Review Article

CME

Thrombolysis in Acute Pulmonary Thromboembolism

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Abstract: Acute pulmonary embolism (PE) is a common clinical condition with presentations that may vary from asymptomatic subsegmental emboli to massive vascular obstruction and shock with high risk of death. Identifying patients at highest risk for death is critical to select those who would benefit most from thrombolytic therapy. New and evolving clinical prediction models, serum tests, and imaging modalities are being used to improve our ability to identify potential thrombolytic candidates. We review the evolution of the present guidelines on the management of PE, specifically regarding the evolving role of thrombolytics; outcomes following thrombolytic therapy, including mortality, hemorrhage, hemodynamic improvement, and prevention of chronic thromboembolic pulmonary hypertension; and our strategy for risk stratification of pulmonary embolism.

Key Words: pulmonary embolism/drug therapy, risk assessment/methods, thrombolytic therapy

Physicians managing acute pulmonary embolism (PE) have a number of therapeutic options from which to choose, ranging from mechanical devices to intravenous anticoagulants and thrombolytics. Given the bleeding risks associated with thrombolytic therapy, a working knowledge of the evidence regarding patient selection for thrombolysis in acute PE is essential for managing this disease in a timely and accurate fashion.

The reported annual incidence of venous thromboembolism (VTE) is 23 to 69/100,000 cases per year,[1,2] with one-third of those presenting with acute PE.[3] Presentations vary from incidentally found, asymptomatic subsegmental emboli to massive vascular obstruction and shock, with mortality ranging from <1% to as high as 60%.[4] Rapid and accurate identification of patients at highest risk for death is crucial to correctly deliver thrombolytics to those in whom the benefits outweigh the risks. This article reviews the current US and European guidelines for the use of thrombolytics and the predictors of adverse outcomes in acute PE.

Evolution of the Definitions of PE Severity

In 2000, the European Society of Cardiology (ESC) developed a guideline to characterize PE by disease burden, classifying patients into "massive" and "nonmassive" PE (Appendix 1). The society defined massive PE as PE with shock or hypotension, defined as a systolic blood pressure (SBP) of <90 mm Hg or a drop of 40 mm Hg for >15 minutes not caused by new-onset arrhythmia, hypovolemia, or sepsis. They further subdivided the group that did not meet criteria for massive PE into submassive PE and nonmassive PE. Submassive PE was defined as acute PE with evidence of right ventricular (RV) strain without evidence of shock, whereas emboli with no shock or evidence of RV strain were considered nonmassive. The society hypothesized that hemodynamic consequences of PE are directly related to the size and number of PE.[5]

In 2008, the ESC reconvened and proposed an update and reclassification of their guidelines. They proposed the terms "high risk," "intermediate risk," and "low risk" to replace massive, submassive, and nonmassive, and emphasized that the prognosis of PE depends on hemodynamic instability caused by recurrent embolization and deterioration of RV function in the first 24 to 48 hours rather than the amount of pulmonary artery obstruction.[6]

In 2011, to further clarify the role of advanced therapies in the management of VTE, the American Heart Association (AHA) produced a classification of PE severity (Appendix 2). They defined massive PE as acute PE with shock as defined similarly by the ESC, but also included pulselessness or

Key Points

- Acute pulmonary embolism is a common diagnosis with a wide range of clinical presentations and outcomes.
- Although thrombolysis is the treatment of choice in patients at high risk, its role is debatable in patients at intermediate risk.

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Table 1. Classification of acute PE [6,7]

ESC classification	Definition	AHA classification	Definition	Recommended therapy
High-risk PE	Acute PE causing severe right ventricular failure producing arterial hypotension and shock	Massive PE	Acute PE with sustained hypotension, pulselessness, or persistent profound bradycardia with signs and symptoms of shock	Intensive treatment
Intermediate-risk PE	Acute PE with evidence of right ventricular failure in absence of hypotension and shock	Submassive PE	Acute PE without hypotension but with evidence of right ventricular dysfunction or myocardial necrosis	Hospitalization and risk stratification
Low-risk PE	Acute PE without arterial hypotension, shock or evidence of right ventricular dysfunction	Low-risk PE	Acute PE without clinical markers or adverse prognosis related to massive or submassive PE	Early discharge vs home therapy

AHA, American Heart Association; ESC, European Society of Cardiology; PE, pulmonary embolism.

persistent, profound bradycardia (defined as heart rate <40 bpm) in their definition of shock. They defined submassive PE as acute PE without systemic hypotension but with the presence of RV dysfunction (RVD) or laboratory evidence of myocardial necrosis. They chose to characterize the ESC's nonmassive PE group as low-risk PE defined as acute PE in the absence of clinical markers or adverse prognosis as defined in massive or submassive PE (Table 1).[7]

The 2012 American College of Chest Physicians (ACCP) updated their VTE guidelines but did not use specific terms to define the severity of PE (Appendix 3).[8]

Role of Thrombolysis in Management of Massive PE/High-Risk PE

Ten percent of all of the diagnosed cases of PE meet the definitions of high risk or massive PE.[9] Short-term mortality associated with massive/high-risk PE in untreated patients is as high as 60%.[4] Massive/high-risk PE typically is diagnosed by clinical presentation and multidetector computed tomography (MDCT); however, if suspicion for PE is high and MDCT is not available or the patient is too hemodynamically unstable to transfer for MDCT, European guidelines recommend bedside echocardiography to assess RVD and consider for thrombolysis if identified (class I recommendation, level of evidence: C).[6] Although no clinical trials have directly addressed the clinical outcomes of massive PE, subsets of trials demonstrate more rapid improvement in hemodynamic status in thrombolysis over heparin.[10–14] A subset of a meta-analysis concluded that thrombolysis had a benefit over heparin for the composite outcome prevention of recurrence or death (9.4% vs 19%, odds ratio [OR] 0.45, 95% confidence interval [CI] 0.22–0.92, number needed to treat 10, P for heterogeneity = 0.1).[15] Both European and US guidelines recommend treatment of massive/high-risk PE with thrombolysis in patients with an acceptable bleeding risk (ESC guidelines: class I recommendation, level of evidence: A; AHA guidelines: class IIa recommendation, level of evidence: B; ACCP guidelines: grade 2C recommendation).[6–8]

Role of Thrombolysis in Submassive PE/Intermediate-Risk PE

Although the true incidence of submassive/intermediate risk PE is not known, it is known that 90% of PE are hemodynamically stable at presentation.[9] Studies of RV function in PE suggest that 50% of patients with PE have evidence of RVD by echocardiogram,[10] suggesting that submassive/intermediate-risk PE may comprise nearly half of the nonmassive group. Because studies have reported higher mortality rates in patients who are hemodynamically stable with evidence of RVD (4%) as compared with those with normal RV function (0.9%),[16,17] experts have called for a reexamination of the use of thrombolytics in this higher-risk subgroup.

In 1993, Goldhaber et al[10] performed a randomized trial of 101 hemodynamically stable patients with acute PE to assess the effect of thrombolysis and heparin versus heparin alone on RV function and on pulmonary artery perfusion. They found more rapid improvement in RV function (39% vs 17%; $P = 0.005$) and pulmonary artery perfusion (14.6% vs 1.5%; $P < 0.0001$) at 24 hours with thrombolysis. They also showed a decrease in recurrent PE (0% vs 9%; $P = 0.06$) with thrombolysis after 14 days.[10] In 2002, a large randomized trial of patients with submassive/intermediate-risk PE conducted by Konstantinides et al[18] showed a significant decrease in adverse events, requiring escalation in management within 30 days of acute PE with recombinant tissue-plasminogen activator (rt-PA) plus heparin compared with heparin alone (10.2% vs 34%; $P = 0.004$). No significant difference in mortality (3.4% vs 2.2%; $P = 0.71$) and PE recurrence (3.4% versus 2.9%; $P = 0.89$) was noted. Also, rt-PA was not associated with an increased risk of major bleeding (0.8% vs 3.6%; $P = 0.29$) in this study.[18] In 2009, a meta-analysis that included both of the above studies confirmed a lack of mortality benefit of rt-PA over heparin in patients with hemodynamically stable PE (3.5% vs 4.6%, relative risk 0.97, 95% CI 0.38–2.51; $P = 0.73$). Again, the meta-analysis did not show an increased risk of major bleeding with the use of rt-PA (4.9% vs 4.6%, relative risk 0.94, 95% CI 0.39–2.27; $P = 0.61$) (Table 2).[19]

Table 2. Major studies comparing rt-PA plus heparin vs heparin alone in submassive PE [10,18,19]

Study	Study design/size	Follow-up period	Outcomes with rt-PA (rt-PA + heparin vs heparin)	Major hemorrhage (rt-PA + heparin vs heparin)
Goldhaber et al, 1993[10]	Randomized trial, n = 101	24 h and 14 d	Improvement in RV wall motion at 24 h (39% vs 17%, $P = 0.005$)	No difference in major hemorrhage (7% vs 2%, RR 3.59, 95% CI 0.39–33.3)
			Improvement in pulmonary perfusion at 24 h (14.6% vs 1.5%; $P < 0.0001$)	
			No significant difference in PE mortality (0% vs 4%; $P = 0.06$)	
			No significant difference in PE recurrence at 14 d (0% vs 9%; $P = 0.06$)	
Konstantinides et al, 2002[18]	Randomized trial, n = 256	30 d or hospital discharge	Decrease requirement of escalation of treatment (10.2% vs 34%; $P = 0.004$)	No significant difference in major hemorrhage (0.8% vs 3.6%; $P = 0.29$)
			No significant difference in mortality (3.4% vs 2.2%; $P = 0.71$)	
			No significant difference in PE recurrence (3.4% vs 2.9%; $P = 0.89$)	
Tardy et al, 2009[19]	Meta-analysis of 5 randomized trials, 1975–2008 (including above studies), n = 464	7 d–12 mo	No statistically significant reduction of death associated with PE or recurrent PE (3.5% vs 4.6%, RR 0.97, 95% CI 0.38–2.51; $P = 0.73$)	No significant difference in major hemorrhage (4.9% vs 4.6%, RR 0.94, 95% CI 0.39–2.27; $P = 0.61$)
			No statistically significant reduction of recurrent PE (2.3% vs 2.6%, RR 1.04, 95% CI 0.31–3.49; $P = 0.98$)	

"Major" studies indicate studies with >100 subjects participating.
CI, confidence interval; PE, pulmonary embolism; RR, relative risk; rt-PA, recombinant tissue-plasminogen activator.

Many questions remain, especially regarding the role of thrombolytics in the prevention of chronic thromoembolic pulmonary hypertension (CTEPH). Although >50% of patients have detectable thromboemboli at 6 months after diagnosis of acute PE,[20] 7% of patients with submassive/intermediate-risk PE have evidence of persistently elevated RV pressure by echocardiogram 6 months later[21]; however, only 3% of all patients with PE will develop symptomatic CTEPH.[22] Whether immediate thrombolysis can prevent this uncommon but significant morbidity to offset the known bleeding risks is being hotly debated.[23,24] Guidelines by the ESC and the AHA for the management of submassive/intermediate-risk PE suggest thrombolysis in selected cases in whom there is not an elevated risk of bleeding.[6,7] (AHA guidelines: class IIb, level of evidence: C; ESC guidelines: class IIb, level of evidence: B). The revised 2012 ACCP guideline recommends thrombolysis "in selected patients with acute PE not associated with hypotension and with a low risk of bleeding whose initial clinical presentation or clinical course after starting anticoagulation therapy suggests a high risk of developing hypotension" (grade 2C recommendation). The guideline does not specify how to identify those at high risk for hypotension.[8]

Although there is no mortality benefit to thrombolysis in intermediate-risk PE, there is immediate improvement in pulmonary hemodynamics and RVD. It is also notable that there is no increase in fatal bleeding risk with rt-PA versus heparin in large meta-analyses. Whether this translates into lower risks of CTEPH is an important question for future studies.

Risk Stratification in PE

Early risk stratification of PE is crucial to identify candidates for thrombolysis because these patients are at highest risk of death.[25] We review the current prognostic evidence of all of the available clinical, laboratory, and radiological markers below.

Clinical Markers

Hemodynamic status and underlying comorbid disease are independent risk factors associated with 30-day mortality.[26] Hemodynamic instability is defined as SBP <90 mm Hg, a decrease in SBP by >40 mm Hg for more than 15 minutes, or positive shock index. Shock index is defined as the cardiac rate divided by SBP, with a positive index as any value ≥1. Compared with SBP <90 mm Hg, the shock index is more sensitive for mortality at 1 month (30% vs 8%) but less specific (86% vs 96%) in one study of a registry of PE patients. The hazard ratio (HR) for shock index was 2.3 (95% CI 1.5–3.6P < 0.001) and for SBP <90 mm Hg the HR was 1.7 (95% CI 0.9–3.2; P = 0.08) (Table 3).[27]

Risk stratification for underlying comorbid clinical conditions can be performed by using the Pulmonary Embolism Severity Index. The index includes 11 clinical criteria incorporated into a predictive model that has been shown to be a valid predictor of 3-month mortality when low-risk scores (classes I and II) are compared with high–risk scores (classes III–V), with a sensitivity and specificity of 96% and 47%, respectively (Tables 4 and 5).[28]

Table 4. Variables of Pulmonary Embolism Severity Index[28]

Variables	Points
Demographic variables	
Age	1/y
Sex, male	10
Comorbid illness	
Cancer	30
Heart failure	10
Chronic lung disease	10
Clinical findings	
Heart rate >110 bpm	20
Systolic blood pressure <100 mm Hg	30
Respiratory rate ≥30/min	20
Temperature <36°C	20
Altered mental status	60
Arterial oxygen saturation <90%	20

Table 3. Sensitivity and specificity of prognostic factors in predicting 30-day all-cause mortality in acute PE

Prognostic factors	Cutoff values	Sensitivity, %	Specificity, %	OR/HR (95% CI)*	Statistical significance
Clinical markers	SBP <90[26]	8	97	HR 1.7 (CI 0.9–3.2)	P = 0.08
	Shock Index ≥1[26]	31	86	HR 2.3 (CI 1.5–3.6)	P < 0.001
	Low-risk (class I, II) vs high-risk (III,IV,V) PESI score†[27]	96	47		NR
D-dimer†	<1500 μg/mL[28]	95	26		NR
	>5500 μg/mL[28]	42	77	OR 4.1 (CI 1.1–73.5)	NR
ECG findings	Atrial arrhythmia[30]	25	88	OR (for any ECG finding) 2.56 (CI 1.49–4.57)	P < 0.001
	Complete RBBB[30]	29	87		
	Low voltage[30]	35	79		
	Q in III and aVF[30]	14	93		
	ST elevation in I, II, V4–V6[30]	16	94		
	ST depression in I, II, V4–V6[30]	49	62		
RVD by echo	RV/LV >0.9‡[40]	72	58	OR 2.66 (CI 1.68–5.99)	P = 0.01
	RV hypokinesis[34]	52	62	OR 1.94 (CI 1.23–3.06)	NR
RVD by MDCT	RV/LV >0.9[37]	78	38	HR 5.17 (CI 1.63–16.35)	P = 0.005
BNP‡	>75–100 pg/mL[40]	85	56	OR 6.5 (CI 2.0–21)	P = 0.002
Pro-BNP‡	600–1000 pg/mL[40]	95	43	OR 8.7 (CI 2.8–27)	P = 0.0002
Troponin‡	T_I >0.1 to >2; T_t >0.01 to >0.1[42]	70	72	OR 5.24 (CI 3.28–8.38)§	P < 0.001

**In multivariate analysis.*
†90-day all-cause mortality; <1500 μg/mL predicted favorable outcome, >5500 μg/mL predicted unfavorable outcome.
‡In-hospital mortality only.
§Univariate analysis only.
BNP, B-type natriuretic peptide; CI, confidence interval; ECG, electrocardiogram; echo, echocardiogram; HR, hazard ratio; LV, left ventricle; MDCT, multidetector computed tomography; NR, not reported; OR, odds ratio; PESI, Pulmonary Embolism Severity Index; RBBB, right bundle branch block; RV, right ventricle; RVD, right ventricular dysfunction; SBP, systolic blood pressure.

Table 5. Risk stratification based on Pulmonary Embolism Severity Index score[28]

Class	Points	30-d mortality, %	Risk
I	<65	0	Very low
II	66–85	1	Low
III	86–105	3.10	Intermediate
IV	106–125	10.40	High
V	>125	24.40	Very high

Cancer is an important clinical risk factor and comorbidity associated with PE. According to one study, immediate angiographic response to thrombolysis was similar in 57 patients with cancer compared with 254 patients without cancer (77% vs 73%; $P = 0.65$); however the extent of reperfusion was attenuated at 24 hours in patients with cancer (6% vs 13%; $P = 0.007$). Furthermore, major bleeding was not increased in patients with cancer compared with patients without cancer (12% vs 21%; $P = 0.12$).[29] Other authors have shown that thrombolytics can be safely used without significant bleeding complications in catheter-directed thrombolysis[30] and to treat occluded catheters.[31] This evidence suggests that thrombolysis carries similar risks and benefits in patients with and without cancer and may be safely used in acute PE. For chronic therapy, patients with cancer may benefit from long-term heparinoids over vitamin K antagonists.[8]

D-Dimer

The risk of mortality increases with increase in serum D-dimer level. According to one prospective study of 366 patients, predicted mortality within 3 months with D-dimer <1500 μg/L is 1.1%, which increases to 9.1% with a D-dimer level >5500 μg/L. Sensitivity and specificity of D-dimer level <1500 μg/L to predict low mortality is 95% and 26%, respectively, whereas sensitivity and specificity of D-dimer level >5500 μg/L to predict high mortality is 42% and 77%, respectively (OR 4.1, 95% CI 1.1–73.5; *P* not reported).[32] Specificity for D-dimer in elderly patients, patients with recurrent VTE, and patients with cancer is low.[33] Although D-dimer is a highly valuable tool for the diagnostic evaluation of low and intermediate-risk PE, it does not yet have a role in the risk stratification of PE.[6]

B-Type Natriuretic Peptide and Pro-BNP

B-type natriuretic peptide (BNP) and pro-BNP are associated with ventricular stress.[34] A systemic review and meta-analysis showed that elevated levels of BNP and pro-BNP were significantly associated with in-hospital mortality.[35] Sensitivity of BNP (using cutoffs of 75–100 pg/mL) to predict in-hospital mortality in a meta-analysis of 4 studies was 85%, whereas specificity was 43% (OR 6.5, 95% CI 2.0–21; $P = 0.002$). For pro-BNP (using cutoffs of 600 pg/mL in 2 studies, 1000 pg/mL in 2 studies), sensitivity was 95% with a specificity of 56% (OR 8.7, 95% CI 2.8–27; $P = 0.0002$) for in-hospital all-cause mortality.[35] BNP and pro-BNP were found to correlate with RVD as determined by echocardiogram.[36] Although these markers are not useful as individual risk-stratifying markers because of their low specificity and low positive predictive value, some authors argue that they can be useful in risk stratification by combining them with echocardiographic findings of RVD.[37]

Serum Troponin

According to a meta-analysis that used a wide range of troponin I cutoffs (>0.1 – >2.0) and troponin T cutoffs (>0.01 – >0.1), sensitivity was 70% and specificity was 72% for predicting in-hospital mortality (OR 5.24, 95% CI 3.28–8.38; $P < 0.01$).[38] Although studies in this meta-analysis used a wide range of cutoffs, the AHA guidelines recommend using troponin I of >0.4 and troponin T of >0.1 to identify RVD.[7] A prospective study using troponin, BNP, and echocardiogram found that troponin was not independently correlated with 30-day mortality when other covariables were controlled.[26]

Electrocardiogram

According to a study on 508 patients with massive or submassive PE from a large prospective registry, electrocardiogram (ECG) findings of RV strain were an independent predictor of 30-day mortality (29% vs 11%; Table 3). Sensitivity and specificity of various ECG findings to predict 30-day mortality ranges from 15% to 50% and 60% to 90%, respectively. Although no single finding on ECG is independently associated with adverse outcomes, the presence of any one of the group of the above ECG findings predicted 30-day mortality (OR 2.56, 95% CI 1.49–4.57; $P < 0.001$).[39]

RVD by Imaging

Most deaths from high-risk or intermediate-risk PE are associated with RVD.[40] Recent studies correlating RVD findings by echocardiogram as well as MDCT scan have been shown to predict short-term prognosis in acute PE.

Findings of RV strain pattern on echocardiography include RV dilatation and hypokinesis, flattening or paradoxical movement of interventricular septum toward the left ventricle, pulmonary hypertension, tricuspid regurgitation, and inspiratory collapse of the inferior vena cava.[41] Unfortunately, there is a lack of consensus on the standardization of these criteria.[42] Post hoc analysis of 1035 hemodynamically stable patients with PE in the International Cooperative Pulmonary Embolism Registry study demonstrated that RV hypokinesis detected by echocardiography is an independent risk factor for 30-day mortality, with sensitivity of 52% and specificity of 62% (OR1.94, 95% CI 1.23–3.06; *P* not reported).[43] A retrospective study of 950 patients from a large French registry showed that an RV/LV (left ventricle) end-diastolic diameter ratio of ≥0.9 was an independent risk factor for in-hospital mortality, with sensitivity of 72% and specificity of 58% (OR 2.66, 95%

CI 1.68–5.99; $P = 0.01$).[44] Specificity of RVD by echocardiography as a prognostic marker can be improved by combining it with biomarkers of myocardial injury.[45]

RV dilatation also can be detected by MDCT. In a retrospective study of 454 patients with acute PE, 30-day mortality rate was found to be 15% with RVD detected by MDCT (defined as an RV/LV ratio of >0.9) versus 7.7% without RVD identified.[46] Sensitivity and specificity of CT findings of RVD from this study are 78% and 38%, respectively (HR 5.17, 95% CI 1.63–16.35; $P = 0.005$). Although MDCT can provide anatomic information and diagnosis simultaneously, one disadvantage of MDCT over echocardiogram is that MDCT can only assess RV size but cannot determine other dynamic parameters such as hypokinesis of the RV wall.[36]

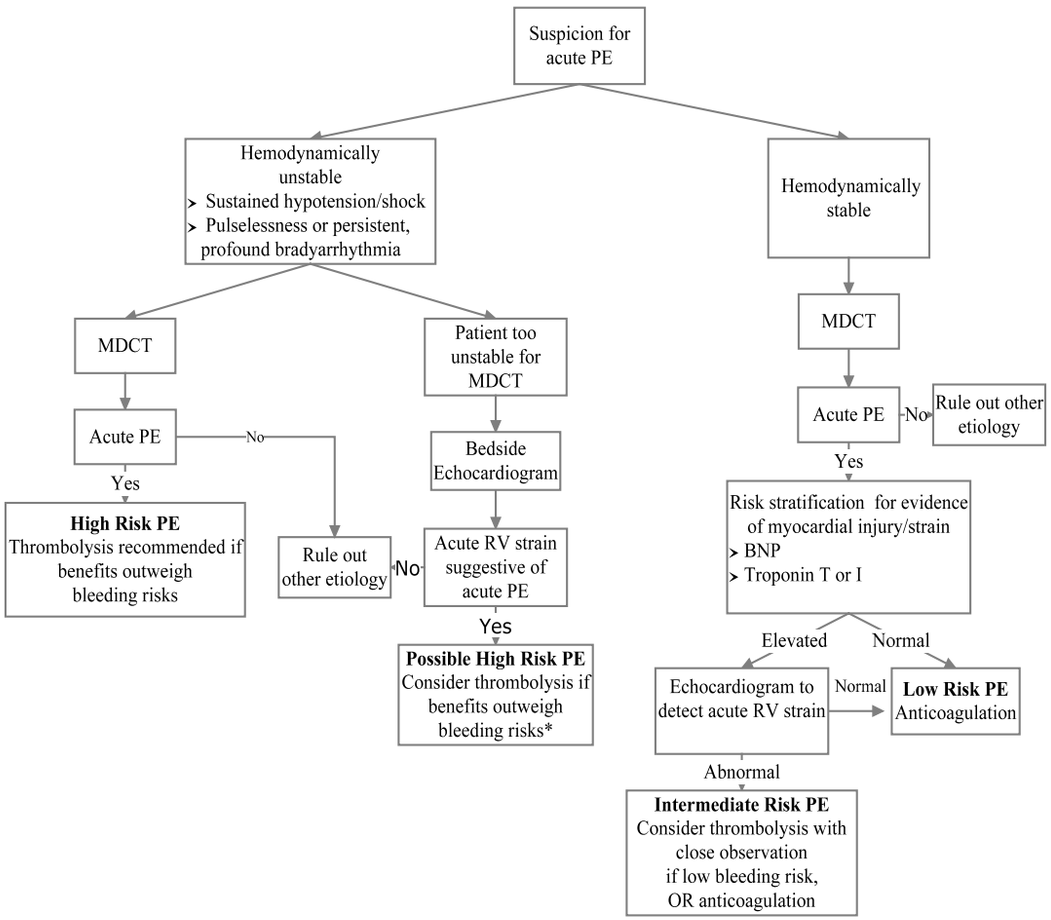
Suggested Prognostic Strategy for Clinical, Laboratory, and Radiological Markers

The following outlines our suggested management strategy for acute PE (Fig.):

1. All patients with hypotension (massive/high-risk PE) should be considered for thrombolysis (ESC guidelines: class I recommendation, level of evidence: A; AHA guidelines: class IIa recommendation, level of evidence: B; ACCP guidelines: grade 2C recommendation).[6–8]
2. In normotensive patients, determining clinical predictors, troponin elevation, and BNP elevation can add further prognostic information by detecting evidence of RVD and assist in triaging intermediate-risk from low-risk patients (ESC guidelines: class IIa recommendation, level of evidence: B). The AHA defines RVD as any one of the following criteria[7]:

- Echocardiographic evidence of RV/LV >0.9 or RV systolic dysfunction
- MDCT evidence of RV/LV >0.9
- BNP >90 pg/mL
- N-terminal pro-BNP >500 pg/mL
- ECG findings suggesting new complete or incomplete right bundle branch block, anteroseptal ST depression or elevation, or T-wave inversion.

3. Given that echocardiograms are not highly sensitive for predicting short-term mortality, the ESC recommends against routinely ordering them for hemodynamically stable patients (ESC guidelines: class III, level of evidence: C).[6] In light of the 2011 AHA guidelines, however, we believe that patients with elevated clinical



*European Society of Cardiology (ESC) Class 1 recommendation (Level of evidence: C)

Fig. Suggested management of acute pulmonary embolism (PE).

or biochemical markers would benefit from the additional prognostic information obtained from echocardiography. Unfortunately, urgent echocardiogram is not available at every hospital, which is a major limitation for this recommendation.

4. Thrombolytic therapy comes with both significant cost (US $2300) and bleeding risk, and physicians should consider all risks and benefits to intermediate-risk patients given the absence of proven mortality benefit.

Contraindications of Thrombolytic Therapy

The contraindications of thrombolytic therapy[47] (Table 6) for PE are the same as those used for contraindications for patients with acute myocardial infarction.

Future of Acute Pulmonary Thromboemboli Management

The role of thrombolysis in submassive/intermediate-risk PE remains a topic of debate. Although individual clinical and laboratory markers are too nonspecific to predict outcomes, combinations of these predictors may better identify those thrombolysis candidates who may gain short-term mortality benefits and long-term prevention of CTEPH.[37] New biomarkers for PE risk stratification, including heart-type fatty acid–binding protein and growth differentiation factor-15 may provide additional prognostic information.[48]

Given that bleeding from thrombolysis is the most limiting complication, dose reduction and alternative thrombolytics are being investigated. A randomized controlled trial showed equal efficacy in terms of improvement in RVD, lung perfusion and pulmonary artery obstruction, and fewer bleeding complications with alteplase 50 mg as compared with the presently used 100-mg dose.[49] Alternative thrombolytics such as reteplase and tenecteplase are also being studied.[34]

A large, multicenter, international, double-blind, placebo-controlled trial (NCT00639743), the Pulmonary Embolism International Thrombolysis trial, began enrolling subjects in 2007 and will involve 1000 patients in 12 countries. The study will compare tenecteplase plus standard anticoagulation with standard anticoagulation alone for submassive PE, with a primary endpoint of hemodynamic collapse and mortality at 7 days. Completion of the trial is expected around 2013.

Table 6. Contraindications of thrombolytic therapy[47]

Absolute
History of intracranial hemorrhage
History of cerebrovascular lesion
Known intracranial neoplasm
Ischemic stroke in last 3 mo
Aortic dissection
History of head or facial trauma within 3 mo
Active bleeding/bleeding diathesis
Relative
History of chronic severe uncontrolled hypertension
Systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg at presentation
Ischemic stroke before >3 mo, dementia, other intracranial pathology not included in absolute contraindications
Traumatic or prolonged (>10 min) cardiopulmonary resuscitation within <3 wk
Major surgery within <3 wk
History of internal bleeding within 2–4 wk
Noncompressible vascular puncture
Pregnancy
Active peptic ulcer
Active use of other anticoagulants
For streptokinase/anistreplase: prior exposure or history of allergic reaction to these agents

Conclusions

PE is a common, important diagnosis with a wide range of clinical outcomes. The identification of patients with the highest risk of death who are candidates for thrombolytic therapy is essential. Clinical markers, biomarkers, and radiological techniques assist in identifying patients without overt hypotension, and combinations of these may improve our future diagnostic accuracy. More study is needed to determine long-term prognosis, including persistence of abnormal pulmonary hemodynamics, in patients treated with and without thrombolysis.

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Appendix 1. Classes of recommendations and levels of evidence: European Society of Cardiology Guidelines

Classes of recommendations	
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful
Levels of evidence	
A	Data derived from multiple randomized clinical trials* or meta-analyses
B	Data derived from a single randomized clinical trial* or large nonrandomized studies
C	Consensus of opinion of experts and/or small studies, retrospective studies, registries

**Or large accuracy or outcome trial(s) in the case of diagnostic tests or strategies.*
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Appendix 2. Classes of recommendations and levels of evidence: American Heart Association

	Class I	Class IIa	Class IIb	Class III
	Benefit >>> risk	Benefit >> risk	Benefit ≥ risk	Risk ≥ benefit
Level of evidence	Procedure/treatment should be performed/ administered	Additional studies with focused objectives needed	Additional studies with broad objectives needed; additional registry data would be helpful	Procedure/Treatment should not be performed/administered because it is not helpful and may be harmful
A: Multiple populations evaluated*; data derived from multiple randomized clinical trials or meta-analysis	Recommendation that procedure or treatment is useful/effective	Recommendation in favor of treatment or procedure being useful/effective	Recommendation's usefulness/ efficacy less well established	Recommendation that procedure or treatment is not useful/effective and may be harmful
	Sufficient evidence from multiple randomized trials or meta-analyses	Some conflicting evidence from multiple randomized trials or meta-analyses	Greater conflicting evidence from multiple randomized trials or meta-analyses	Sufficient evidence from multiple randomized trials or meta-analyses
B: Limited population evaluated*; data derived from a single randomized trial or nonrandomized studies	Recommendation that procedure or treatment is useful/effective	Recommendation in favor of treatment or procedure being useful/effective	Recommendation's usefulness/ efficacy less well established	Recommendation that procedure treatment is not useful/effective and may be harmful
	Evidence from single randomized trial or nonrandomized studies	Some conflicting evidence from single randomized trial or nonrandomized studies	Greater conflicting evidence from single randomized trial or nonrandomized studies	Evidence from single randomized trial or nonrandomized studies
C: Very limited population evaluated*; only consensus opinion of experts, case studies, or standard of care	Recommendation that procedure or treatment is useful/effective	Recommendation in favor of treatment or procedure being useful/effective	Recommendation's usefulness/ efficacy less well established	Recommendation that procedure or treatment is not useful/effective and may be harmful
	Only expert opinion, case studies, or standard of care	Only diverging expert opinion, case studies, or standard of care	Only diverging expert opinion, case studies, or standard of care	Only expert opinion, case studies, or standard of care

**Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with level of evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a clear clinical consensus that a particular test or therapy is useful or effective.*

For recommendations (classes I and IIa, levels of evidence A and B only) regarding the comparative effectiveness of one treatment with respect to another, these words or phrases may be accompanied by the additional terms "in preference to" or "to choose" to indicate the favored intervention. For example, "Treatment A is recommended in preference to treatment B for …" or "It is reasonable to choose treatment A over treatment B for …." Studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

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Appendix 3. Strength of the recommendations and grading system: American College of Chest Physicians Guideline

Grade of recommendation	Benefit vs risk and burdens	Methodologic strength of supporting evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

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