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JACC FOCUS SEMINAR: VENOUS THROMBOEMBOLISM

JACC FOCUS SEMINAR

Advanced Management of Intermediate- and High-Risk Pulmonary Embolism

JACC Focus Seminar

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ABSTRACT

Intermediate-risk (submassive) pulmonary embolism (PE) describes normotensive patients with evidence of right ventricular compromise, whereas high-risk (massive) PE comprises those who have experienced hemodynamic decompensation with hypotension, cardiogenic shock, or cardiac arrest. Together, these 2 syndromes represent the most clinically challenging manifestations of the PE spectrum. Prompt therapeutic anticoagulation remains the cornerstone of therapy for both intermediate- and high-risk PE. Patients with intermediate-risk PE who subsequently deteriorate despite anticoagulation and those with high-risk PE require additional advanced therapies, typically focused on pulmonary artery reperfusion. Strategies for reperfusion therapy include systemic fibrinolysis, surgical pulmonary embolectomy, and a growing number of options for catheter-based therapy. Multidisciplinary PE response teams can aid in selection of appropriate management strategies, especially where gaps in evidence exist and guideline recommendations are sparse. (J Am Coll Cardiol 2020;76:2117–27) Published by Elsevier on behalf of the American College of Cardiology Foundation.

Heterogeneity of clinical presentation, limited randomized controlled trial data, and a burgeoning number of advanced treatment options have established pulmonary embolism (PE) as one of the most challenging cardiovascular disorders in clinical medicine. The incidence of PE in the United States is estimated to be 121 per 100,000 population (1). Greater sensitivity of diagnostic imaging, an aging population, and increasing prevalence of venous thromboembolism risk factors, such as obesity and cancer, can be expected to continue to drive PE incidence. Although case fatality rates appear to be decreasing, PE-related mortality in the United States continues to be high, with estimates ranging from 19.4 to 32.3 per 100,000 (2,3). In-hospital mortality approaches 7% for all patients with PE and 33% for those presenting with hemodynamic instability (4). Death due to PE is largely from progressive right heart failure and occurs most commonly in patients with signs of right ventricular (RV) dysfunction (intermediate-risk PE) or hemodynamic instability (high-risk PE) (5).

PATHOPHYSIOLOGY

HEMODYNAMICS. Acute PE results in an abrupt increase in pulmonary vascular resistance and RV afterload through direct physical obstruction, hypoxemic vasoconstriction, and release of pulmonary artery vasoconstrictors (**Figure 1**). Acute increases in

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

CTEPH = chronic thromboembolic pulmonary hypertension

DOAC = direct oral anticoagulant

DVT = deep vein thrombosis

ECMO = extracorporeal membrane oxygenation

FDA = U.S. Food and Drug Administration

IVC = inferior vena cava

LV = left ventricular

PE = pulmonary embolism

PESI = Pulmonary Embolism Severity Index

RV = right ventricular

sPESI = simplified PESI

t-PA = tissue-plasminogen activator

afterload lead to RV dilation and hypokinesis, tricuspid regurgitation, and ultimately acute RV failure. Patients with RV failure may abruptly decompensate, with systemic arterial hypotension, cardiogenic shock, and cardiac arrest.

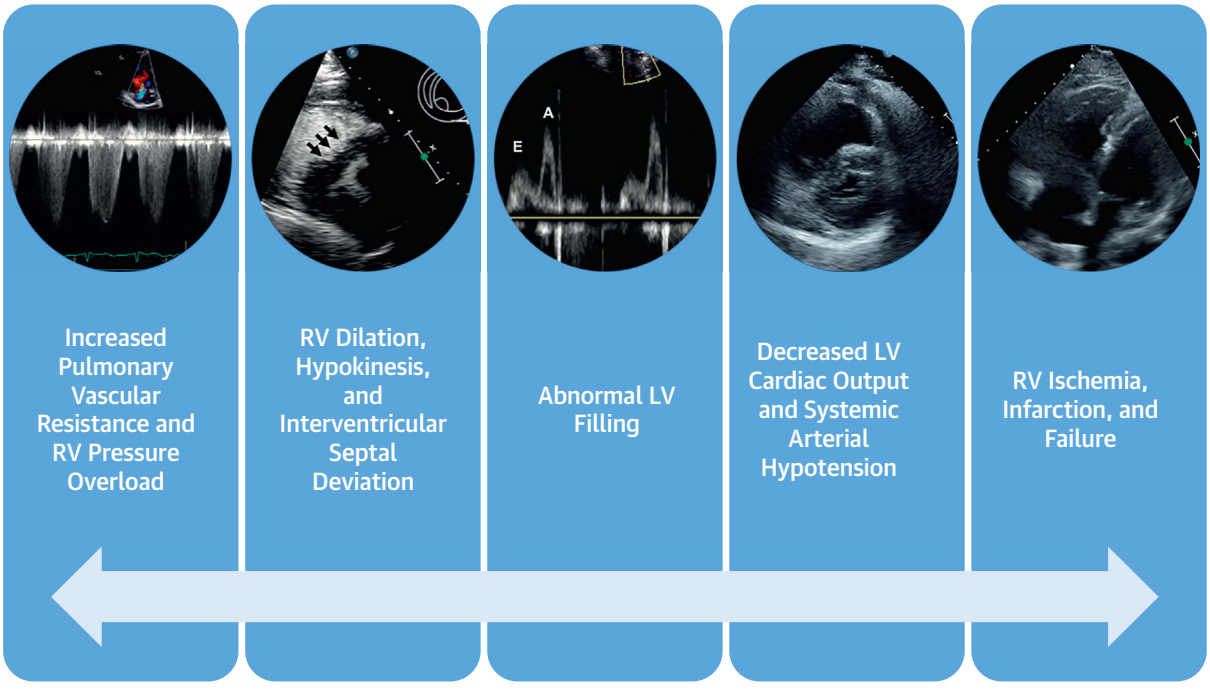
RV pressure overload may also result in interventricular septal deviation toward the left ventricle (LV), thereby limiting LV diastole. Abnormal LV filling can be detected echocardiographically by transmitral Doppler with left atrial contraction, represented by the A-wave, making a paradoxically greater contribution to diastole than passive filling, represented by the E-wave (Figure 1). RV pressure overload produces increased wall stress and resultant ischemia by increasing myocardial oxygen demand while simultaneously limiting supply.

GAS EXCHANGE. Ventilation-to-perfusion mismatch, increases in total dead space, and right-to-left shunting contribute to perturbations of gas exchange in patients with acute PE.

HIGHLIGHTS

- Patients with intermediate- and high-risk PE represent the populations at highest risk for early mortality.
- Although immediate anticoagulation is the cornerstone of management, patients with intermediate- to high-risk PE who deteriorate despite anticoagulant therapy and those with high-risk PE should be considered for advanced therapies.
- Options for pulmonary reperfusion include systemic fibrinolysis, surgical embolectomy, and a growing number of catheter-based therapies.
- Clinical outcome-driven, randomized controlled trials are needed to define the place of these advanced therapies in management pathways for intermediate- and high-risk PE.

FIGURE 1 The Spectrum of RV Pathophysiological Changes in Acute PE as Demonstrated by Transthoracic Echocardiography



Increased pulmonary vascular resistance results in RV dilation and hypokinesis, interventricular septal deviation, and abnormal LV filling. Decreased left-sided cardiac output results in systemic arterial hypotension, coronary artery hypoperfusion, and RV ischemia. LV = left ventricular; PE = pulmonary embolism; RV = right ventricular.

The 2 most common gas exchange abnormalities are hypoxemia and increased alveolar-arterial oxygen gradient. Some patients with acute PE may hyperventilate, leading to hypocapnia and respiratory alkalosis. Hypercapnia may accompany high-risk PE due to impaired minute ventilation and increased anatomic and physiological dead space.

LONG-TERM SEQUELAE

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION. Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by persistent pulmonary arterial obstruction, pulmonary vasoconstriction, and a secondary small-vessel arteriopathy resulting in chronic dyspnea and functional limitation and occurs in 2% to 4% of patients after PE (6). Pulmonary thromboendarterectomy is the most effective and durable therapy for CTEPH. Pulmonary vasodilators, such as riociguat, offer the potential for improved symptoms and functional capacity to patients with CTEPH who are inoperable and or have post-thromboendarterectomy pulmonary hypertension (7). A growing experience in balloon pulmonary angioplasty provides an additional option for patients who are not candidates for surgery (8). Advanced therapy for PE, in particular systemic fibrinolysis, has not been proven to prevent CTEPH (9). Because the evaluation and treatment are complex and evolving, patients with CTEPH should be referred to specialized centers.

POST-PE SYNDROME. The post-PE syndrome is characterized by persistent symptoms, including chest pain and dyspnea, functional limitation, and exercise intolerance in the absence of pulmonary hypertension and is more common than CTEPH (10). The relative contribution of deconditioning versus persistent cardiopulmonary limitations due to PE on such symptoms is unclear (10). The impact of advanced therapies such as systemic fibrinolysis or catheter-based intervention on the frequency of the post-PE syndrome remains undefined. However, in long-term follow-up from the PEITHO (Pulmonary Embolism International Thrombolysis) trial, systemic fibrinolysis did not reduce symptom burden or functional limitation in patients with intermediate-risk PE (9).

PE SYNDROMES AND THE APPROACH TO RISK STRATIFICATION

SPECTRUM OF PE SYNDROMES. Although most patients with PE have normal blood pressure, preserved RV function, and normal cardiac biomarkers, a subset present with risk factors for adverse outcomes (2). Patients with high-risk (also termed massive) PE present with syncope, systemic arterial hypotension, cardiogenic shock, or cardiac arrest. Patients with catastrophic, or "super-massive," PE demonstrate refractory shock or require ongoing cardiopulmonary resuscitation and may require mechanical circulatory support such as extracorporeal membrane oxygenation (ECMO). Intermediate-risk (also called submassive) PE comprises a heterogeneous population characterized by initially normal hemodynamics and evidence of RV dysfunction. Intermediate-risk PE may be particularly challenging because a subset may suddenly, often without warning, develop systemic arterial hypotension, cardiogenic shock, and sudden death, despite prompt therapeutic anticoagulation. Intermediate-risk PE demonstrates considerable heterogeneity with regard to degree of RV dysfunction and prognosis, and may be further subcategorized (**Figure 2**). Intermediate-high-risk patients with evidence of RV dysfunction on imaging and positive cardiac biomarkers are more likely to clinically deteriorate than intermediate-low-risk patients who have RV dysfunction on imaging, positive cardiac biomarkers, or neither.

RISK STRATIFICATION. Bedside scoring systems for prognostication of the risk of adverse outcomes and therapeutic decision making, such as the PESI (Pulmonary Embolism Severity Index) and simplified PESI (sPESI), are validated tools for stratification of patients with PE based on clinical parameters. High PESI and sPESI scores define a subset of patients with increased 30-day mortality.

Elevations in cardiac biomarkers, in particular cardiac troponin and brain-type natriuretic peptide, correspond with RV pressure overload and result from RV microinfarction and increased shear stress, respectively. Increased cardiac troponin and brain-type natriuretic peptide are associated with increased short-term mortality and adverse outcomes in patients with acute PE. Among normotensive patients, cardiac biomarkers distinguish intermediate-risk from low-risk PE.

Detection of RV enlargement by contrast-enhanced chest computed tomography (CT) has become an especially convenient risk stratification tool because it uses data acquired from the initial diagnostic scan. Based on measurements from an axial CT view, RV enlargement, defined as an RV diameter-to-left ventricular (LV) diameter (RV-to-LV) ratio of >0.90, is an independent predictor of 30-day PE mortality. A systematic approach to echocardiography provides accurate assessment of RV dysfunction while also

FIGURE 2 Risk Categories for Patients Presenting With Acute PE

Guidelines	Category	Hemodynamic Status	PE Severity Index (PESI) (or Simplified PESI)	Evidence of RV Dysfunction
American Heart Association (AHA, 2011)	Massive	Unstable	High	Typically Abnormal RV on Imaging, Elevated Troponin, OR Both
	Submassive	Stable	High	May Have Abnormal RV on Imaging OR Elevated Troponin OR Both
	Low Risk	Stable	Typically Low	None
European Society of Cardiology (ESC, 2019)	High Risk	Unstable	High	Typically Abnormal RV on Imaging, Elevated Troponin, OR Both
	Intermediate-High Risk	Stable	High	Abnormal RV on Imaging, AND Elevated Troponin
	Intermediate-Low Risk	Stable	High	May Have Abnormal RV on Imaging OR Elevated Troponin But Not Both
	Low Risk	Stable	Low	None

Although terminology may differ, risk stratification strategies are consistent in considering hemodynamics, clinical presentation, and evidence of RV dysfunction.
PESI = Pulmonary Embolism Severity Index; RV = right ventricular.

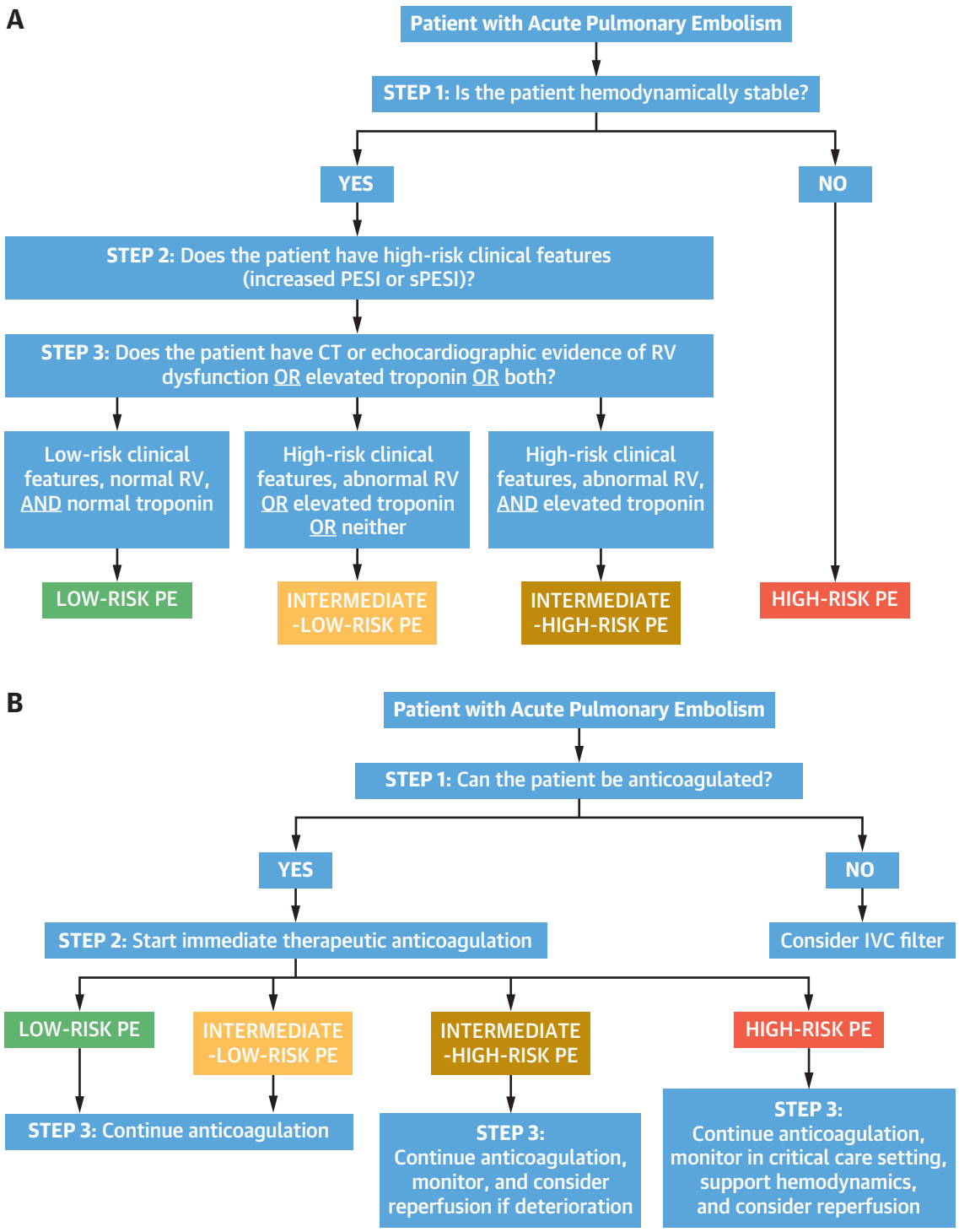
evaluating for pulmonary hypertension in patients diagnosed with PE (2). Echocardiographic evidence of RV dysfunction defines intermediate-risk PE and detects patients with an increased risk of systemic arterial hypotension, cardiogenic shock, and death. Echocardiography should be performed in patients with acute PE and clinical evidence of RV failure, elevated cardiac biomarkers, suspected pulmonary arterial hypertension, or clinical deterioration.

Risk stratification algorithms should integrate clinical prognostic indicators, cardiac biomarkers, and evidence of RV dysfunction as detected by either echocardiography or contrast-enhanced chest CT (**Central Illustration**) (2). Patients with high-risk PE should be considered for advanced therapies for reperfusion because of a high mortality with anticoagulation alone. A subset of patients with intermediate-high-risk PE may be considered for rescue reperfusion on a case-by-case basis based on clinical deterioration or failure to improve despite therapeutic anticoagulation (11).

THE ROLE OF MULTIDISCIPLINARY RESPONSE TEAMS

Multidisciplinary PE response teams have emerged in response to the clinical challenges of limited high-quality comparative data regarding advanced therapies, rapidly advancing technology for device therapy, and a number of evidence-based clinical practice guidelines with varying and sometimes conflicting recommendations for patients with intermediate- or high-risk PE (12). Modeled after established "heart team" approaches to myocardial infarction, stroke, and acute aortic syndromes, this rapid response strategy harnesses multidisciplinary expertise, including cardiovascular medicine, pulmonology, hematology, radiology, cardiac surgery, and interventionalists, to individualize PE care. Widespread adoption of a multidisciplinary response team concept has been predicated on the promise of reduced heterogeneity of PE management both within individual medical centers and across health care systems, improved access to advanced therapies

CENTRAL ILLUSTRATION **Approach to Risk Stratification and Risk-Based Management of Acute Pulmonary Embolism Syndromes**



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Risk stratification incorporates assessment of hemodynamics and clinical features, cardiac biomarker determination, and detection of RV dysfunction on imaging. Selection of advanced therapy should consider the risk of hemodynamic decompensation and early mortality with interventional complications and bleeding. **(A)** Approach to risk stratification of patients with acute PE. **(B)** Risk-based management of acute PE syndromes. CT = computed tomogram; IVC = inferior vena cava; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index.

for those patients at increased risk of adverse outcomes, more appropriate use of interventional therapies, improved clinical outcomes, and reduced length of stay and health care costs (13). Despite the rapid proliferation of this multidisciplinary approach internationally, there have been limited reported data regarding its real-world impact. The 2019 European Society of Cardiology Guidelines encourage a multidisciplinary response team approach in management of patients with intermediate- and high-risk PE (2).

ANTICOAGULATION IN INTERMEDIATE- AND HIGH-RISK PE

Regardless of whether patients receive advanced therapy, prompt therapeutic-intensity anticoagulation comprises the cornerstone of treatment for intermediate- and high-risk PE (**Figure 3**). Anticoagulant strategies for immediate treatment of acute PE include intravenous unfractionated heparin or injectable therapy with low-molecular weight heparin or fondaparinux with transition to a direct oral anticoagulant (DOAC) or vitamin K antagonist, or completely oral monotherapy with a DOAC, such as apixaban or rivaroxaban. Because it can be discontinued and rapidly reversed, unfractionated heparin has been the preferred anticoagulant for patients undergoing advanced therapy with fibrinolysis, catheter-based intervention, or surgery for PE. However, greater awareness regarding the danger of subtherapeutic anticoagulation associated with unfractionated heparin has driven a growing preference for the consistent antithrombotic effect of low-molecular weight heparin in patients with PE with increased risk of adverse outcomes. DOACs represent a considerable advancement in anticoagulation for acute PE with comparable efficacy to vitamin K antagonists but substantial reductions in bleeding complications and greater convenience (14). Evidence-based clinical practice guidelines recommend DOACs as first line for oral anticoagulation in patients with acute PE (2,11).

ADVANCED THERAPIES FOR INTERMEDIATE- AND HIGH-RISK PE

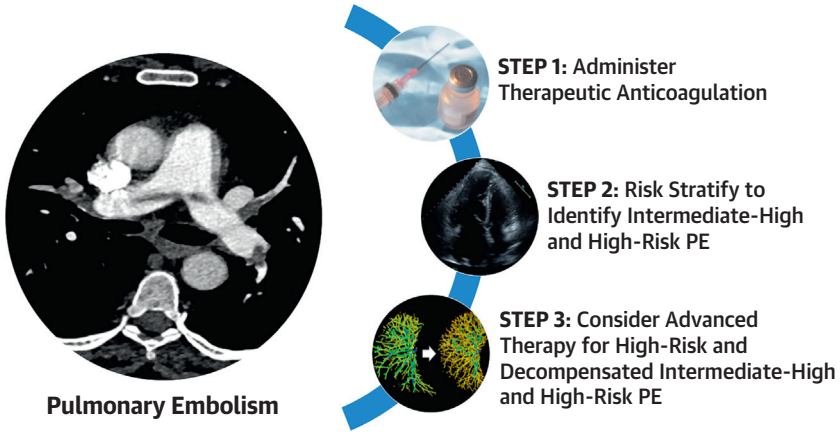
Advanced therapies for acute PE include systemic fibrinolysis, catheter-based intervention, surgical pulmonary embolectomy, and mechanical circulatory support (**Table 1**). Choosing a particular advanced therapy depends on the individual patient's risk for adverse outcomes due to PE and for major bleeding, most importantly intracranial hemorrhage (**Central Illustration**).

SYSTEMIC FIBRINOLYSIS. The rationale for systemic fibrinolysis in intermediate-risk PE is to avert impending hemodynamic collapse and death from progressive right-sided heart failure. In patients with high-risk PE, systemic fibrinolytic therapy is administered to rapidly reverse hemodynamic compromise, RV dysfunction, and gas exchange abnormalities. Systemic fibrinolysis is considered a lifesaving therapy in patients presenting with intermediate- and high-risk PE (15,16). The Europe-based PEITHO is the largest randomized controlled trial of systemic fibrinolysis in PE to date, enrolling 1,006 patients with intermediate-risk PE (17). The study evaluated the impact of systemic fibrinolysis with tenecteplase followed by anticoagulation with heparin versus heparin alone on the primary outcome of all-cause mortality or hemodynamic collapse within 7 days of randomization. Systemic fibrinolysis reduced the frequency of the primary outcome (2.6% vs. 5.6%, $p = 0.015$) with most of the benefit due to a reduction in hemodynamic collapse within 7 days (1.6% vs. 5%, $p = 0.002$). However, the benefit of fibrinolysis came at the cost of increased major hemorrhage (6.3% vs. 1.5%, $p < 0.001$), with approximately 2% of the tenecteplase-treated patients suffering intracranial hemorrhage.

The U.S. Food and Drug Administration (FDA) has approved 100 mg tissue-plasminogen activator (t-PA) as a continuous infusion via a peripheral vein over 2 h for the fibrinolysis of acute PE. Patients being considered for fibrinolysis should be meticulously assessed for contraindications. Concern over the risk of intracranial hemorrhage, which approaches 3% to 5% outside of clinical trials has dampened clinician enthusiasm for full-dose systemic fibrinolysis and has sparked development of alternative fibrinolytic strategies with lower bleeding risk.

One alternative strategy has focused on half-dose systemic fibrinolysis. Initial enthusiasm for this strategy was based on limited international and single-center experiences (18,19). However, a more recent propensity score-matched study comparing outcomes in 3,768 patients receiving 50 mg versus full-dose 100 mg of alteplase for PE demonstrated that half-dose fibrinolysis was associated with increased frequency of treatment escalation (53.8% vs. 41.4%; $p < 0.01$), driven largely by secondary fibrinolysis (25.9% vs. 7.3%; $p < 0.01$) and catheter-directed therapy (14.2% vs. 3.8%; $p < 0.01$) (20). Furthermore, hospital mortality (13% vs. 15%; $p = 0.3$), intracranial hemorrhage (0.5% vs. 0.4%; $p = 0.67$), gastrointestinal bleeding (1.6% vs. 1.6%;

FIGURE 3 Advanced Management of Intermediate- and High-Risk Pulmonary Embolism



A step-wise approach to management of pulmonary embolism (PE) begins with prompt initiation of therapeutic anticoagulation. Next, risk stratification identifies patients with normal blood pressure but evidence of right ventricular dysfunction (intermediate-risk PE) and those with hemodynamic instability (high-risk PE). Patients with intermediate-high-risk PE are monitored closely and considered for rescue reperfusion if they develop subsequent clinical deterioration. Patients with high-risk PE should undergo expeditious reperfusion therapy, or if in refractory cardiogenic shock, mechanical circulatory support.

$p = 0.99$), and acute blood loss anemia (6.9% vs. 4.6%; $p = 0.11$) were similar.

CATHETER-BASED THERAPY. Catheter-based therapy for treatment of acute PE includes pharmacomechanical therapy, catheter-directed fibrinolysis, and mechanical embolectomy. Catheter-based therapy combining local fibrinolysis with mechanical thrombectomy offers the potential advantage of increased efficacy of thrombus dissolution due to the synergistic effects of higher local fibrinolytic drug concentrations and mechanical disruption with greater exposed thrombus surface area. Because higher local drug concentration is achieved with lower overall dose of fibrinolytic agent, catheter-based therapy may offer the advantage of decreased hemorrhagic complications. The evidence base for the efficacy and safety of these various catheter-based techniques varies and is lacking the randomized controlled trials powered to evaluate clinical outcomes (21).

The most extensively studied percutaneous technique for treatment of acute PE is ultrasound-facilitated, catheter-directed fibrinolysis (Boston Scientific Corporation, Marlborough, Massachusetts) (22–24). In a European randomized controlled trial of 59 patients with intermediate-risk PE, ultrasound-facilitated, catheter-directed fibrinolysis with low-dose t-PA (20 mg total) plus anticoagulation reduced a surrogate endpoint, RV-to-LV ratio, from baseline to 24 h to a greater extent than anticoagulation (22). In the U.S.-based single-arm, multicenter SEATTLE (Prospective, Single-Arm Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) II trial, the safety and efficacy of ultrasound-facilitated, catheter-directed fibrinolysis (24 mg t-PA) was assessed in 150 patients with high- ($n = 31$) or intermediate-risk ($n = 119$) PE (23). Mean RV-to-LV ratio decreased by 25% (1.55 vs. 1.13; mean difference, −0.42; $p < 0.0001$), mean pulmonary artery systolic pressure decreased by 30% (51.4 mm Hg vs. 36.9 mm Hg; mean difference, −14.4 mm Hg; $p < 0.0001$), and mean modified Miller angiographic obstruction index diminished by 30% (22.5 vs. 15.8; mean difference, −6.6; $p < 0.0001$) from pre-procedure to 48 h post-procedure. Major bleeding occurred in 10% of patients, with none experiencing intracranial hemorrhage. On May 21, 2014, the FDA cleared ultrasound-facilitated, catheter-directed fibrinolysis with the EkoSonic Endovascular System for treatment of PE. In a subsequent dose-ranging trial, 4 accelerated-dosing regimens (8 min/2 h, 8 min/4 h, 12 min/6 h, and 24 min/6 h) for ultrasound-facilitated, catheter-directed fibrinolysis were evaluated in 101 patients with intermediate-risk PE (24). All 4 regimens improved RV function comparable to 24 mg of t-PA administered over 12 to 24 h, based on the CT-calculated RV-to-LV ratio from baseline to 48 h. Major bleeding was observed in 4% of patients, with intracranial hemorrhage in 1 patient who received an

TABLE 1 Options for Advanced Therapy in Acute PE

Option	Indications	Advantages	Disadvantages
Systemic fibrinolysis	High- and intermediate-high-risk PE	• Rapid administration • Decreases mortality • Prevents hemodynamic collapse • Expedites RV recovery and symptom relief	• 2%–5% risk of ICH
Catheter-directed therapy	High- and intermediate-high-risk PE	• Expedites RV recovery and symptom relief • Reduced risk of ICH • Option for mechanical embolectomy with some devices	• Limited long-term and comparative data • May take time to mobilize
Surgical embolectomy	High- and intermediate-high-risk PE	• Expedites RV recovery and symptom relief • Reduced risk of ICH • Avoids need for fibrinolysis	• Limited long-term and comparative data • May take time to mobilize • Limited to more centrally located PE
ECMO	Refractory cardiogenic shock	• Supports hemodynamics and oxygenation in patients with refractory shock or hypoxemia	• Limited long-term and comparative data • May take time to mobilize

ECMO = extracorporeal membrane oxygenation; ICH = intracranial hemorrhage; PE = pulmonary embolism; RV = right ventricular.

additional 50 mg of t-PA intravenously and another with baseline pancytopenia and previously unknown arteriovenous malformation. In 1-year follow-up, these accelerated lower-dose t-PA regimens for ultrasound-facilitated, catheter-directed fibrinolysis resulted in sustained RV recovery as assessed by serial echocardiography and continued improvements in functional status and quality of life (25). A study using a novel technique for 3-dimensional reconstruction of the pulmonary vasculature from chest CT data obtained in the SEATTLE II trial demonstrated that reduction in RV volume correlated with increased blood volume through the distal, rather than proximal, pulmonary arteries (26). These data suggest that ultrasound-facilitated, catheter-directed fibrinolysis may function to relieve RV pressure overload through distal pulmonary artery reperfusion.

Purely mechanical catheter embolectomy techniques may be advantageous in patients with PE with contraindications to fibrinolytic therapy. The FlowTriever system (Inari Medical, Irvine, California) is a large-bore device that mechanically engages thrombus via 3 self-expanding nitinol disks and then aspirates trapped thrombus. In typical practice, the device is used as a simple large-bore aspiration catheter without deployment of the nitinol disks. In a U.S.-based single-arm, multicenter study of 106 patients with intermediate-risk PE, embolectomy with the FlowTriever system resulted in a 25% reduction in CT-measured RV-to-LV ratio (mean difference, −0.38; $p < 0.0001$) and 10% decrease in mean modified Miller index (mean difference, −1.90; $p < 0.001$) (27). In the study, 6 major adverse events occurred in 4 patients within 48 h of the procedure, including 1 major bleeding event. The FlowTriever device received FDA clearance for treatment of PE in May 2018. The Indigo Thrombectomy System (Penumbra, Inc., Alameda, California) is a smaller-bore aspiration catheter that does not require fibrinolytic administration and that was evaluated in a single-arm study of 119 patients with intermediate-risk PE (EXTRACT-PE [Evaluating the Safety and Efficacy of the Indigo Aspiration System in Acute Pulmonary Embolism]; NCT03218566). Treatment with the Indigo device resulted in a 27% reduction in the mean CT-measured RV-to-LV diameter ratio and was associated with 3 major adverse events in 2 patients (28). The AngioVac system (AngioDynamics, Inc., Latham, New York) is a veno-veno bypass system that includes a 22-F suction thrombectomy catheter. Evidence for the use of the AngioVac system to treat PE has been limited (29).

Other devices for catheter-based therapy in acute PE are in various stages of development and study (21). Catheter-direct therapy, using local fibrinolysis without targeted mechanical thrombus disruption, has undergone limited prospective evaluation and may be a consideration for patients with high-risk or intermediate-high-risk PE (30). Important knowledge gaps, such as the impact on clinical outcomes compared with anticoagulation alone and implications of time to catheter placement, procedure time, operator learning curve, procedural volumes, and cost, hinder the integration of catheter-based therapies into clinical practice pathways for treatment of PE (2,21). A number of guidance documents have highlighted the lack of mortality data and the need for randomized controlled trials to elucidate the clinical benefits versus risks of catheter-based therapy in intermediate-high-risk and high-risk PE (2,11,21,31).

Current evidence-based clinical practice guidelines reflect the limitations in the data in their positions on

catheter-based therapy. The 2019 European Society of Cardiology Guidelines offer catheter-based therapy as an alternative to surgical embolectomy for patients with high-risk PE in whom systemic fibrinolysis has failed or is contraindicated (Class IIa; Level of Evidence: C) and as an alternative to systemic fibrinolysis in other patients with PE who have experienced hemodynamic deterioration despite anticoagulation (Class IIa; Level of Evidence: C) (2). In patients with acute PE associated with hypotension and have a high risk of bleeding, have failed systemic fibrinolysis, or have shock that is likely to result in death before systemic fibrinolysis can take effect, the 2016 American College of Chest Physicians Guidelines suggest catheter-directed therapy over no intervention, if the expertise and resources are available (Grade 2C) (11).

SURGICAL EMBOLECTOMY. Surgical pulmonary embolectomy is considered in patients with intermediate-high- or high-risk PE in whom fibrinolysis has failed or is contraindicated (32). Rescue surgical pulmonary embolectomy after failed fibrinolysis is preferred over repeat fibrinolytic administration. Other indications include paradoxical embolism, "clot-in-transit," and hemodynamic collapse or respiratory failure requiring cardiopulmonary resuscitation. Surgical pulmonary embolectomy is most effective in patients with large centrally located PE. In experienced centers, surgical pulmonary embolectomy has been shown to be safe and effective (33). Optimal results are achieved when the patient is referred before the development of pressor-dependent hypotension or cardiogenic shock.

HEMODYNAMIC SUPPORT FOR HIGH-RISK PE

Although the initial strategy to manage hemodynamic instability is often to augment RV preload with bolus administration of intravenous fluids, excessive volume resuscitation may exacerbate RV failure by overdistending the RV, increasing wall stress, worsening RV ischemia, decreasing contractility, and causing further interventricular septal shift toward the LV, thereby limiting LV filling and systemic cardiac output. An initial trial of intravenous volume is most likely to be successful in patients without signs of increased right-sided preload, such as those with central venous pressures of <15 mm Hg. In patients with central venous pressures of >15 mm Hg, volume loading should be avoided, and administration of vasopressors and inotropes should be the initial step in hemodynamic support.

The optimal agent for the hemodynamic support of patients with high-risk PE should augment RV function through positive inotropic effects while also maintaining systemic arterial perfusion pressure. Norepinephrine, epinephrine, and dopamine have dual mechanisms of action as both inotropes and vasopressors and therefore may be preferred in the initial support of patients with high-risk PE. Inotropes such as dobutamine may be required to augment cardiac output but may also cause systemic arterial hypotension. In these cases, the addition of a vasopressor may be necessary to support end-organ perfusion while administering inotropes. In other patients with high-risk PE and tachycardia, a primary vasopressor such as vasopressin or phenylephrine may be most appropriate to avoid accelerating the heart rate further. Although pulmonary vasodilators have the theoretical benefit of reducing pulmonary vascular resistance and improving RV function, a multicenter randomized placebo-controlled trial of inhaled nitric oxide in patients with intermediate-risk PE demonstrated no benefit on a primary endpoint of complete RV recovery and normalization of cardiac troponin and a secondary endpoint of normalization of brain-type natriuretic peptide and Borg dyspnea score <3 (34).

ECMO is indicated for hemodynamic and ventilatory support in patients with severe RV failure and refractory cardiogenic shock due to acute PE. Analysis of the U.S. National Inpatient Sample has shown in upward trend in utilization of ECMO for patients with high-risk PE over the time period from 2005 to 2013 (35). In-hospital mortality for high-risk PE patients receiving ECMO during this time period remained high at 61.6%. Predictors of increased mortality with the use of ECMO for high-risk PE included increasing age, female sex, obesity, heart failure, and chronic lung disease. Although ECMO has been traditionally used as a temporizing measure until advanced therapy, such as surgical embolectomy, can be instituted, more recent data suggest that most patients who present with high-risk PE and are supported with ECMO will recover with anticoagulation alone (36). Recent cannulation for ECMO is often viewed as a contraindication to systemic fibrinolysis.

INFERIOR VENA CAVA FILTERS

Inferior vena cava (IVC) filter insertion is considered in patients with acute PE with contraindications to anticoagulation or with recurrent PE despite therapeutic anticoagulation (2,11). IVC filter insertion had also been considered on an individual basis for patients with intermediate- or high-risk PE who were receiving therapeutic anticoagulation but who had limited cardiopulmonary reserve, such that a subsequent PE would likely be fatal. This indication was the focus of

the PREPIC2 (Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption) trial, which randomly assigned 399 normotensive patients with acute PE, concomitant lower extremity deep vein thrombosis (DVT), and at least 1 risk factor for adverse outcomes to retrievable IVC filter implantation plus anticoagulation versus anticoagulation alone (37). Adjunctive insertion of a retrievable IVC filter, compared with anticoagulation alone, did not reduce the risk of symptomatic recurrent PE or mortality at 3 or 6 months. Based on these findings, IVC filters should not be routinely inserted in patients with intermediate- and high-risk PE who can be treated with anticoagulation. In a meta-analysis summarizing data from randomized controlled trials and prospective controlled observational studies, IVC filters appear to reduce the short-term risk of subsequent PE, increase the long-term risk for DVT, and have no impact on overall mortality (38).

After an FDA advisory regarding IVC filter utilization in 2010 and updates to societal guidelines, annual IVC filter use has declined in the United States (39). Despite data demonstrating the safety and ease with which retrievable IVC filters can be removed, up to 50% remain permanently indwelling (40,41). Device-related complications include strut fracture, filter migration, strut embolization, device tilt, IVC penetration, perforation of surrounding structures, PE, DVT, and IVC thrombosis. To avoid such complications, IVC filters should be retrieved as soon as no longer necessary and anticoagulation has been safely initiated.

FUTURE DIRECTIONS IN ADVANCED CARE FOR INTERMEDIATE- AND HIGH-RISK PE

Although the past decade was marked by remarkable growth in PE-related clinical investigation, several critical research needs persist. More precise risk stratification tools to pre-emptively identify patients with intermediate-risk PE with the highest risk of clinical deterioration will be necessary for selection of those who would benefit from advanced therapies. The mortality rate for high-risk PE remains unacceptably high. Strategies for selection of the optimal advanced therapy and hemodynamic support in patients with high-risk PE are sorely needed. Although gaining widespread acceptance and demonstrating great potential, multidisciplinary PE response teams warrant similarly rigorous clinical evaluation as have been demanded from medical and device therapies to better understand their benefits and costs. Finally, the burgeoning area of device therapies for PE calls for appropriately powered, clinical endpoint-driven, randomized controlled trials to define their place in clinical pathways for intermediate- and high-risk PE management.

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