

# High-Risk Pulmonary Embolism: Current Evidence-Based Practices

CHRISTOPHER D. THEROUX, MD, MS; JASON M. ALIOTTA, MD; CHRISTOPHER J. MULLIN, MD, MHS

## ABSTRACT

Acute pulmonary embolism (PE) causes significant morbidity and mortality, particularly for patients with subsequent right ventricular (RV) dysfunction. Once diagnosed, risk stratification is imperative for therapeutic decision making and centers on evaluation of RV function. Treatment includes supportive care, systemic anticoagulation, and consideration of reperfusion therapy. In addition to systemic anticoagulation, patients with high-risk PE should receive reperfusion therapy, typically with systemic thrombolysis. The role of reperfusion therapies, which include catheter-based interventions, systemic thrombolysis, and surgical embolectomy, are controversial in the management of intermediate risk PE. Catheter directed thrombolysis (CDT) can be considered in certain intermediate risk patients although prospective, comparative data for its use are lacking. Surgical or catheter embolectomy are viable treatment options for high-risk patients in whom reperfusion therapy is warranted but who have absolute contraindications to thrombolysis. Further research is needed to better elucidate which patients with PE would most benefit from advanced reperfusion therapies.

**KEYWORDS:** pulmonary embolism, catheter-directed thrombolysis, systemic thrombolysis

## INTRODUCTION

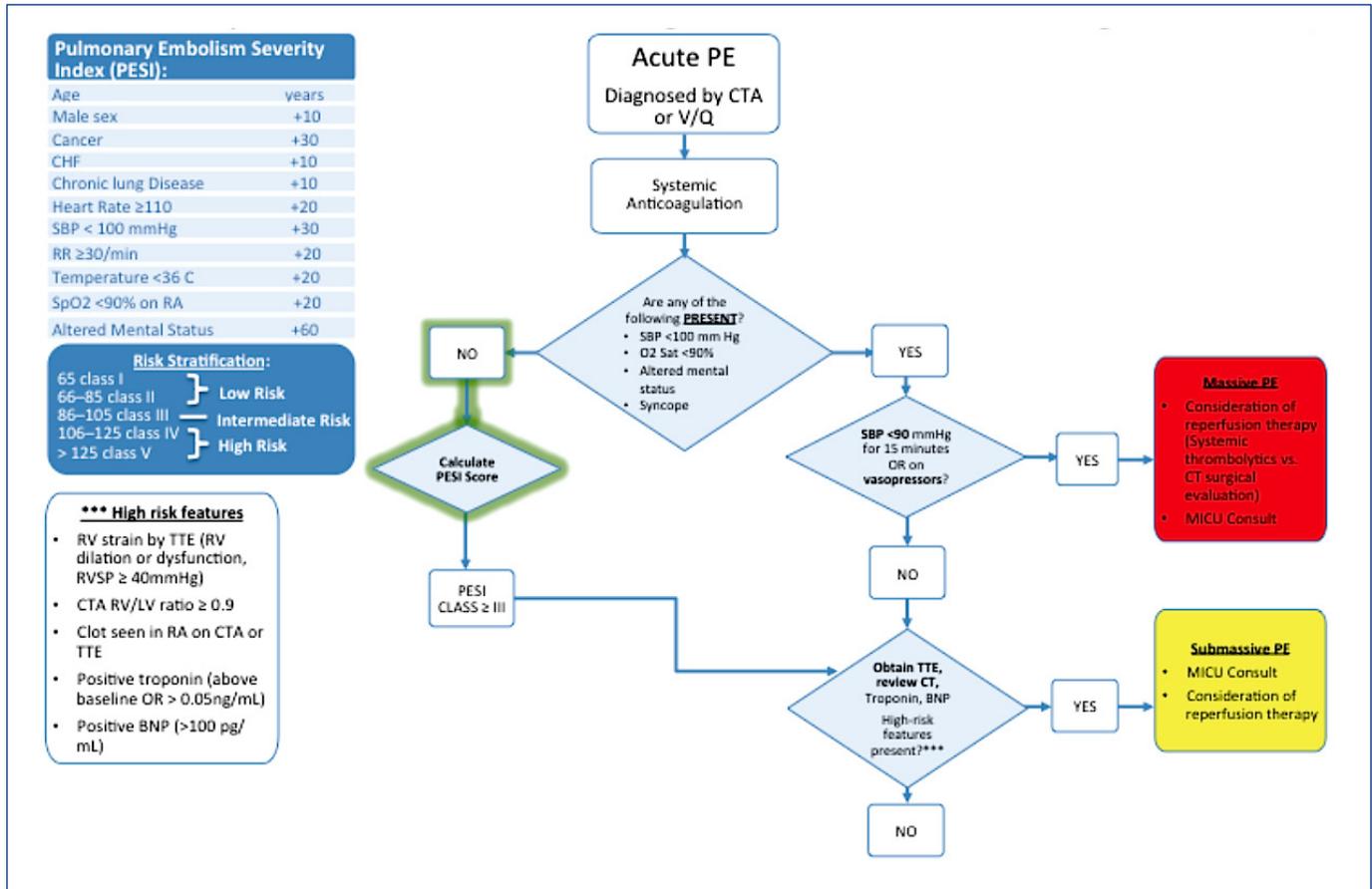
Pulmonary embolism (PE) is both common and a significant cause of morbidity and mortality worldwide. There are an estimated 900,000 cases of venous thromboembolism (VTE) every year in the United States. Although mortality from acute PE is reported to be as high as 100,000 per year, this is likely to be an underestimate, given that approximately 25% of patients with PE present with sudden death.<sup>1,2</sup> There is also a 10–30% mortality rate within one month of acute PE diagnosis.<sup>1</sup> Acute PE is a common indication for intensive care unit (ICU) admission and is associated with high short-term mortality.<sup>3</sup> As such, an understanding of diagnosis, risk stratification, and treatment of acute PE is paramount for critical care physicians.

## DIAGNOSIS AND RISK STRATIFICATION

The diagnosis of acute PE can be challenging, and diagnostic algorithms have been proposed.<sup>4,5</sup> According to all current diagnostic algorithms, contrast-enhanced chest computed tomography angiography (CTA) is the preferred imaging modality for diagnosis of acute PE. Once acute PE is diagnosed, risk stratification is essential to guide treatment decisions. In general, risk stratification for acute PE incorporates several factors, including clinical appearance, vital signs, validated PE risk scores, and right ventricular (RV) function assessed by imaging modalities and cardiac biomarkers. **Figure 1** demonstrates a risk stratification algorithm used by the Pulmonary Embolism Response Team at Rhode Island Hospital. The initial step in risk stratification is to assess for shock or hemodynamic instability, defined as a systolic blood pressure less than 90mmHg for more than 15 minutes or a need for vasopressors. Acute PE that causes hemodynamic instability is referred to as massive PE or high-risk PE, and warrants immediate consideration of reperfusion therapies. In acute PE patients who present without shock or hemodynamic instability, multimodal risk stratification is used to identify patients at low and intermediate risk.

The Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI) are validated clinical scores used to predict 30-day mortality in acute PE.<sup>6,7</sup> Patients with PESI class III-VI or sPESI  $\geq 1$  (see **Figure 1**), or who have signs of RV dysfunction on CTA or echocardiography, or elevated cardiac biomarkers (Brain natriuretic peptide or BNP and troponin above the normal lab values) have intermediate risk, or sub-massive PE. These patients can be sub-classified into intermediate-low and intermediate-high risk, the latter defined by the presence of RV dysfunction by both imaging and biomarkers.<sup>4</sup> Patients with PESI class I-II or sPESI=0 are classified as low risk, indicating a low likelihood of mortality, and are unlikely to be encountered in the ICU setting. In addition to informing treatment decisions, risk stratification can be helpful in assessing the need for ICU level of care. In our practice, patients with high or intermediate-high risk PE are routinely admitted to the medical ICU for initial evaluation, although clinical gestalt is used in conjunction with risk scores and risk stratification algorithms when making these decisions.

**Figure 1.** Adaptation of the risk stratification algorithm for acute pulmonary embolism used by the Pulmonary Embolism Response Team at Rhode Island Hospital.



PE: pulmonary embolism; CTA: chest computed tomography angiography; V/Q: Ventilation Perfusion Scan; CHF: congestive heart failure; SBP: systemic blood pressure; RR: respiratory rate; SpO2: peripheral oxygen saturation, TTE: transthoracic echocardiogram, RV: right ventricle; LV: left ventricle; BNP: brain natriuretic peptide.

**TREATMENT OF ACUTE PULMONARY EMBOLISM**

Once the diagnosis of acute PE is made, treatment focuses on supportive care, systemic anticoagulation, and consideration of reperfusion therapy. Unless there are contraindications, systemic anticoagulation should be started after the diagnosis of acute PE is established. For higher risk patients, intravenous unfractionated heparin is typically the preferred agent as its pharmacokinetics allow the ability to stop if thrombolysis or interventional procedures are indicated. In addition to anticoagulation, hemodynamic and respiratory support should be provided. Clinicians should be extremely cautious with intravenous volume expansion as this may worsen right ventricular function and precipitate rapid clinical decompensation. Pulmonary Embolism Response Teams (PERT) are multi-disciplinary teams that can be activated similarly to teams for acute myocardial infarction or acute stroke. These can be constituted by a wide variety of specialists, including pulmonologists, cardiologists, intensivists, radiologists, hematologists, pharmacists, emergency medicine physicians, and cardiac and vascular surgeons. PERT

can be activated for intermediate or high risk PE, or in any case where there is uncertainty about diagnosis or optimal treatment strategy.<sup>5</sup>

**SYSTEMIC THROMBOLYSIS**

Systemic thrombolysis is well established for the management of high risk or massive PE. Thrombolytics reduce pulmonary artery resistance and pressure, and in hemodynamically unstable patients decrease mortality.<sup>8</sup> Guidelines routinely recommend systemic thrombolysis for patients with massive PE without contraindications to thrombolytics.<sup>4</sup> The use of systemic thrombolytics for intermediate-risk PE remains controversial.<sup>4,9</sup> This question was addressed in the Pulmonary Embolism Thrombolysis (PEITHO) trial, a multicenter, randomized, double-blind, placebo-controlled trial that is the largest trial to examine systemic thrombolytics in intermediate-risk PE.<sup>10</sup> In this study, 1006 acute PE patients (symptoms less than 15 days) were randomized to receive either unfractionated heparin alone or in conjunction

with tenecteplase. PE was confirmed by VQ scan, CTA, or pulmonary angiogram, and right ventricular dysfunction confirmed by echocardiogram or CTA and elevated troponin. At seven days, the tenecteplase group had a significant decrease in a composite endpoint of all-cause mortality and hemodynamic decompensation (2.6% vs 5.6%;  $p=0.02$ ), although there was no difference in mortality. The incidence of extracranial bleeding (6.3% vs 1.2%,  $p<0.001$ ) and stroke (2.4% vs 0.2%,  $p=0.003$ ) were higher in patients that received tenecteplase compared to heparin alone, suggesting an unfavorable risk-benefit ratio for the use of systemic thrombolytics for hemodynamically stable PE with RV dysfunction. Subsequent meta-analyses have shown that systemic thrombolysis reduces overall mortality but is associated with a higher risk of fatal or intracranial hemorrhage.<sup>11,12</sup> Reduced dose thrombolytics have been studied in small trials, but this is also not recommended for routine use in intermediate-risk PE. In the PEITHO study, 23 patients in the heparin alone group required open-label thrombolysis after randomization. Only 2 of these patients died, suggesting, as is our current clinical practice, a role for close observation of patients with intermediate-risk PE, and consideration of the use of rescue systemic thrombolysis if clinical deterioration subsequently occurs.<sup>10</sup> Further study is needed in this particular area as sample size is a limiting factor.

### CATHETER-BASED INTERVENTIONS

Several catheter-based interventions are currently available for the treatment of acute PE. These broadly fit into two categories: catheter directed thrombolysis (CDT) and catheter embolectomy. The two are currently proposed for use in intermediate-high risk patients who are at risk for clinical deterioration based on vital signs, severity of RV dysfunction, tissue perfusion, and/or gas exchange, and who have absolute or relative contraindications to or failed response to systemic thrombolysis.<sup>5</sup> CDT uses imaging guidance to place an infusion catheter to the site of the clot in order to locally deliver low-dose thrombolytics over the course of several hours. The thrombolytic dose is significantly lower than what is administered systemically. Depending on the specific device used, this can be accompanied by low-power, high-frequency ultrasound, which is referred to as ultrasound-assisted catheter-directed thrombolysis (UACDT). There is only one prospective, randomized trial comparing CDT to anticoagulation alone for the management of acute PE.<sup>13</sup> The ULTIMA trial randomized 59 patients with acute main or lower lobe PE and a transthoracic echocardiogram RV/LV ratio  $>1.0$  to receive either unfractionated heparin alone or with a UACDT regimen of 10 to 20mg recombinant tissue plasminogen activator (tPA) over 15 hours. Compared to the heparin alone group, the UACDT group had a greater decrease in mean RV/LV ratio from baseline to 24 hours, although at 90 days there was no difference in RV/LV

ratio improvement. Another retrospective, comparative study found no difference in echocardiographic RV/LV ratio at 30 days between patients who received CDT compared to anticoagulation alone.<sup>14</sup> Although these and other non-comparative studies<sup>15, 16</sup> have shown that CDT improves RV function and PA pressures in the short term, it remains unclear if CDT confers any meaningful long-term benefit. The only patient that died in the ULTIMA study was in the heparin-alone group. Pooled mortality estimates from studies for CDT are similar to the mortality estimates of the anticoagulation groups of the larger studies of systemic thrombolysis in intermediate risk PE.<sup>10,11,17</sup> While these may represent slightly different patient populations, it seems unlikely that CDT carries a mortality benefit. The rate of bleeding complications for UACDT are likely less than that of systemic thrombolysis, but more than that of systemic anticoagulation alone.<sup>16,17,18</sup> It is our opinion that prospective, randomized trials with more meaningful or validated clinical outcomes are necessary before CDT can be used routinely for intermediate-risk PE. In our clinical practice, CDT is considered on a case-by-case basis and is reserved for patients with high likelihood of clinical decompensation. It is possible that improvement in risk stratification of intermediate risk PE might allow for better identification of those patients at higher risk of decompensation who might benefit from early intervention with CDT.

Catheter embolectomy is feasible with devices currently on the market in the United States. All have a similar mechanism of action, and work by introducing a catheter to the site of clot for retrieval by aspiration. In the FLARE study, 104 acute PE patients with elevated RV/LV ratio on CT were treated with catheter embolectomy using the FlowTrieve System (Inari Medical, Irvine, California) in addition to systemic anticoagulation. This resulted in a significant reduction of RV/LV ratio, but only a modest decrease in PA pressure. Adverse event rate was 3.8% with no reported cases of intracerebral hemorrhage and only one case of adverse bleeding.<sup>19</sup> This is currently the only embolectomy device that is FDA-approved for treatment of acute PE, although trials remain ongoing for several other catheter embolectomy systems. While catheter embolectomy offers the possibility of clot removal without exposure to thrombolytics, there are no trials comparing this to anticoagulation alone or to CDT. Similar to CDT, it remains to be seen if catheter embolectomy results in outcomes that are more clinically meaningful than an acute reduction in RV/LV ratio. The utility of CDT and catheter embolectomy systems as an effective treatment modality for acute PE depends largely on equipment availability at centers as well as requisite expertise of providers and staff. Its use remains an option in patients with contraindications to systemic thrombolysis or failure of thrombolysis, when surgical embolectomy is unavailable or infeasible, if the institution has the requisite capabilities. In our opinion, catheter-based interventions

can be considered on a patient case-by-case basis so long as local technical capabilities allow and the decision should be made after a multi-disciplinary or PERT discussion.

### SURGICAL EMBOLLECTOMY

Current indications for surgical embolectomy include high-risk and intermediate-risk PE with an absolute contraindication to thrombolysis, failed thrombolysis, or hemodynamic collapse that may result in death prior to full effect of systemic thrombolysis.<sup>5</sup> Pre-surgical systemic thrombolysis is not an absolute contraindication to surgical embolectomy. Presently, no randomized trials exist comparing systemic thrombolytics to surgical embolectomy, although both are associated with improvement in RV function and PA systolic pressure.<sup>20</sup> Compared to systemic thrombolytics, surgical embolectomy is associated with a decreased risk of major bleeding,<sup>21</sup> however, mortality from surgical embolectomy is estimated to be 4–11%.<sup>22</sup> This modality should be used as reperfusion therapy in higher-risk patients who warrant reperfusion therapy but have an absolute contraindication to systemic thrombolysis. Surgical embolectomy is frequently considered in acute PE patients with presence of right heart thrombi<sup>23</sup>, although optimal treatment for acute PE with “clot in transit” remains uncertain.

### CONCLUSION

The management of high- and intermediate-risk PE is an evolving area that requires appropriate risk stratification, monitoring, and supportive care after acute PE diagnosis is made. Hemodynamically unstable patients should receive systemic thrombolysis unless there is a clear contraindication. The use of catheter-based interventions and surgical embolectomy should be reserved for patients with an absolute contraindication to systemic thrombolysis. There are currently insufficient data to recommend the use of CDT for acute intermediate-risk PE. As such, prospective, comparative randomized, clinical trials for CDT in acute PE are necessary in order to elucidate the possible role of this treatment modality in this subpopulation.

### References

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. (2010). Venous thromboembolism: a public health concern. *Am J Prev Med*, 38(4):S495-S501.
2. Nicolaides AN, Breddin HK, Fareed J, Goldhaber S, Haas S, Hull R, Kalodiki E, Myers K, Samama M, Sasahara A, for the Cardiovascular Disease Educational and Research Trust and the International Union of Angiology. (2001). Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence. *Int Angiol*, 20:1–37.

3. Winterton D, Bailey M, Pilcher D, Landoni G, Bellomo R. (2016). Characteristics, incidence and outcome of patients admitted to intensive care because of pulmonary embolism. *Respirology*, 22:329–337.
4. Konstantinides S, et al. (2014). ESC Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *European Heart Journal*, 35(43):3033–3080.
5. Rivera-Lebron, et al. (2019). Diagnosis, Treatment and Follow up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium. *Clinical and Applied Thrombosis/Hemostasis*, 25: 1-16.
6. Aujesky D, Obrosky DS, Stone RA, et al. (2005). Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*, 172:1041–1046.
7. Jiménez D, Aujesky D, Moores L, et al. (2010). Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism. *Arch Intern Med*, 170(15):1383–1389.
8. Wan S, Quinlan DJ, Agnelli G, Ekelboom JW. (2004). Thrombolysis compared with heparin for the initial treatment of pulmonary embolism. *Circulation*, 110: 774-749.
9. 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. (2011). 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*, 123(16):1788-1830.
10. Meyer G, Vicaut E, Danays T, et al. (2014). Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*, 370(15):1402–11.
11. Chatterjee S, Chakraborty A, Weinberg I, et al. (2014). Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage. *JAMA*, 311(23): 2414-2421.
12. Marti et al. (2015). Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *European Heart Journal*, 36(10):605–614.
13. Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, et al. (2014). Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*, 129:479–486.
14. Avgerinos ED, et al. (2018). Design and rationale of a randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism. *Journal of Vascular Surgery Venous and Lymphatic Disorders*, 6(1):126–132.
15. Kuo WT, Banerjee A, Kim PS, DeMarco FJ Jr, Levy JR, Facchini FR, et al. (2015). Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest*, 148:667–673.
16. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. SEATTLE II Investigators. (2015). 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*, 8:1382–1392.
17. Furfaro D, et al. Catheter-directed Thrombolysis for Intermediate-Risk Pulmonary Embolism. (2018). *Ann AM Thorac Soc*, 15(2): 134-144.

18. Schissler AJ, Gylmn RJ, Sobieszczyk PS, Waxman AB. (2018). Ultrasound-assisted catheter-directed thrombolysis compared with anticoagulation alone for treatment of intermediate-risk pulmonary embolism. *Pulmonary circulation*, 8(4).
19. Tu T, et al. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism. (2019). *JACC: Cardiovascular Interventions*, 12(9):859-869.
20. Azari, A, Beheshti, AT, Moravvej, Z, Bigdelu, L, Salehi, M. (2015). Surgical embolectomy versus thrombolytic therapy in the management of acute massive pulmonary embolism: Short- and long-term prognosis. *Heart Lung*, 44(4):335-339.
21. Aymard T, Kadner A, Widmer A. (2013). Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy—should surgical indications be revisited? *Eur J Cardiothorac Surg*, 43(1):90-94.
22. Keeling WB, Sundt T, Leacche M. (2016). Outcomes after surgical pulmonary embolectomy for acute pulmonary embolus: a multi-institutional study. *Ann Thorac Surg*, 102(5): 1498-1502.
23. Athappan G, Sengodan P, Chacko P, Gandhi S. (2015). Comparative efficacy of different modalities for treatment of right heart thrombi in transit: A pooled analysis. *Vascular Medicine*, 20(2): 131-138.

**Authors**

Christopher D. Theroux, MD, MS, Department of Medicine, Alpert Medical School of Brown University.

Jason M. Aliotta, MD, Department of Medicine and Division of Pulmonary, Critical Care and Sleep Medicine, Alpert Medical School of Brown University.

Christopher J. Mullin, MD, MHS, Department of Medicine and Division of Pulmonary, Critical Care and Sleep Medicine, Alpert Medical School of Brown University.

**Correspondence**

Christopher Mullin, MD, MHS  
 Assistant Professor of Medicine, Clinician Educator  
 Brown University  
 593 Eddy Street, POB Suite 224  
 Providence, RI 02903  
 401-444-2670  
 Fax 401-444-8447  
[christopher\\_mullin@brown.edu](mailto:christopher_mullin@brown.edu)