et al. was alteplase, whereas tenecteplase was studied in TIPES and PEITHO [28, 29, 32•, 33••]. See Table 2 for a summary of the pharmacokinetic and pharmacodynamic properties with fibrinolytics.

Adjunctive Anticoagulation

According to both AHA and ACCP, patients with confirmed PE and without contraindications should be initiated on therapeutic anticoagulation regardless of whether fibrinolytics are to be utilized [3••, 4••]. Heparin anticoagulation is an option and includes intravenous or subcutaneous unfractionated heparin (UFH) targeted to an activated partial thromboplastin time (aPTT) of 2- to 2.5-times the control. Other options include subcutaneous low-molecular-weight heparin and subcutaneous fondaparinux, a synthetic pentasaccharide [3••, 4••]. For patients with a history of heparin-induced thrombocytopenia, alternative anticoagulants, such as argatroban, lepirudin, or bivalirudin, should be utilized [4••]. There have been no trials comparing the efficacy and safety of various anticoagulation regimens in conjunction with fibrinolysis, but in general most experience lies with intravenous UFH.

Practices regarding the concomitant administration of anticoagulants with fibrinolytics differ amongst countries. In the US, it is recommended to suspend intravenous UFH infusions during fibrinolytic administration [3••]. This cessation of anticoagulation, however, is not routinely performed in other countries, perhaps due to the differing administration requirements of the various fibrinolytics utilized; no studies have compared the two schemes [3••]. It is nevertheless recommended to recheck the aPTT immediately following the fibrinolytic infusion to ensure it is not at supratherapeutic levels prior to restarting the intravenous UFH infusion [3••].

Long-term anticoagulation with either a vitamin K antagonist (VKA) or an oral target-specific factor Xa inhibitor should commence as recommended for PE by the ACCP guidelines [3••]. If a VKA is selected, heparin or a heparin-alternative anticoagulant should continue for at least 5 days and until the international normalized ratio (INR) is therapeutic (2.0–3.0) for at least 24 h [3••]. Caution is warranted if heparin alternatives are utilized given the INR can be elevated in the presence of certain agents; therefore, modifications in INR monitoring and VKA dosage adjustments are recommended [40]. For the latter option, rivaroxaban is currently the only FDA-approved oral target-specific anticoagulant for prevention of recurrent PE, and conversion to this therapy from parenteral anticoagulants is agent-specific [41]. It is important to note, however, that fibrinolysis-treated patients were excluded from the pivotal trial that investigated rivaroxaban use for acute PE [42]. Duration of long-term anticoagulation for PE is dependent upon whether the event is the first occurrence, whether a probable cause can be identified, and also the patient's bleeding risk; nonetheless, treatment should generally continue for a minimum of 3 months [3••].

Conclusion

The role of adjunctive fibrinolysis in patients with submassive PE is controversial. Consistent evidence has demonstrated that the presence of RVD and/or myocardial necrosis identifies a subgroup of normotensive PE patients at elevated risk for early mortality and adverse outcomes. It has, therefore, been hoped that routine use of fibrinolytics may improve survival and prevent recurrent PE in this patient population given its established benefit in massive PE. The published and preliminary findings from the MAPPET-3 and PEITHO trials, respectively, have proven otherwise and revealed similar rates of both outcomes between treatment groups; this is not too surprising given the poor positive predictive values of RVD and/or myocardial necrosis for estimating mortality. The co-administration of fibrinolysis did yield a favorable effect on in-hospital clinical deterioration and possible benefit on quality of life. However, given the potential for serious hemorrhagic complications associated with fibrinolytic therapy, its regular use in the broad range of submassive PE

patients who have various levels of bleeding risks cannot be recommended.

The MAPPET-3 and PEITHO trials both enrolled patients with broad severities of risk. It is quite possible that adjunctive fibrinolysis may confer survival advantages and prevent PE recurrence in the severest subset of submassive PE patients. Current literature has not been able to clearly characterize these individuals. However, the presented findings of PEITHO are only preliminary, and its final results may shed some light onto this question. Future studies should attempt to identify and explore the use of fibrinolytics in this higher-risk subgroup.

In summary, the decision to administer adjunctive fibrinolytics in patients with submassive PE should be made on an individual basis. Particularly, it should be considered in those with more severe PE-related clinical manifestations, as outlined by ACCP and AHA, and a low risk of bleeding to help reduce the risk of in-hospital clinical deterioration and treatment escalation. Since there is currently no validated tool for predicting bleeding risk with fibrinolytics in acute PE, careful attention should be paid to the presence of comorbidities, such as kidney disease, and contraindications.

Compliance with Ethics Guidelines

Conflict of Interest Rathasen Prom, Ryan Dull, Stephanie Z. Kujawski, Iwona Rybak, and John Fanikos declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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