Pulmonary embolism critical care update: prognosis, treatment, and research gaps

Jason D. Chodakowski and Daniel Mark Courtney

Purpose of review
We provide a timely update on treatment care issues facing clinicians and patients with acute pulmonary embolism accompanied by either right ventricular strain (sub-massive pulmonary embolism) or shock (massive pulmonary embolism).

Recent findings
Care and research changes over the last several years have resulted in four important trends: more consensus and accuracy in the way acute pulmonary embolism severity is described and communicated among acute care clinicians and researchers, increased availability and use of risk prediction scoring systems, increased use of advanced invasive therapy in the setting of severe right ventricular dysfunction, and emergence of multidisciplinary pulmonary embolism response teams to guide standard care decision-making.

Summary
Pulmonary embolism with shock should be treated with either systemic or catheter-based thrombolytic therapy in the absence of contraindications. Patients with sub-massive pulmonary embolism accompanied by right heart dysfunction who are treated with thrombolytic therapy likely will experience more rapid improvement in RV function and are less likely to progress to hemodynamic decompensation. This comes, however, with an increased risk of major bleeding. Our recommendation is to consider catheter-based or systemic fibrinolytic therapy in sub-massive pulmonary embolism cases where patients demonstrate high-risk features such as: severe RV strain on echo or CT, and importantly worsening over time trends in pulse, SBP, and oxygenation despite anticoagulation. Understanding the impact of advanced therapy beyond standard anticoagulation on patient-centered outcomes, such as functional status and quality of life represent a research knowledge gap.

Keywords
pulmonary embolism, risk stratification, thrombolytic therapy

INTRODUCTION

Pulmonary embolism continues to be a major threat to health with significant mortality and morbidity [1]. It remains the third most common cause of cardiovascular disease and death after myocardial infarction and stroke. Despite trends toward improved all-cause mortality [2] with advances in diagnosis and treatment, short-term mortality, hospital readmission, and burden of long-term complications remain high.

Future work to improve the pulmonary embolism-specific mortality requires identification and improvement in the care of higher risk pulmonary embolism subgroups, as these patients account for the highest mortality burden. This article focuses on these higher risk pulmonary embolism subgroups, providing an overview of current definitions, classification, and risk stratification approaches, as well as a discussion of available treatments focusing on recently completed or ongoing clinical trials.

PATHOPHYSIOLOGY

Acute severe pulmonary embolism results in circulatory and gas exchange failure, with right ventricle (RV) pressure overload being the ultimate cause of

Department of Emergency Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

Correspondence to Daniel Mark Courtney, MD, MS, Associate Professor of Emergency Medicine, Department of Emergency Medicine, Feinberg School of Medicine, Northwestern University, 211 E. Ontario Suite 200, Chicago, IL 60611, USA. Tel: +1 312 694 7000; e-mail: d-courtney@northwestern.edu

Curr Opin Crit Care 2018, 24:000–000
DOI:10.1097/MCC.0000000000000558

KEY POINTS

- Use of thrombolytic therapy either by systemic intravenous infusion or catheter-directed local infusion in the pulmonary vasculature is indicated for patients with massive pulmonary embolism (defined as pulmonary embolism causing shock or hypotension) in the absence of contraindications.
- There is uncertainty about the optimal role for systemic thrombolytic therapy and catheter-based therapy for patients with sub-massive pulmonary embolism (defined as acute RV dysfunction in the absence of shock/hypotension).
- Early data suggest low-dose thrombolytics may deliver the benefit of reduction in both clot burden and RV strain to sub-massive pulmonary embolism patients, while reducing the bleeding risk compared with full-dose thrombolytics. Low-dose thrombolytic therapy administered systemically or locally via catheters is a promising area for future investigation.
- Much of the recent work with catheter-directed therapy has reported image-based outcomes such as improvement in RV/LV ratio, whereas patient functional outcomes such as persistent dyspnea and reduced quality of life remain largely under investigated.

collapse. With sufficient obstruction and hypoxemic/hypercarbic, pulmonary artery vasoconstriction occurs, which further increases pulmonary artery pressure, resulting in a cascade of self-reinforcing decompensation: increased RV afterload, increased RV wall tension, increased RV ischemia, decreased RV contractility and further RV failure. These RV effects, if severity and duration is sufficient, can then impact the left ventricle (LV) with interventricular septal bowing, decreased LV preload, decreased cardiac output, decreased coronary perfusion pressure, global ischemia, cardiogenic shock, and eventually death [3].

CLASSIFICATION OF ACUTE PULMONARY EMBOLISM

As acute pulmonary embolism presents with such a wide clinical spectrum, early categorization of patients into different subgroups reflecting increasing clinical severity is important for prognostication, selection of appropriate level of care, and decisions regarding treatment and adjunctive therapy. Correlation between initial clot burden alone and clinical outcome is weak and in the last several years, more clinically predictive classification approaches were sought that account for the patient's underlying hemodynamic reserve and resulting physiologic response [9]. In short, burden of clot alone does not tell the whole picture of who is likely to do well and who is at risk for deterioration or persistent symptoms.

To this end, the most current classification systems have incorporated validated risk scores, biomarkers, and cardiovascular imaging findings to risk-stratify patients [3,4,5▪]. Although guidelines appear to widely agree on what defines massive (or high-risk) pulmonary embolism as well as nonmassive (or low-risk) pulmonary embolism, they differ with respect to intermediate-risk pulmonary embolism, reflecting the wide clinical spectrum and heterogeneity of acute pulmonary embolism. Patients with intermediate risk do not have systemic hypotension, but do exhibit some degree of cardiopulmonary stress by way of biomarker derangement or right ventricular (RV) hypokinesis/dysfunction (Table 1). Three international pulmonary embolism guidelines outline slightly different classification systems. The American College of Chest Physician guidelines[5▪] simply categorize patients into massive pulmonary embolism and nonmassive pulmonary embolism. The American Heart Association guidelines [4] categorize patients into massive pulmonary embolism, sub-massive pulmonary embolism, and all other pulmonary embolism. And the European Society of Cardiology provides the most granularity, with four categories created by sub-categorizing sub-massive pulmonary embolism into two additional categories [3]. Regardless, all approaches focus on two questions: first, is there hypotension or shock? and second, is there RV strain? How and where to manage these patients continues to be a major source ongoing debate and need for additional research [6▪,7].

MANAGEMENT

Thrombolysis in massive pulmonary embolism

Systemic thrombolytic therapy is supported by most major guidelines as first-line treatment for massive (high-risk) pulmonary embolism [3,4,5▪]. This recommendation is largely supported by a meta-analysis of RCTs that included massive pulmonary embolism and estimated a reduction in pulmonary embolism recurrence or death from 19.0 to 9.4%, with a number needed to treat (NNT) of 10 and a number needed to harm (NNH) of 8 for nonmajor bleeding [8]. Moreover, estimated near-term mortality of pulmonary embolism in the context of massive pulmonary embolism is 30% or greater, typically outweighing the likelihood of fatal or intracranial bleeding in patients without overt contraindications to thrombolytic drugs. Though case reports and small case series have described the use

Table 1. Classification systems of pulmonary embolism severity as defined by three international guidelines

AHA guidelines [4]	ESC guidelines [3]	ACCP/CHEST guidelines [5▪]
Massive Acute pulmonary embolism with sustained hypotension (SBP <90 mmHg) for at least 15 min or requiring inotropic support, not because of a cause other than pulmonary embolism (arrhythmias, hypovolemia, sepsis, LV dysfunction, pulselessness, profound bradycardia)	High risk Acute pulmonary embolism with shock or hypotension (SBP <90 mmHg) or SBP drop by greater than 40 mmHg for at least 15 min, not because of a cause other than pulmonary embolism	Pulmonary embolism with hypotension Acute pulmonary embolism with sustained hypotension (SBP <90 mmHg for at least 15 min, not because of a cause other than PE)
Submassive Acute pulmonary embolism without systemic hypotension (SBP >90 mmHg) and either RV dysfunction (RV/LV ratio >0.9, RV dysfunction on echo, RV dilation on CT scan) or elevated biomarkers (elevated BNP >100 pg/ml (NT-proBNP >900 pg/ml), elevated troponin I >0.1 ng/ml or above reference range of normal for lab)	Intermediate high risk Acute pulmonary embolism without hypotension and PESI[a] class III–V with BOTH RV dysfunction AND elevated biomarkers[b] Intermediate Low Risk Acute PE without hypotension but with elevated PESI score AND either one or none of the following: RV dysfunction on imaging OR elevated biomarkers	Pulmonary embolism without hypotension Acute pulmonary embolism without systemic hypotension and using clinical judgment and testing (imaging, serology) to determine level of monitoring and support needed
Nonmassive Acute pulmonary embolism without clinical markers of adverse prognosis (without signs of RV strain on CT or echo or troponin or BNP)	Low Risk Acute PE with low PESI score	

AACP, American college of chest physicians, AHA, American heart association; ESC, European society of cardiology; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; LV, left ventricle; RV, right ventricle.
[a]PESI Class III: 86–105 points; 30-day mortality estimate 3.2–7.1% [3]. PESI Class IV: 106–125 points; 30-day mortality estimate 4.0–11.4% [3]. PESI Class V: greater than 125 points; 30-day mortality 10.0–24.5% [3].
[b]Cutoff levels of biomarkers are not explicitly stated in ESC guidelines but it is reasonable to use similar cutoffs as AHA guidelines or whatever is considered above the normal value for local lab.

of thrombolytics in cardiac arrest suspected to be because of pulmonary embolism [9], widespread generalizability and definition of which patients are likely to benefit, and in what ways, is still unknown. There are four settings in which use of thrombolytics can be considered and we highlight our opinion here: known pulmonary embolism and shock without cardiac arrest – yes, thrombolytics should be used absent clear contraindication; known pulmonary embolism with return of spontaneous circulation (ROSC) and shock following cardiac arrest – yes, thrombolytics should be considered but extracorporeal life support is becoming more widely used in this scenario; patient currently in cardiac arrest with ongoing cardiopulmonary resuscitation (CPR) and suspected pulmonary embolism but confirmatory imaging not completed yet – no, thrombolytics have little utility here and should be avoided; shock after ROSC from cardiac arrest with suspected pulmonary embolism but confirmatory imaging not completed yet – yes, thrombolytics can be considered if there is a significant delay or barrier to confirmatory testing and a strong suspicion for pulmonary embolism, but our experience is that if patients are too unstable for computed tomography (CT), they are unlikely to adequately perfuse a systemic thrombolytic, may not have pulmonary embolism, and extracorporeal life support is a better option if available.

Thrombolysis in submassive pulmonary embolism

Thrombolytics for submassive (intermediate-risk) pulmonary embolism is controversial and presents a dilemma for clinicians because of: lack of large number and adequately powered studies, lack of consensus in guidelines, uncertainty as to what outcome is most likely to be positively impacted, and potential equipoise with respect to the risk/benefit analysis. The results of multiple registries following the outcomes of patients with pulmonary embolism indicate a short-term (in-hospital to 90 days) mortality of less than 3% in sub-massive pulmonary embolism [4], leaving little room for thrombolytics to improve mortality. The results of the two most recently published randomized controlled trials (RCTs) comparing thrombolysis vs. anticoagulation alone, TOPCOAT [10] and the larger PEITHO [11▪▪] trial have only served to confirm this state of

equipoise. Although PEITHO showed a number needed to treat (NNT) of 30 for the primary outcome of death or hemodynamic decompensation, this came at cost of numbers needed to harm (NNH) of 20 and 46 for major bleeding and intracranial hemorrhage (ICH), respectively [12]. Moreover, the benefit in PEITHO was predominantly driven by prevention of hemodynamic decompensation rather than mortality in the combined endpoint.

Proponents of thrombolytics for submassive pulmonary embolism have noted that past trials of thrombolytics in pulmonary embolism have been inadequately powered to detect a difference in mortality, overly focused on radiographic outcomes, and neglected to evaluate important functional outcomes. The latter point was partially addressed in the TOPCOAT trial, which reported a composite patient-oriented outcome that not only included mortality but also persistent RV dysfunction and quality of life at 90 days. Although there was no mortality benefit, this work did show improvement in these other outcomes [10]. A recently published follow-up to the much larger PEITHO trial failed to show benefit in mortality, dyspnea, functional limitation, or RV dysfunction with long-term follow-up [13▪▪]. This sub-analysis of the original PEITHO sample examined status at a median of 38 months and was not primarily powered for these outcomes, but it is informative that a third of all patients with submassive pulmonary embolism had some functional limitation this far remote from incident pulmonary embolism, regardless of thrombolytic receipt.

Much effort has been made to identify patients within the heterogeneous sub-massive category at higher risk for mortality. Evidence from multiple observational studies suggests that biomarkers and imaging findings of RV dysfunction in combination may improve prognostication and identification of patients who could benefit the most from thrombolysis [7,14]. However, no prospective studies have been published evaluating benefit of thrombolysis in these key clinical subgroups. Of note, a standard dose of systemic thrombolytic therapy for pulmonary embolism is 100 mg of alteplase over 2 h of intravenous infusion. It has been suggested that lower dose thrombolysis (to a maximum of 50 mg alteplase intravenously) could be effective for acute pulmonary embolism while reducing bleed risk [15,16]. A recently published meta-analysis that included patients undergoing recanalization (systemic full dose or systemic reduced dose or catheter delivery of thrombolytics) vs. anticoagulation alone reported no significant mortality difference in patients undergoing recanalization. However, the group receiving reduced dose systemic thrombolytics had the lowest probability of major bleeding [17▪▪]. The number of studies to date of reduced dose systemic thrombolytic therapy is small but finding the ideal dose that balances adverse outcome reduction with risk of bleeding remains an area of interest for future trials. In summary, benefits of full-dose systemic thrombolysis in unselected sub-massive pulmonary embolism patients may be offset by increased bleeding and should only be used in select patients at risk for deterioration after anticoagulation and without major contraindication to thrombolysis[3,4]. Without additional data, it is difficult to adopt a one size fits all approach. Patients who are at the higher end of the spectrum of risk for deterioration, based on ESC intermediate–high-risk classification, severity of RV strain on echo or CT, worsening over time trends in pulse and SBP despite anticoagulation, should be considered for systemic thrombolytics. It is reasonable to expect this will reduce the likelihood of further decompensation of hemodynamics and will improve work of breathing and oxygenation, but comes at an increased risk of major bleeding from approximately 2–10%. There are insufficient data at this time to recommend reduced dose systemic thrombolysis as a standard treatment.

Catheter-directed therapy

CDT utilizes intravascular delivery of thrombolytics as a continuous infusion in combination with devices for mechanical fragmentation or aspiration of emboli. Infusion is local and the dose is significantly lower than systemic therapy, potentially offering benefits of thrombolysis while minimizing systemic bleeding risk [18]. ULTIMA compared ultrasonic pulse-augmented CDT with unfractionated heparin vs. unfractionated heparin alone in 59 patients with intermediate-risk acute pulmonary embolism. It showed significantly improved RV-to-LV ratio reduction at 24 h for CDT vs. heparin alone, with no major bleeding, but was not powered to detect mortality differences [19]. The SEATTLE-2 and the ongoing PERFECT trials, two subsequent prospective, single-arm studies have shown improved RV-to-LV ratio reduction and improved hemodynamics, respectively, within the same patient following CDT [20,21]. The recently completed OPTALYSE trial [22▪▪] suggests these results can be achieved with shorter duration and smaller doses of local thrombolysis. Catheter-delivered thrombolytic therapy is a complicated intervention to test. There is important variance in the type of catheters used and duration and dose of thrombolytic drug delivered. Additionally, there is uncertainty if ultrasonic or other mechanical disruption or removal of the clot confer improved outcomes when used in

combination with local thrombolytic infusion. Two ongoing trials are evaluating standard CDT with thrombolytic therapy only vs. ultrasound-assisted CDT with thrombolytic therapy (clinical trials.gov #NCT02758574, and #NCT03086317).

In summary, available evidence for CDT shows improved image-based outcomes such as RV/LV ratio, but no studies to date report clear benefit for patient-oriented outcomes. There is also no randomized trial of CDT vs. systemic thrombolysis to date. Using this evidence base, the 2016 American College of Chest Physicians guidelines recommend systemic thrombolytics (rather than CDT) for pulmonary embolism patients with hypotension (Grade 2B) or cardiopulmonary deterioration after standard anticoagulation (Grade 2C). These same guidelines suggest CDT be considered in centers with expertise in the procedure for patients with hypotension that is complicated by either high-bleed risk, failed systemic thrombolytics, or likely collapse before systemic lytic effect is available (Grade 2C) [5▪]. However, in the majority of settings where collapse is imminent and catheter based interventions are not immediately available, our opinion and experience is that systemic thrombolytics would be the best option.

Extracorporeal life support

In the unstable, massive pulmonary embolism patient, ECLS can be a lifesaving intervention for patients who either have failed reperfusion therapy (catheter or systemic thrombolytics) or who are deteriorating so rapidly that arrest is imminent. These patients demonstrate clear worsening shock despite vasopressors and typically have severe work of breathing and respiratory failure. Published case series report a mortality rate between 40 and 60% for patients with massive pulmonary embolism treated with ECLS [23,24▪▪]. Mechanical intervention (CDT and surgical embolectomy) has been described as an adjunct to ECLS, improving mortality, hemodynamics, and early weaning off ECLS in selected patients [25]. However, there are no guidelines defining a clear role for ECLS in high-risk pulmonary embolism, and success is highly dependent on preparation, interdisciplinary teamwork, and available expertise.

Inhaled nitric oxide

Inhaled nitric oxide (INO) has the useful property of dilating the pulmonary vasculature without inducing systemic hypotension, making it a potentially useful adjunct in the treatment of sub-massive and massive pulmonary embolism by reducing RV strain and improving RV function. Results from a small case series showed some benefit from INO in oxygenation and hemodynamics [26]. The unpublished but completed iNOPE RCT (NCT01939301) compared INO with oxygen vs. oxygen alone in submassive pulmonary embolism for the combined primary outcome of improved RV systolic function, reduced RV strain by imaging, absence of cardiac injury as measured by high-sensitivity troponin T, and improved dyspnea [27▪].

Pulmonary Embolism Response Team approach

The concept of a multidisciplinary Pulmonary Embolism Response Team (PERT) has been popularized in the United States over the last few years [28▪▪,29▪]. This effort started as a grass roots effort highlighting the belief that optimal care of patients with pulmonary embolism in hemodynamic distress mandates a team-based approach from both interventional specialists (interventional radiology or interventional cardiology) and noninterventional specialists from emergency medicine, pulmonary medicine, critical care, and hematology. The basic concept is a central means of contacting this interdisciplinary team 24 h a day to assist patients, families, and clinicians in optimal risk stratification (Table 2), initial decisions regarding management (Table 3), and consideration of advanced treatment decisions including thrombolysis, CDT and ECLS [24▪▪]. Composition of the team is institution-dependent [30▪], but in most sites includes at minimum two to three persons from both interventional and noninterventional care teams, all of whom are

Table 2. Risk stratification scoring systems for pulmonary embolism

Pulmonary Embolism Severity Index (PESI)	Classifies acute pulmonary embolism into classes of increasing risk for 30-day mortality. Externally and prospectively validated.
Simplified Pulmonary Embolism Severity Index (sPESI)	Classifies acute pulmonary embolism into low-risk or high-risk for 30-day mortality. Externally validated but not in a newly prospective cohort.
BOVA Score	Classifies acute pulmonary embolism in three categories of increasing risk for pulmonary embolism-related complications (death from pulmonary embolism, hemodynamic collapse, or recurrent nonfatal pulmonary embolism) at 30 days. Externally validated but not in a newly-prospective cohort.

Table 3. Checklist after massive or sub-massive pulmonary embolism diagnosis

Checklist after massive or sub-massive pulmonary embolism diagnosis:
Assessment of hemodynamic/cardiopulmonary stress
Vitals – key to follow over time. Trends can be more important than initial values
Evaluate for right heart dysfunction on imaging (CT or echo images for RV >LV diameter at minimum).
Biomarkers (troponin, BNP or NT-proBNP)
Categorize pulmonary embolism based on one of the classification systems in Table 1
Initial resuscitation and hemodynamic support
Address hypoxemia; treat with oxygen to maintain oxygen saturation at least 92%
Careful fluid resuscitation (avoid RV overload; 250–500 cc test bolus)
Consider vasopressors and inotropes (norepinephrine considered first line but no strong evidence of superiority)
Risk-stratification for mortality and morbidity using scoring systems in Table 2
Assessment of immediate bleeding risk and contraindications to thrombolytics
Initiate anticoagulation therapy
if the patient is a potential candidate for catheter-directed therapy, confer with invasive team as to if they favor intravenous unfractionated heparin over subcutaneous low-molecular weight heparin or oral Xa inhibitor.
If the patient is not a potential candidate for catheter-directed therapy, time to anticoagulation and completeness of anticoagulation may be more reliable with subcutaneous low-molecular weight heparin than unfractionated heparin.
Use of Xa inhibitors is increasing as an alternative to low-molecular weight heparin but no clear superiority data in sub-massive pulmonary embolism exist and they likely have suboptimal absorption in massive pulmonary embolism with shock.
Decide appropriate management and level of care (ICU, floor)

BNP, brain natriuretic peptide; CT, computed tomography; LV, left ventricle; RV, right ventricle.

committed to work toward a standardized, process-based, care model. A PERT consortium exists as a nonprofit interdisciplinary specialty society in support of this effort globally. Ongoing work from the PERT consortium will describe and seek to reduce variance in practice patterns and care processes. To date, there are no effectiveness data on the PERT team approach.

CONCLUSION

Although the definition and management considerations for massive pulmonary embolism with hypotension and shock are straightforward, sub-massive pulmonary embolism is a heterogeneous disease with a wide spectrum of severity, resulting in uncertainty with respect to optimal treatment strategies. Although the majority of patients with sub-massive pulmonary embolism survive to hospital discharge, some exhibit worsening cardiopulmonary function with gradually increasing pulse, work of breathing, and declining oxygen saturation and blood pressure. Imprecise methods using vital signs, RV imaging patterns, and cardiac biomarkers have been developed for identifying patients with sub-massive pulmonary embolism with increased mortality and morbidity. Better methods to risk stratify sub-massive pulmonary embolism and clarifying, which patients with sub-massive pulmonary embolism (if any) benefit from advanced therapies beyond standard anticoagulation remain important knowledge gaps for future research.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Huang W, Goldberg RJ, Anderson FA, *et al.* Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE Study (1985-2009). Am J Med 2014; 127:829.e5–839.e5.
2. Jiménez D, de Miguel-Diez J, Guijarro R, *et al.*, RIETE Investigators. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE Regsitry. J Am Coll Cardiol 2016; 67:162–170.
3. The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35:3033–3073.
4. Jaff MR, McMurtry MS, Archer SL, *et al.*, American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011; 123:1788–1830.

5. Kearon C, Akl EA, Ornelas J, *et al.* Antithrombotic therapy for VTE disease:
■ CHEST Guideline and Expert Panel Report. Chest 2016; 149:315–352.

These are the most recently updated guidelines on pulmonary embolism care used globally. Experts surveyed and graded quality of all literature to date prior to publication. These guidelines offer somewhat conservative recommendations for treatment, which largely avoid interventional or systemic thrombolysis other than in patients at risk for acute hemodynamic collapse.

6. Becattini C, Agnelli G. Acute pulmonary embolism: mortality prediction by the
■ 2014 European Society of Cardiology risk stratification model. Eur Respir J 2017; 49:1601732.

This reflects European Cardiology guidelines that break sub-massive pulmonary embolism into two groups, intermediate–high–low-risk pulmonary embolism and intermediate–high-risk pulmonary embolism . Recommended treatment in the high-risk subcategory of sub-massive pulmonary embolism includes systemic or catheter-based thrombolysis.

7. Fernandez C, Bova C, Sanchez O, *et al.* Validation of a model for identification of patients at intermediate to high risk for complications associated with acute symptomatic pulmonary embolism. Chest 2015; 148:211–218.

8. Wan S. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004; 110:744–749.

9. Sharifi M, Berger J, Beeston P, *et al.,* ''PEAPETT'' investigators. Pulseless electrical activity in pulmonary embolism treated with thrombolysis (from the 'PEAPETT' study). Am J Emergency Med 2016; 34:1963–1967.

10. Kline JA, Nordenholz KE, Courtney DM, *et al.* Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost 2014; 12:459–468.

11. Meyer G, Vicaut E, Danays T, *et al.* Fibrinolysis for patients with intermediate-
■■ risk pulmonary embolism. N Engl J Med 2014; 370:1402–1411.

PEITHO: The first large randomized controlled trial of a single bolus thrombolytic in normotensive pulmonary embolism with right heart strain. Authors report a decrease in combined endpoint of hemodynamic collapse or death, but a significant increase in major bleeding. This report has resulted in a pullback in use of systemic thrombolytics in sub-massive pulmonary embolism.

12. Chatterjee S, Chakraborty A, Weinberg I, *et al.* Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 2014; 311:2414–2421.

13. Konstantinides SV, Vicaut E, Danays T, *et al.* Impact of thrombolytic therapy on
■■ the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol 2017; 69:1536–1544.

Follow-up of PEITHO showed no difference in all-cause mortality in systemic thrombolysis plus anticoagulation vs. anticoagulation alone at median of 38 months (20% treatment, 18% control). No difference in persistent dyspnea or functional limitation was seen, with approximately a third of the entire study population having that outcome.

14. Jiménez D, Kopecna D, Tapson V, *et al.* Derivation and validation of multimarker prognostication for normotensive patients with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med 2014; 189:718–726.

15. Sharifi M, Bay C, Skrocki L, *et al.,* 'MOPETT' Investigators. Moderate pulmonary embolism treated with thrombolysis (from the 'MOPETT' Trial). Am J Cardiol 2013; 111:273–277.

16. Zhang Z, Zhai Z-G, Liang L-R, *et al.* Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. Thromb Res 2014; 133:357–363.

17. Jiménez D, Martin-Saborido C, Muriel A, *et al.* Efficacy and safety outcomes of
■■ recanalisation procedures in patients with acute symptomatic pulmonary embolism: systematic review and network meta-analysis. Thorax 2018; 73:464–471.

Large meta-analysis pooling data from 22 randomized trials and 2494 patients that showed no difference in all-cause mortality between standard anticoagulation vs. systemic or catheter-based thrombolysis [odd ratio (OR) for mortality and 95% confidence interval (CI) were: full-dose thrombolysis: 0.60 (0.36–1.01); low-dose thrombolysis: 0.47 (0.14–1.59); catheter-associated thrombolysis: 0.31 (0.01–7.96). Full-dose thrombolysis was associated with increased risk of major bleeding whereas low-dose thrombolysis was associated with the lowest probability of death or bleeding. However, only 419 participants were enrolled in studies testing low-dose thrombolytics.

18. De Gregorio MA, Guirola JA, Lahuerta C, *et al.* Interventional radiology treatment for pulmonary embolism. World J Radiol 2017; 9:295–303.

19. Kucher N, Boekstegers P, Muller OJ, *et al.* Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014; 129:479–486.

20. Piazza G, Hohlfelder B, Jaff MR, *et al.* A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II Study. JACC Cardiovasc Interv 2015; 8:1382–1392.

21. Kuo WT, Banerjee A, Kim PS, *et al.* Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): initial results from a prospective multicenter registry. Chest 2015; 148:667–673.

22. Tapson VF, Sterling K, Jones N, *et al.* A randomized trial of the optimum
■■ duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE Trial. JACC Cardiovasc Interv 2018; 11:1401–1410.

This study sought to determine the optimal dose of alteplase when used in conjunction with ultrasound-assisted catheter-directed therapy for the outcome of RV/LV ratio improvement in 101 patients randomized to one of four alteplase dose groups (from 4 to 24 mg). The highest dose group had a fatal hemorrhage resulting in the highest dose arm of the trial closing early. Overall, results showed stepwise increase in clot clearance with increased dose.

23. Corsi F, Lebreton G, Bréchot N, *et al.* Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. Crit Care 2017; 21:76.

24. Al-Bawardy R, Rosenfield K, Borges J, *et al.* Extracorporeal membrane
■■ oxygenation in acute massive pulmonary embolism: a case series and review of the literature. Perfusion 2018; doi:10.1177/0267659118786830. [Epub ahead of print]

This study showed that ECMO can be feasibly implemented in patients who suffer cardiac arrest from pulmonary embolism with an overall 30-day mortality rate of 30% in this small case series of 13 patients. Care decisions were guided by an interdisciplinary PERT team and all patients received additional therapy (systemic thrombolysis or CDT or surgical embolectomy).

25. Dolmatova EV, Moazzami K, Cocke TP, *et al.* Extracorporeal membrane oxygenation in massive pulmonary embolism. Heart Lung 2017; 46: 106–109.

26. Summerfield DT, Desai H, Levitov A, *et al.* Inhaled nitric oxide as salvage therapy in massive pulmonary embolism: a case series. Respir Care 2012; 57:444–448.

27. Kline JA, Hall CL, Jones AE, *et al.* Randomized trial of inhaled nitric oxide to
■ treat acute pulmonary embolism: the iNOPE trial. Am Heart J 2017; 186:100–110.

This is the first study to randomize sub-massive pulmonary embolism patients to inhaled nitric oxide using a rigorous blinding technique as study design. Results are pending publications. Primary outcome was a combined endpoint of improvement of RV function, avoidance of cardiac injury as measured by high-sensitivity troponin T, and improved dyspnea at or after 24 h.

28. Kabrhel C, Rosovsky R, Channick R, *et al.* A multidisciplinary pulmonary
■■ embolism response team: initial 30-month experience with a novel approach to delivery of care to patients with submassive and massive pulmonary embolism. Chest 2016; 150:384–393.

This is one of the original studies describing the initiation and observations of starting a PERT team at a single center. This article provides definitions for a PERT team and suggestions on how one could be operationalized de novo.

29. Sista AK, Friedman OA, Dou E, *et al.* A pulmonary embolism response team's
■ initial 20 month experience treating 87 patients with sub-massive and massive pulmonary embolism. Vasc Med 2017; 23:65–71.

The PERT team concept is dependent on multidisciplinary team work. This article describes the integral role of interventional radiology in this team approach and early challenges and successes in coordinating care in this manner.

30. Barnes G, Giri J, Courtney DM, *et al.* Nuts and bolts of running a pulmonary
■ embolism response team: results from an organizational survey of the National PERT Consortium members. Hospital Pract 2017; 45:76–80.

This survey reports on the 19 institutions that had a functional PERT team in 2016. Nature of who composes the PERT team and description of services available and means of decision-making are described.