Intermediate-Risk and High-Risk Pulmonary Embolism: Recognition and Management

Cardiology Clinics: Cardiac Emergencies

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KEYWORDS

• Pulmonary embolism • Risk stratification • Thrombolysis • Catheter-directed therapy
• Pulmonary embolism response team (PERT)

KEY POINTS

- Pulmonary embolism risk-stratification is dependent on identifying evidence of right ventricle dysfunction, by imaging and by biomarkers.
- The highest risk PE patients need urgent and definitive therapy to support hemodynamics and to clear the pulmonary artery of clots.
- There are limited randomized and comparative effectiveness data to rigorously choose 1 interventional PE therapy over another.
- Intermediate risk PE patients represent a management challenge, in that some of these patients will experience clinical deterioration, and the ultimate hope is to identify such patients and consider definitive PE therapy early.
- Pulmonary embolism response teams (PERT) are essential in contemporary practice to individualize care and decision-making, by marshaling the combined experiences of clinicians with specialized expertise in PE.

INTRODUCTION AND NATURE OF THE PROBLEM OF PULMONARY EMBOLISM

Pulmonary embolism (PE) remains both difficult to diagnose and complex to treat despite over 50 years of recognition as a cause of significant morbidity and mortality.[1] Behind ischemic heart disease and stroke, PE is the third leading cause of cardiovascular death worldwide.[2,3]

The estimated annual population incidence of venous thromboembolism (VTE), including PE, ranges from 0.2 to 1.1 per 1000.[4–7] While the incidence of PE is low in younger populations, the incidence increases approximately 8-fold between the fourth decade and the eighth decade of life.[8,9] In addition, longitudinal data suggest that the annual incidence of PE is increasing, and the 1% to 3% of hospitalized patients with PEs who are in shock or ventilator-dependent have approximately 10-fold higher case fatality rates.[10–14] While not completely explained, this observed increase is likely multifactorial, including more

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sensitive imaging modalities (computed tomographic pulmonary angiography [CTPA]), and an increase in the number of individuals with severe comorbidities associated with developing PEs.[10,15–19]

The spectrum in PE ranges from asymptomatic to hemodynamic instability and right-sided heart failure.[20] PE represents obstruction of the pulmonary artery, and can be caused by multiple sources including tumors, fat, air, amniotic fluid, and septic emboli, though the vast majority are thromboembolic—the focus of this review.[21] VTE, including PE, develop secondary to factors known as Virchow triad: stasis in blood flow, endothelial injury, and hypercoagulability, either inherited or acquired.[22] The majority of PEs are caused by embolization of a deep venous thrombosis (DVT).[9] Acute PE results in abnormal gas exchange and circulation whereas mortality in PE is caused by increased right ventricular (RV) afterload causing a cascade leading to obstructive shock and death.[10]

Acute PE has been stratified into 3 categories: high-risk (formerly massive), intermediate-risk (formerly submassive), and low-risk based on both imaging findings and patient characteristics. High-risk PE is defined by sustained hypotension (systolic blood pressure [SBP] < 90 mm Hg) for at least 15 minutes or a vasopressor requirement where there is no other reasonable explanation for shock.[23,24] Intermediate-low risk PE is defined by evidence of imaging RV dysfunction or biomarker evidence (myocardial necrosis or chamber dilatation) in the absence of sustained hypotension.[10,24] A subcategory of intermediate-high risk PE features patients with both imaging *and* biomarker evidence of RV dysfunction. Low-risk PE does not meet the classification criteria for a high-risk or intermediate-risk PE.[10,24]

The goal of this review is to outline recent advances in the recognition and management of the intermediate-risk and high-risk PEs.

RECOGNITION: DIAGNOSIS AND PROGNOSIS

PE represents the double-edged sword of being a clinical diagnosis that is over-tested yet often missed. One study found that 5.3% of all emergency department (ED) patients had a diagnostic study for PE.[25,26] Despite this, in a systematic review of diagnostic errors, PE was found to be the second highest missed diagnosis behind cancer.[27] Another systematic review characterizing the missed diagnosis of PE found that 27.5% of the ED patients and 53.6% of the hospital inpatients with PE were misdiagnosed with other medical conditions including respiratory infections, heart failure, and acute coronary syndrome.[28] Furthermore, it was found that 37.9% of the patients who die in the intensive care unit and subsequently undergo autopsy had PEs.[28] This paradox in the clinical recognition of PE largely stems from the broad spectrum of clinical presentations ranging from asymptomatic to obstructive shock and protean symptomatology that mimics other cardiopulmonary pathologies.

History and Physical Examination

Diagnostic assessment of PE should focus on determining pre-test probability, to determine if further objective testing for PE is warranted. Accurate assessment of pre-test probability for PE relies on patient's risk factors, predisposing conditions, and the physical examination.

Approximately 60% of patients who present with VTE have a known predisposing factor.[10,29] The strongest predisposing factors include prior VTE, lower limb fractures, hip or knee replacements, major trauma, history of myocardial infarction in the last 3 months, or hospitalization for atrial dysrhythmia or heart failure within the last 3 months.[10,30–32] There are many moderate risk factors including history of cancer, obesity, diabetes mellitus, pregnancy, oral contraceptive therapy, bed rest > 3 days, and prolonged immobilization.[10,30–32] Overall incidence of VTE is higher in men compared to women. However, women under 45 and over 80 years of age are more likely to develop VTE compared to men in the same age categories. It is hypothesized that these trends are most likely secondary due to increased VTE risk with oral contraception use and pregnancy in younger women and the overall increased life expectancy for women compared to men.[9,33]

The most common signs and symptoms of PE include dyspnea (with or without exertion), pleuritic chest pain, cough, lower extremity swelling, tachypnea, and tachycardia (**Table 1**).[34] Dyspnea, chest pain, and hemoptysis—considered a classic triad of PE symptoms—occur in only 5% to 7% of patients with PE.[35]

In 67% of cases, onset of PE-related dyspnea occurs within seconds to minutes.[34] One of the more challenging symptoms associated with PE is syncope. One study estimated the prevalence of PE in hospitalized patients with first-time syncope to be as high as 17.3%, while a subsequent study found the prevalence of all VTEs in patients with first-time syncope admitted to the hospital to be only 1.4%.[36,37] Furthermore, a study of patients presenting to the ED with first time-syncope, regardless of hospitalization, found the prevalence of PE to range from 0.06% to

Table 1
Signs and symptoms of pulmonary embolism[34]

Symptoms	
Dyspnea	79%
Pleuritic Chest Pain	47%
Cough	43%
Calf or Thigh Swelling	39%
Wheezing	31%
Non-pleuritic Chest Pain	17%
Calf or Thigh Pain	16%
Signs	
Tachypnea (≥20/min)	57%
Tachycardia (>100/min)	26%
Decreased Breath Sounds	21%
Rales (Crackles)	21%
Increased P2 Heart Sound	15%
Jugular Venous Distension	13%

0.55%.[38] While syncope is not a common presenting symptom, PE should be considered in patients with syncope, and it may be a marker of higher PE risk.

Other manifestations like cough, fever, or diaphoresis may represent sequelae of pulmonary infarction with pleuritis.[39,40]

Clinical Decision Rules and Algorithms

While experienced clinicians have been shown to be effective at determining a patient's pre-test probability for PE based on history, presentation, and laboratory findings alone, clinical decision rules derived from large patient cohorts have supplanted clinical gestalt, and can help inform the need for more testing.[41] The most commonly used and most widely tested PE clinical decision rules include the Wells' Criteria, the YEARS Algorithm, the Revised Geneva Score, and the Pulmonary Embolism Rule out Criteria (PERC) Rule.[42–45]

The Wells' Criteria is a points-based algorithm which assigns patients into 3 probability groups.[46] In an ED population, the incidence of PE was 1.3% in the low probability group, 16.2% in the medium probability group, and 40.6% in the high probability group.[42] In patients with low Wells' pre-test probability, a negative D-dimer assay effectively rules out PE but a positive D-dimer requires definitive diagnostic imaging. All patients with medium or high pre-test probability of PE require definitive diagnostic imaging without consideration of a D-dimer assay.[42] The Wells' Criteria has been well-validated and has several validated variations including the simplified Wells' Criteria.[47–49]

The YEARS Algorithm is a 2-step algorithm that requires consideration of pre-test probability for PE and D-dimer testing. The pre-test probability for PE is based on 3 clinical features: clinical signs of a DVT, hemoptysis, and PE as the most likely diagnosis. If none of these features are present and the patient's D-dimer is <1000 ng/mL, PE can be excluded. If any of these features are present and the patient's D-dimer is <500 ng/mL, PE can also be excluded. If neither of these scenarios is true, the patient requires definitive diagnostic imaging.[45] In this study, PE was detected in 3.2% of the patients with 0 YEARS criteria and 23% of patients with 1 or more YEARS criteria. When the YEARS algorithm was applied in the initial study set, 48% of the patients could be ruled out for PE without definitive diagnostic imaging compared to 34% of the same population when the Wells' Criteria was applied.[45] Performance of the YEARS algorithm has been well-validated.[50,51] More recent work has attempted to adapt the YEARS Algorithm for pregnant patients, a population which has been previously excluded from all PE clinical decision rules.[52]

The revised Geneva Score is a modified version of the Geneva Score, which does not require evaluation with arterial blood gas or chest x-ray prior to determining pre-test probability for PE.[43,53] Unlike the Wells' Criteria and YEARS Algorithm, the revised Geneva Score does not incorporate subjective measurements such as the clinical gestalt of likelihood of PE as a diagnosis. Within a validation cohort, 7.9% of the patients had a PE in the low probability group, 28.5% in the intermediate probability group, and 73.7% in the high probability group.[43] Patients in the low and moderate probability groups had D-dimer testing which ruled out PE if the value was < 500 ng/mL and was followed by definitive diagnostic imaging if the value was ≥500 ng/mL. Patients in the high probability group received definitive diagnostic imaging.[43] The revised Geneva score has been well-validated through several trials; however, a study has shown that clinical gestalt alone is superior.[48,54,55]

Unlike the Wells' Criteria, YEARS Algorithm, and revised Geneva Score, the PERC rule aims to rule out PE without any diagnostic testing if 8 binary features are all negative.[44,56–58] A variation on the PERC rule for patients presenting at altitudes > 4000 ft (1219 m) where the O_2 saturation cut-off is decreased from < 95% to <90% had a slightly decreased sensitivity.[59,60]

These prediction rules are likely most helpful for excluding PE, including low-risk, while high-risk PE will be clinically overt, and in contemporary EDs, the patient with protean cardiopulmonary symptoms will likely already have had biomarkers

and electrocardiogram done before being fully evaluated by an ED physician.

Laboratory Studies

Laboratory testing in the diagnosis of PE primarily focuses on the quantitative D-dimer. The D-dimer molecule is generated alongside the coagulation cascade as breakdown product of fibrin in fibrinolysis.[61] Thus, presence of D-dimer in the bloodstream can indicate the presence of intravascular coagulation and conversely low D-dimer levels are suggestive of the absence of DVT and PE.[61] The D-dimer assay is highly sensitive, but poorly specific, using the Food and Drug Administration D-dimer cut-off of 500 ng/mL. Based on this cut-off, PE can be ruled out in patients with a probability < 2% with an already low pre-test probability based on a clinical decision rule.[62] More recently, an age-adjusted D-dimer cut-off has been established where the age-specific D-dimer cut-off is age multiplied by 10 ng/mL when age > 50, or 500 ng/mL for age < 50.[63,64] The use of the age-adjusted D-dimer has been validated for use in conjunction with the Wells' Criteria, YEARS Algorithm, and the revised Geneva Score for determining pre-test probability.[51,65]

In addition to D-dimer, other laboratory tests including arterial blood gas, lactate, cardiac troponins, and brain natriuretic peptide have been studied as possible markers of PE. While none of these are diagnostically useful, they can potentially serve as markers of prognosis and risk-stratification.[10,53,66–87]

Electrocardiogram

The EKG is neither sensitive nor specific for the diagnosis of PE.[72,73] and over one-quarter of patients with PE may have no EKG changes.[74] EKG changes seen in PE occur secondary to the development of acute RV dysfunction meaning any condition that can cause acute RV dysfunction can mimic EKG patterns associated with PE. EKG findings that have been associated with PE include tachyarrhythmias (sinus tachycardia, atrial fibrillation), right bundle branch block (RBBB), right-sided axis deviation, nonspecific ST changes, T-wave inversions (in particular in early precordial or less commonly inferior leads), and the $S_1Q_3T_3$ sign, among others.[75–86] However, only sinus tachycardia and an incomplete RBBB were found to be statistically significantly more likely in patients diagnosed with PE.[72] EKG indicia of right heart strain may be considered with biomarker and imaging data as evidence toward intermediate-risk stratification.[24,73]

Imaging

Diagnostic imaging is the primary means of both diagnosing PE and determining its severity.[24,72,88] The definitive diagnosis of PE is contemporarily made using either CTPA, with other modalities like ventilation/perfusion (V/Q) lung scintigraphy less commonly used if for example, renal dysfunction precludes iodinated contrast. Transthoracic echocardiography (TTE) has insufficient sensitivity for excluding PE, but is essential in risk-stratification; TTE may have roles as an adjunct diagnostic in patients with renal dysfunction or critically ill patients who cannot travel to a CT scanner. In this manner, leg ultrasound has positive predictive value when a DVT is identified in a patient with high pre-test probability of PE. Chest radiograph (CXR), while not diagnostically useful in ruling in a PE can be critical in ruling out other causes of PE-like symptoms. Finally, magnetic resonance angiography (MRA), while not yet clinically validated for diagnosing PE, has shown promise in some investigations, though the duration of the study may preclude patients with possible instability.

Transthoracic echocardiography

Due to increased pulmonary vascular resistance (PVR), echocardiographic signs of RV overload and dysfunction can manifest in acute PE.[10,24,87] Due to complex 3D RV geometry and retrosternal location, no single echocardiographic measure of RV function has been found to be reliable in isolation.[10] The most commonly described ultrasonographic measures for evaluating RV overload and dysfunction include increased RV to left ventricle (LV) linear ratio,[88] abnormal septal wall motion (flattening or bowing of the RV into the LV), McConnell sign (diffuse RV hypokinesis with apical sparing), tricuspid regurgitation (TR), decreased tricuspid annular plane systolic excursion (TAPSE), decreased systolic excursion velocity of the RV basal free wall (S′), pulmonary artery Doppler systolic notching, and decreased RV free wall strain.[89,91] A systematic review found that measures of RV strain are generally specific, with no sign having a specificity < 80%, though some signs are seen with acute RV myocardial infarction. As signs are poorly sensitive, these ultrasonographic findings should be considered "rule in" tests as opposed to PE "rule out" tests.[92]

Finding clot-in-transit (CIT) virtually confirms pulmonary VTE; however, this finding is relatively rare in all PE patients (~4-8%).[93,94] In patients with PE, CIT is associated with increased morbidity and mortality with morality rates ranging from 80% to 100% if left untreated.[94–97]

The overall sensitivity for PE diagnosis by TTE is approximately 50% to 70%, and some of the markers above which are mainly for prognosis can be marshaled to not only assist in diagnosis by suggesting that a presenting syndrome is due to PE rather than another pulmonary or left heart cause including cardiac tamponade, hypovolemia, acute valvular dysfunction, aortic dissection, and LV dysfunction, but also quickly evaluate for evidence of significant right heart dilatation and dysfunction.[10]

TTE remains important in contemporary PE-risk stratification by sorting patients among intermediate-high, intermediate-low, and low-risk.[10] Normotensive acute PE with echocardiographic evidence of RV dysfunction would meet classification as an intermediate-risk PE.[24,98–100] Evolving metrics of ventricular-vascular uncoupling, including a ratio describing RV-pulmonary artery coupling (such as TAPSE/Pulmonary Arterial Systolic Pressure (PASP)), are showing promise not only in PE but also in other states of RV afterload.[101] One caveat when using TTE, or any modality, is that the chronicity of findings is unknown, and that chamber dilatation, TR, elevated RV systolic pressure, or chamber dysfunction could be chronic and secondary to intrinsic heart disease or chronic lung disease.[71,102]

Additionally, in patients with a high-probability of PE who are unstable and where CTPA is unattainable, TTE demonstrating signs of RV pressure overload without other obvious cause of RV overload should be considered for reperfusion therapy.[10,90,103,104]

Chest radiograph

Overall, changes in the CXR due to PE are both poorly sensitive and specific and are not routinely required specifically for the diagnosis of PE.[52,105,106] Previous work has found that the CXR is normal in 25% of patients with PE, with the 3 most common abnormal radiograph findings: cardiomegaly (27%), pleural effusion (23%), and elevated hemidiaphragm (20%).[106] Additionally, several CXR findings can be seen due to pulmonary infarct from PE: Hampton hump (a dome-shaped pleural opacification), Westermark sign (peripheral oligemia, due to pulmonary artery obstruction), atelectasis, and pleural effusion.[105,107–109] Of course, all of these findings are better evaluated with CT.[105,110] CXR still however has value in the urgent evaluation: first, for diagnosing alternative causes of symptoms including pneumothorax, pneumonia, and heart failure,[111] and second, a normal CXR is useful in assessing the utility of ventilation/perfusion (V/Q) scanning. V/Q scanning is a reasonable alternative to CTPA when the CXR is normal, but when the CXR is abnormal, V/Q is inferior to CTPA.[111]

Computed tomographic pulmonary angiogram

The gold standard for diagnosis of PE is contrast-enhanced multidetector CTPA.[10] In most cases, CTPA is able to evaluate for evidence of PE to the level of the subsegmental pulmonary vessels.[10,112] The Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED-II) trial found that the sensitivity and specificity for PE in a multidetector CTPA was 83% and 96%, respectively,[113] though the sensitivity value has only increased over time with advances in CT technology. When considering low and intermediate pretest probability for PE, the negative predictive value (NPV) for PE was 96% and 89%, respectively, while the positive predictive value (PPV) was 58% and 92%, respectively. This is compared to a high pre-test probability where the NPV is 60% and the PPV is 96%.[113] These data suggest that a negative CTPA in a low-risk and intermediate-risk patient essentially rules out PE while a negative CTPA in patient with high pretest probability or high clinical suspicion may warrant additional evaluation.[113]

In addition to its front-line diagnostic role, CTPA may be simultaneously useful in risk-stratifying for intermediate-risk PE.[24] CTPA may manifest signs analogous to echocardiography including chamber dilatation, interventricular septal bowing, and contrast reflux to the inferior vena cava (suggesting substantial TR). TTE may have better test characteristics for signs of RV dysfunction and strain, with CT similarly sensitive, though less specific.[114,115] Evidence of RV strain on CTPA confers an increased risk for short-term adverse outcomes.[114,116,117] When coupled with TTE, the predictive value for negative outcomes from CTPA increases, suggesting that when evaluating for RV strain, CTPA with TTE is possibly useful for guiding treatment decisions.[114]

Multiple investigations have also assessed metrics of CTPA “clot burden” to predict PE severity; however, these in general do not correlate with the hemodynamic and cardiopulmonary sequelae of PE, and can be cumbersome to calculate in clinical use.

Ventilation/perfusion lung scintigraphy

Using inhaled radioactive tracers, ventilation/perfusion lung scintigraphy (V/Q scan) assesses ventilation and perfusion mismatch, which gives evidence of pulmonary artery obstruction.[10] A primary benefit of V/Q scanning is that it does not require iodinated contrast media and therefore

offers a method to evaluate for PE in patients with anaphylaxis to contrast media or renal failure.[10,118,119] A study comparing CTPA and V/Q scan found both to be equivalent in ruling out clinically significant PE; however, it also found that CTPA diagnosed more PEs.[120] Notably, results of the V/Q scan are reported as positive, negative, and non-diagnostic.[121] One of the challenges of V/Q scanning is that up to 50% of studies are reported as inconclusive or non-diagnostic, thus requiring further diagnostic evaluation.[10] In addition, unlike CTPA, V/Q scanning is less readily available and has higher interobserver interpretation variability.[10] This modality has now been mostly replaced by CTPA except in select instances, such as pregnant women.

Magnetic resonance angiography

The possibility of magnetic resonance angiography (MRA) for PE diagnosis is of interest as there is no associated radiation exposure and it uses gadolinium-based contrast instead of iodinated contrast.[122] However, in several studies, MRA has generally been shown to have a large number of inconclusive or inadequate studies (up to 25%), and low sensitivity,[123,124] with higher sensitivity for proximal PE but more inconclusive for distal PE.[123] Nevertheless, among patients who were evaluated with MRA for PE, a study found that the NPV of 97% and 96% at 3 month and 1 year, respectively, was equivalent with CTPA.[125] While this suggests that MRA may be less effective at evaluating for distal PEs, these may not be a clinically significant finding; however, at present, MRA is not used in the contemporary evaluation of PE.

MANAGEMENT OF INTERMEDIATE-HIGH AND HIGH-RISK PULMONARY EMBOLISM

Delineating Intermediate-Risk and High-Risk Pulmonary Embolism

The management and appropriate therapeutic strategy for diagnosed acute PE depends on severity. Risk-stratification is thus essential to align treatments with clinical scenarios, in order to properly balance PE risk with expected treatment benefits and risk.

High-risk PE includes those with sustained hypotension or vasopressor requirements, as well as those with cardiac arrest or severe arrhythmia, or rapid respiratory failure; such patients generally are clinically manifest, without the need for specific rules or other prognostic information.[88,94] These are the rarest presentations of PE but mandate emergent response in terms of cardiopulmonary stabilization and clearing of PE from the pulmonary arterial tree, which can include considerations like extracorporeal membrane oxygenation (ECMO) and surgical and percutaneous thrombectomy.[10,24,87]

Low-risk PE represents the most common PE phenotype, and a class of patients that generally experiences good outcomes with anticoagulation alone.

The intermediate-risk PE category, those patients without vital sign instability, but varying levels of imaging evidence of RV dysfunction, or biomarkers indicating myocardial necrosis or chamber dilatation, represent a clinical conundrum in contemporary care.[23,24] The intermediate-low risk stratum, akin to lower-risk PE, generally do well with anticoagulation. However, of normotensive PE patients with the highest evidence of PE-related RV dysfunction by biomarkers and imaging (intermediate-high risk), approximately 10% will experience cardiopulmonary deterioration and thereby require more emergent, and advanced PE-debulking therapies. Identifying these intermediate-risk PE patients who are in jeopardy of deterioration is the "holy grail" of modern risk stratification, so that the inherent risks of interventional PE therapy can be juxtaposed with and balanced judiciously with the potential benefits.[24,87,126]

High-index of suspicion is always required, as one-third of all intermediate-risk PE patients in a contemporary PE registry had depressed cardiac index ("normotensive shock").[127]

In addition to guideline-based definitions of intermediate-risk and high-risk PEs, substantial work has been invested to create quantitative metrics of PE severity, including the Pulmonary Embolism Severity Index (PESI), simplified PESI (sPESI), and Bova score for PE complications.[128–130] Of these scores, the PESI score is the most widely validated.[131,132] The PESI score, based on 11 patient characteristics encompassing both PE severity and known comorbidities (**Table 2**), segregates PE patients into 5 severity classes based on predicted 30-day mortality.[129] Points are added for PESI factors that are present, along with the patient's age, and the combined score translates into a risk prediction class (see **Table 2**).

A simplified version, sPESI, has also been well-validated in observation cohort studies and only requires 6 features including age > 80, history of cancer, history of cardiopulmonary disease, tachycardia (≥110 bpm), tachypnea (≥30 bpm), hypotension (SBP < 100 mm Hg), and oxygen saturation (SpO_2 < 90%).[130,133] Presence of any parameter accrues 1 point, and an sPESI of 0 reflects 30-day low risk (1.1% mortality), while a score ≥1 represents high risk (30 day 8.9% mortality).

The 2019 European Society of Cardiology (ESC) guidelines for acute PE recommend considering

Table 2
Pulmonary embolism severity index criteria and interpretation

Pulmonary Embolism Severity Index Clinical Criteria		Points	In simplified Pulmonary Embolism Severity Index?
Age	Years	Years	✓
Sex	Female	Male+10	
Altered Mental Status	No	Yes+60	
Systolic Blood Pressure (BP) <100 mm Hg	No	Yes+30	✓
History of Cancer	No	Yes+30	✓
Temperature <36 °C	No	Yes+20	
Heart Rate ≥110 bpm	No	Yes+20	✓
Respiratory Rate ≥30	No	Yes+20	
Oxygen Saturation <90%	No	Yes+20	✓
History of Heart Failure	No	Yes+10	✓
History of Chronic Lung Disease	No	Yes+10	✓

PESI Score	Class	Risk Profile	30-d Mortality
0–65	I	Very-low risk	0.0%–1.6%
66–85	II	Low-risk	1.7%–3.5%
86–105	III	Intermediate-risk	3.2%–7.1%
106–125	IV	High-risk	4.0%–11.4%
≥125	V	Very high-risk	10%–24.5%

incorporating PESI or sPESI and evidence of RV strain via imaging or biomarkers when considering PE severity (Class IIa recommendation, **Table 3**).[10] Interestingly, while the use of mortality risk scores has been increasingly recommended in evaluation of PE, a recent review found that the PESI, sPESI, Bova, and the recommended 2019 ESC guideline approach had limited model discrimination of patients with low-mortality versus high-mortality risk and poor inter-model correlation.[134]

Pulmonary Embolism Response Team

The depth of expertise required and the need for improvement in PE outcomes have propelled the growth of hospital-based PE Response Teams (PERTs).[24,135] The PERT concept borrows from contemporary best-practice concepts of Heart Teams and Rapid Response teams, and thereby allows for the diagnosing clinician ("afferent arm") to quickly respond to PE patients at risk and to trigger a multi-disciplinary response (efferent arm) to collaboratively evaluate a patient, and determine and implement the best treatment strategy.[135–137] The PERT incorporates experts from several specialties including cardiovascular medicine and surgery, emergency medicine, hematology, pulmonary/critical care, cardiac imaging (radiology and echocardiography), vascular medicine and intervention, and interventional radiology, with differences across centers.[135]

Initial 30-month evaluation at the Massachusetts General Hospital (MGH) found rapid growth in activations by 16% every 6 months with 72% of all activations for intermediate-risk and high-risk PEs, and extrapolation across the United States and world.[138,139] MGH also reported approximately 17% of patients received an advanced reperfusion therapy (catheter or systemic thrombolysis or thrombectomy), but overall similar bleeding risk in patients treated with catheter-directed modalities versus anticoagulation alone.[138] Cleveland Clinic reported their retrospective implementation analysis showed approximately 33% received an advanced reperfusion therapy, with no bleeding events in patients receiving systemic thrombolysis.[140]

Data on the effectiveness of PERTs are emerging,[139,141–144] some showing improvements in PE-related outcomes and mortality. Current ESC guidelines give a class IIa recommendation to set-up of PERT teams to manage intermediate-risk and high-risk PE, depending on the needs and capabilities of the hospital.[10] The mechanisms of benefit of PERT may be multifactorial, and

Table 3
Guidelines-based classification of pulmonary embolism severity[10,24]

		Indicators of Risk			
Early Mortality Risk		Hemodynamic Instability	Clinically Severe Pulmonary Embolism, PESI Class III–V, or sPESI ≥1	RV Dysfunction Transthoracic echocardiography or computed tomographic pulmonary angiography (CTPA)	Elevated Cardiac Troponin Levels
High		(+)	(+)	(+)	(+)
Intermediate	Int.-High	-	+	+	+
	Int.-Low	-	+	One (or none) positive	
Low		-	-	-	-

include protocolization of care, democratization and access to specialists, consensus evaluation of risk, iterative assessment of acute PE patients, more rapid deployment of therapies, PERT-based follow-up, and quality improvement.[24,135,140] PERT teams should work to provide hub-and-spoke service within a network, to facilitate an organized approach to interhospital transfer in particular of critically ill PE patients and those who require advanced reperfusion therapies.[145]

Respiratory and Hemodynamic Support

The key tenet of initial management of intermediate-risk and high-risk PE is to provide hemodynamic and pulmonary support. PE causes RV obstruction, increased PVR, ventilation-perfusion mismatch, and possibly right to left shunting.[146] Hypoxemia must be addressed and treated, ideally achieving oxygen saturation $\geq$ 90%. Goal blood pressure, while not specifically defined, is targeted to avoid signs of malperfusion, such as altered mental status or decreased urine output, though some authors suggest an optimal mean arterial pressure between 80 and 90 mm Hg for intermediate-risk and high-risk PE.[10,147] Of course, blood pressure goals must always be individualized relative to the patient's baseline blood pressure: clinicians should be cautious about absolute blood pressure cut-offs (including those that are used to define high-risk PE), if for example, the patient has a decline in blood pressure compared to baseline.

Respiratory support

The mainstay of respiratory support patients with intermediate-risk and high-risk PE with hypoxia is supplemental oxygen (O_2). This can be delivered with a nasal cannula, simple facemask, or non-rebreather facemask which is sufficient for the majority of patients.[148] In instances where this is insufficient, a high-flow nasal cannula is preferred over positive-pressure modes of ventilation such as continuous positive airway pressure (CPAP) or biphasic positive airway pressure. This is because increased positive intrathoracic pressure reduces venous return, and contributes to RV afterload.[146,148,149] If positive end-expiratory pressure, either invasive or non-invasive, is necessary, caution is required to keep tidal volumes and plateau pressures low (~6 mL/kg of lean body weight and < 30 cmH_2O, respectively).[10,150] Hypotension and cardiovascular collapse can occur as a result of increased intrathoracic pressure increasing RV afterload, and decreasing preload by limiting blood return.

Additionally, if patients require intubation for respiratory support, there is significant risk of hypotension in patients with RV failure during induction of anesthesia. Given this, anesthetic agents that cause hypotension should be avoided and clinicians should be prepared to provide additional urgent hemodynamic support when using anesthetic agents in patients with acute significant PE.[10]

Supplemental oxygen itself is being re-evaluated as a "drug" in acute PE to improve outcomes. The Air versus Oxygen for Intermediate-Risk Pulmonary Embolism (AIRE) trial (https://classic.clinicaltrials.gov/ct2/show/NCT04003116) was a pilot study that, though being underpowered, found a borderline association between supplemental oxygen therapy and reduced RV dilatation, compared to ambient air.[151] Additional studies examining the mechanism of supplemental oxygen in patients with PE are underway, including Supplemental Oxygen in Pulmonary Embolism (SO-PE) (https://classic.clinicaltrials.gov/ct2/show/NCT05891886).

Hemodynamic support

The etiology of shock in PE is secondary to increased RV afterload as a result of obstruction in the pulmonary vessels as well as secondary effects including vasoconstriction from hypoxia and acidosis.[152] This pathophysiology leads to RV dilation, hypokinesis, tricuspid regurgitation, and RV failure.[153] Further increased RV dilatation, subject to ambient pericardial restraint, impairs LV filling and stroke volume from leftward deviation of the interventricular septum.[153]

A reasoned judicious approach to hemodynamic support for PE with malperfusion, as part of the definitive management strategy, is crucial. While volume resuscitation is standard in many etiologies of shock, its use for managing hypotension and shock in PE is controversial, though most expert authors agree that a small fluid challenge may be appropriate.[10,152–154] A small study giving 500 mL fluid boluses to PE patients found a substantial increase in cardiac output in 12 out of 13 patients.[154] The difficulty is supporting RV preload while avoiding RV overdistention with adverse Frank–Starling consequences[10,146,154]; unfortunately, there is no optimal marker of volume-responsiveness in acute PE. Patients with low central venous pressure or with a small, collapsible IVC may be most likely to benefit from fluid challenge.[10,153] However, volume resuscitation with large fluid boluses is likely to cause RV overdistension and ultimately reduce cardiac output. In fact, there is consideration that *diuresis* may actually be helpful to a failing RV, reducing its distention and wall stress, and relieving impingement of the interventricular septum on the LV.[146] Of course, bolus diuretic can directly cause hypotension, and may impair RV preload; navigating these quandaries requires expert assessment and re-assessment at bedside, with attention to individualization of interventions.

Given the difficulties with fluid assessment and balance in acute PE, vasopressors are a mainstay for hemodynamic support. Ideally, the optimal vasopressor in RV failure should increase RV contractility and systemic arterial pressure while not increasing PVR.[153] The optimal vasopressor for RV failure in PE has not been identified, though norepinephrine seems to be a preferred first-line agent, with its mix of alpha and beta agonism, supporting mean arterial pressure without increasing PVR. Vasopressin is a non-catecholamine that should increase systemic arterial pressure also without increasing PVR.

Parenteral inotropes including epinephrine, dobutamine, and dopamine may have a role when there is insufficient cardiac output, though tachycardia and tachyarrhythmia can occur, which may adversely influence cardiac output.[153,155,156]

The nitric oxide pathway has been considered another possible target intervention, in that this small molecule is a potent, reversible, and selective pulmonary vasodilator. The Inhaled nitric oxide for PE (iNOPE) trial investigated inhaled nitric oxide in intermediate-risk PE, and found that more patients achieved a prespecified secondary endpoint of normalization of RV echocardiographic parameters.[18,157] Nitric oxide has also been evaluated as salvage therapy in high-risk PE but the numbers of studied patients are quite small and do not permit firm conclusions.[158] Analogously, sildenafil, a phosphodiesterase-5-inhibitor, which increases cyclic GMP (the action downstream of nitric oxide) did not improve cardiac index in intermediate-high risk PE, and instead caused hypotension.[159] Overall, treatments of PE with pulmonary vasodilators remain speculative.

Extracorporeal membrane oxygenation

High-risk PE patients with hemodynamic instability despite optimal pharmacologic interventions should be considered for mechanical circulatory support. The most common of these strategies is ECMO, for which there are case studies and case series in highest risk PE, but no randomized control trials. ECMO receives a Class IIb recommendation for acute PE with “refractory circulatory collapse or cardiac arrest” in 2019 ESC guidelines.[10,160,161] The primary goal of ECMO in treating PE is to serve as a bridge to definitive therapy by providing cardiopulmonary support.[162] While there have been rare cases of veno-venous (VV) ECMO used in high-risk PE, it is largely accepted that veno-arterial (VA) ECMO is the optimal modality as it provides both ventilatory and hemodynamic support, whereas VV ECMO only delivers oxygenated blood to the right heart, and does not provide circulatory support.[160,161] Importantly, peripheral VA ECMO bypasses the obstruction of the pulmonary vascular bed, removing blood from the venous system and rerouting it to the femoral artery after oxygenation.[162] Anticoagulation is required for ECMO and thus any patients who cannot be anticoagulated may not be a candidate for ECMO; importantly, this anticoagulation provides treatment of the PE. Other contraindications to ECMO include poor functional status, advanced age, morbid obesity, neurologic dysfunction, chronic organ dysfunction, and prolonged CPR.[162] One systematic review of cases where ECMO was used for high-risk PE found a survival rate of 78% but notes that this survival rate is higher than in many previous studies.[160] Additionally, 2 systematic reviews

of patients on ECMO found that they received varied definitive interventions either in isolation or combination including systemic thrombolysis, catheter-guided thrombolysis, and surgical embolectomy.[160,161] A review of the use of ECMO in patients with high-risk PE who have cardiopulmonary arrest found a 61% survival rate for patients who were cannulated for ECMO either during cardiac arrest or after Return of Spontaneous Circulation (ROSC) was achieved.[163] The study did find that mortality was higher in patients who were cannulated during arrest and for patients over age 65.[163] Overall hospital systems should work on optimization of channels and transitions of care, including mobile ECMO and coordination of transfer of ECMO patients to tertiary centers.[145]

There is a small, growing literature on the use of percutaneous RV assist devices in high-risk PE. These devices generally require access to the pulmonary artery, which may be difficult if not contraindicated in acute PE, and they do not directly provide support for ventilation and oxygenation in contrast to VA ECMO.[87]

Reperfusion and Pulmonary Embolism-Debulking Therapies Anticoagulation

The initial treatment of PE, including intermediate-high and high-risk, is anticoagulation. ESC guidelines give a class I recommendation: "initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, while diagnostic workup is in progress."[10,24] This must be considered in terms of certainty of the diagnosis (pre-test probability, to avoid exposing non-PE patients to bleeding risk), stability of the patient, comorbidities and bleeding risk, and delay until definitive diagnosis can be made (eg CTPA). Data support the correlation between early initiation of anticoagulation and decreased overall mortality.[164] For intermediate-high and high-risk PE, initial anticoagulation is most often achieved with subcutaneous low-molecular weight heparin (LMWH), fondaparinux, or unfractionated heparin (UFH). When not contraindicated, recent data have suggested superiority in using either LMWH or fondaparinux for initial anticoagulation as it decreases both bleeding risk and development of heparin-induced thrombocytopenia.[165,166] However, in high-risk patients where definitive reperfusion and interventional therapy may be needed, UFH may be preferred due to shorter half-life (0.5 - 1.5 hrs) compared to LMWH (3 - 6 hrs) and fondaparinux (17 - 21 hrs).[167] UFH is also preferred in patients with renal dysfunction.[10] In general, contraindications to empiric anticoagulation should be considered in all patients.[10]

Systemic thrombolysis

In addition to anticoagulation, systemic thrombolysis is recommended by both the American College of Chest Physicians guidelines and the ESC guidelines for patients with high-risk PE (hemodynamically unstable patients with a PE, without contraindications to thrombolysis).[10,168] While there is a demonstrated hemodynamic benefit of thrombolysis in intermediate-high risk PE, in terms of hemodynamic deterioration, there is no overall difference in all-cause mortality; benefits of systemic thrombolysis are offset by increased bleeding risk and so thrombolysis is only recommended if patients with intermediate-high risk PE progress to hemodynamic instability.[10,87,168–171]

Both relative and absolute contraindications to systemic thrombolysis must be considered prior to administration (**Table 4**).[172 87,] Some 50% of patients have a contraindication to systemic thrombolysis, limiting its applicability. Additionally, the risk of intracranial or fatal hemorrhage due to

Table 4
Major and Minor contraindications to systemic thrombolysis[87,172]

Major Contraindications	Minor Contraindications
Structural intracranial disease	Prolonged cardiopulmonary resuscitation
Intracranial neoplasm	Systolic BP >180 mm Hg
Previous intracranial hemorrhage	Diastolic BP >110 mm Hg
Ischemic stroke (within 3 mo)	Recent non-intracranial bleeding (within 2–4 wk)
Recent brain or spinal surgery (within 3 mo)	Recent surgery (within 2 wk)
Any known bleeding diathesis or internal bleeding	Recent invasive procedure (within 1 mo)
	Ischemic stroke (>3 mo ago)
	Coagulopathy, thrombocytopenia, oral anticoagulant
	Age <18 y or >75y
	Pregnancy (current, or birth within 1 wk)

thrombolysis leads to underuse, even in the most severe PE.

The ESC guideline-recommended regimens for systemic thrombolysis include recombinant tissue-type plasminogen activator (rtPA).[10] Importantly, UFH can be continued if administering rtPA (but must be stopped if administering first-generation thrombolytics, strepokinase and urokinase).[10,173] While several meta-analyses have found tenecteplase to be safe and effective, there are no head-to-head trials comparing it to other thrombolytics, and it is not yet recommended in the ESC guidelines. The American College of Chest Physicians does not offer specific guidance on optimal thrombolytic choice.[10,168,174–176] Notably, there is a small portion of patients who receive systemic thrombolysis who do not respond, with some estimates as high as 8%.[177] Such patients must be carefully evaluated for rescue therapies, including ECMO or an embolectomy procedure.[24,87]

Catheter-directed therapies

Significant work has been conducted on the use of percutaneous catheter-based modalities for clot thrombolysis or evacuation. While the standard of care for hemodynamically unstable patients with high-risk PE remains systemic thrombolysis, catheter-directed modalities have been studied as adjuncts to or second-line therapies for high-risk PE as well as possible first-line treatment for intermediate-high risk PE.[178,179] There are several modalities for catheter-directed treatment of PE including standard catheter-directed thrombolysis (CDT), ultrasound-assisted CDT, fragmentation, and catheter-directed embolectomy.[178]

Catheter-directed thrombolysis An overall theme and goal of catheter-directed thrombolysis is to achieve the benefits of systemic thrombolysis without the same bleeding risk, by using lower doses of locally delivered thrombolytic via a catheter.[24,87,179,180] Ultrasound-assisted CDT (USCDT) operates on the same principle but additionally utilizes high-frequency, low-power ultrasound waves (from a 5F combined ultrasound and thrombolytic infusion catheter) to assist in fibrinolysis by unwinding fibrin strands to unlock thrombolytic binding sites.[87,179] Many of the trials of these devices are based on surrogate PE-endpoints like ventricular size ratio Ultrasound Accelerated Thrombolysis of PE (ULTIMA[181])trail and PASP, and several are a prospective, Single-arm, Multi-center Trial of EkoSonic(R) Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (Seattle II).[182] ULTIMA randomized intermediate-risk PE patients to USCDT versus anticoagulation, and found that the primary endpoint, 24 h reduction in the dimensionless RV:LV ratio was−0.30 compared to−0.03 with anticoagulation alone. There were no episodes of hemodynamic decompensation or instances of major bleeding events at 90 days in either group.[182] The OPTALYSE PE trial investigated the lower thrombolytic doses and shorter duration of thrombolytic infusions for intermediate-risk PE, and found comparable surrogate outcome (RV:LV ratio) results with lower doses (4 mg per lung similar to 12 mg) and reduced times (2 hours similar to 6 hours).[183-185] While randomized, OPTAYLSE had no control arm, so we cannot compare the RV:LV ratio to a no-treatment or anticoagulation-arm. A meta-analysis of 8 studies comparing CDT and USCDT (7 observational and 1 randomized) showed no overall difference in length of stay, bleeding, or surrogate PE-related measures (though the CDT group had a statistically better reduction in mean pulmonary artery pressure).[184] However, the trials included may have used higher thrombolytic doses with USCDT, and thus not shown a benefit of USCDT on lesser bleeding outcomes. Because the question of whether CDT and USCDT are truly of benefit over anticoagulation alone, there are several ongoing investigations including PE-TRACT (https://www.clinicaltrials.gov/study/NCT05591118) and HI-PEITHO (https://www.clinicaltrials.gov/study/NCT04790370). These trials aim to compare the use of CDT and USCDT, respectively, in intermediate-risk PEs to anticoagulation alone.

Catheter-directed embolectomy Suction embolectomy was first pioneered more than 50 years ago.[87] A large-bore aspiration system (AngioVac) was developed to aspirate intravascular materials with a veno-venous bypass system and filtering mechanism, and has been used for extraction of vena cava and peripheral venous thrombi, right heart vegetations, right heart CIT, and sometimes PE, though the large bore can be difficult to steer in the pulmonary artery. A next generation device (AlphaVac) is being assessed in a single-arm study of intermediate risk PE (APEX-PE, https://classic.clinicaltrials.gov/ct2/show/NCT05318092).

Multiple new catheter-directed embolectomy (CDE) platforms have proliferated in the 2010s. The FlowTriever is a 16, 20, or 24 French catheter for aspiration that also features 3 nitinol-discs that can self-expand and trap thrombus. FlowTriever received approval in 2018 based on the single-arm Flowtriever Pulmonary Embolectomy (FLARE) study showing improved RV:LV ratio in intermediate-risk PE.[24,87,186] Interestingly in practice, the nitinol-discs are not always used relative

to the aspiration functionality; aspiration can be repeated as needed to clear the pulmonary artery. Two lines of investigation on FlowTriever were presented in 2023. FlowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH)[187,188] is a real-world analysis of intermediate-risk (77%) and high-risk (8%) PE patients of whom one-third had a contraindication to thrombolysis. FlowTriever resulted in immediate 8 mm Hg decline (−23%) in mean pulmonary arterial pressure and increased cardiac index 0.3 L/min/sqm (+19%). Thirty-day mortality was 0.8%. FlowTriever for Acute Massive Pulmonary Embolism was presented at American College of Cardiology March 2023, detailing a prospective observational cohort of high-risk PE (hypotension, vasopressor use, arrest); in-hospital mortality was < 2% compared to > 28% in both a literature-based historical goal and a "context" arm which included ~70% systemic thrombolysis (https://clinicaltrials.gov/ct2/show/NCT04795167). Rescue therapy, clinical deterioration, and major bleeding were all lower with FlowTriever. The Indigo aspiration catheter is smaller-bore (eg 6F-12F) and may be able to better navigate the pulmonary arterial tree, but it has less cross-sectional area and capacity for clot extraction; single-arm surrogate-endpoint data has studied this device.[189]

Percutaneous devices comparison The 2 major paradigms of percutaneous therapies are CDT and CDE, but comparisons among these are few. One such study from 2016 to 2019 from the Nationwide Readmission Database propensity matched about 800 high-risk PE patients who received CDE and CDT.[189] The cohort featured 75% mechanically ventilated patients, 15% on vasopressors, 12% who required mechanical circulatory support, and 13% who received systemic thrombolysis. There was no difference in all-cause mortality or major bleeding, but this was a retrospective analysis dependent on administrative coding data, and biases for or against a certain treatment modality cannot be assessed. PEERLESS (https://classic.clinicaltrials.gov/ct2/show/NCT05111613) is a randomized trial of FlowTriever CDE versus any modality of CDT in intermediate-risk PE, designed to assess a composite win-ratio endpoint based on mortality, bleeding, and deterioration or treatment escalation. A 2024 analysis of real-world data comparing USCDT and CDE showed higher overall major bleeding by International Society for Thrombosis and Hemostasis criteria (11.0% versus 17.3%, p=0.0002). There was also less intracranial hemorrhage in the USCDT group compared to CDE (0.4% versus 1.4%, p=0.015). Selection-biases and confounding cannot be excluded. However, this type of big-data approach, with real-world patients, may provide insights not available in clinical trials, where there are many exclusion criteria. If validated, the result may also suggest that there are unappreciated harms to CDE, or may bear on the skill level or expertise required to conduct CDE. (https://www.jscai.org/article/S2772-9303(23)01194-8/fulltext).

Where does this leave the practicing clinician faced with an intermediate-high or high-risk PE? First, each institution and center likely will develop expertise in a certain selection of percutaneous devices, and there is likely a volume-quality relationship in employing interventional therapeutics. Second, we can appreciate some differences between CDE and CDT (**Table 5**). There does seem to be a secular evolution in therapy toward CDE, given immediate debulking of PE and reperfusion of the pulmonary arterial tree. Akin to the history of reperfusion therapy for myocardial infarction, evolving from thrombolysis to primary percutaneous coronary intervention to open the coronary artery, we may be on the precipice of moving treatment of advanced, central PE from a pharmacologic (or combined pharmaco-mechanical CDT paradigm) to a CDE paradigm to open the pulmonary artery. Before standards of care change, however, additional comparative and randomized data will be required to fully define

Table 5
Comparison of Catheter-directed thrombolysis and catheter-directed embolectomy

Catheter-directed thrombolysis	Catheter-Directed Embolectomy
Smaller bore devices	Larger devices, less navigable, learning curve
Able to reach distal pulmonary vasculature	Generally treats proximal PE
	Mechanical embolectomy only
Pharmaco-mechanical strategy	Embolectomy has immediate effect
Thrombolytic action takes time	More suited to central PE
Perhaps better for peripheral PEs	Access site risks, risks of injury to pulmonary artery
Bleeding risk (local and systemic)	
Typically performed by interventional cardiologist or interventional radiologist	Typically performed by interventional cardiologist or interventional radiologist

outcomes and risks, and understand the role for each modality.

Overall, ESC guidelines do not recommend the routine use of percutaneous catheter-directed treatments, but do offer a Class IIa consideration for high-risk PE patients in which thrombolysis has failed or is contraindicated.[10]

Surgical thromboembolectomy

The concept of surgical thromboembolectomy for PE was first described in the early twentieth century.[190] Surgical thromboembolectomy is a highly invasive procedure and requires midline sternotomy and cardiopulmonary bypass.[191,192] Surgical thromboembolectomy had most often been reserved as a salvage procedure when other treatment options have failed; however, there is some evidence to support its use in patients with an extensive proximal thrombus burden such as CIT and impending paradoxic embolism.[190,191,192,193] Traditionally, the mortality of patients undergoing surgical thromboembolectomy has been high—a nationwide sample of patients undergoing surgical thromboembolectmy between 1999 and 2008 found a mortality rate of 27.2%, but this was likely due to selection bias and its use as a salvage procedure.[190] Recent data demonstrate an in-hospital mortality rate in high-risk and intermediate-risk PE patients undergoing surgical thromboembolectomy between 6.6% and 11.7%.[191,194,195] Some authors argue that surgical thromboembolectomy should be considered in the treatment algorithm for intermediate-high and high-risk PE, for example, in central emboli or clot-in-transit.[190] A single-center retrospective study of 55 patients with intermediate-risk PE, high-risk PE without cardiac arrest, and high-risk PE with cardiac arrest found a 93% in-hospital survival rate, in-line with other recent data, but found that in-hospital survival in the intermediate-risk group was 100% compared to 88% and 78% in the high-risk PE without and with cardiac arrest, respectively.[196] Despite this, there are no trials directly comparing surgical thromboembolectomy to medical therapies alone.[196] Current ESC guidelines give a Class I recommendation of surgical thromboembolectomy in high-risk PE patients where thrombolysis (or CDT) is contraindicated or has failed.[10,24] Preoperative thrombolysis increases risk of bleeding, but is not an absolute contraindication.

SUMMARY

While the overall incidence of PE is increasing, the incidence of high-risk PE and mortality from PE is decreasing. This trend suggests that both the recognition of PE generally and the recognition of intermediate-risk and high-risk PE is of paramount importance. Clinicians must remember the protean manifestations of PE and its broad range of presentations. Validated scores for diagnosis and prognosis can guide the clinician. In modern practice, the vast majority of PEs are diagnosed by CTPA. Imaging, in particular TTE, and biomarkers are vital adjuncts to prognosis, but no 1 marker or set of markers is superior, and clinical intuition and individualization are essential.

Respiratory and hemodynamic support, attention to volume status, anticoagulation, and consideration for systemic thrombolysis represent the primary management aims of intermediate-high and high-risk PE. There are growing data on CDT and CDE modalities, while surgical thromboembolectomy may also have a role in the initial treatment approach. Because these technologies and therapeutics cross multi-disciplinary lines, and there is equipoise (or lack of data) in preferring 1 advanced PE therapy over another, PERTs can assist the clinician with decision-making and implementation of a treatment plan.

While this review provides a broad overview of the recognition and treatment of intermediate-risk and high-risk PE, it does not provide important context for the treatment of special populations with PE including patients who are pregnant, have history of heparin-induced thrombocytopenia, have inherited thrombophilias, or have sickle cell disease.

CLINICS CARE POINTS

- PE is a great masquerader, and must be considered as a cause of protean cardiopulmonary symptoms and signs, and by every specialty of medicine.
- PE risk factors from the history and examination can increase the pre-test probability of diagnosing PE. Several validated prediction rules are available to assist the clinician.
- Electrocardiography and echocardiography can show evidence of RV dilatation and dysfunction. Echocardiography can also inform the differential diagnosis, and quantify effects on pulmonary arterial pressures. Biomarkers like troponin and natriuretic peptide provide evidence of RV myocardial necrosis and chamber distention, respectively.
- Risk stratification in PE depends on validated prognostic rules (PESI, sPESI), biomarkers, and echocardiography.

- Therapeutic anticoagulation is the backbone of PE therapy regardless of risk profile.
- The highest risk PE patients require urgent and definitive therapy to support hemodynamics and to clear the pulmonary artery of clots.
- Hemodynamic support for the most severe PE includes VA ECMO, for which there are the most available data; VA ECMO be considered for shock (refractory to parenteral vasoactives), cardiac arrest, and pulmonary collapse.
- Systemic thrombolysis is typically the first treatment considered, though many patients have contraindications, and there is a fear of using this therapy due to intracranial hemorrhage (ICH) risk.
- There are limited randomized and comparative effectiveness data to rigorously choose 1 interventional PE therapy over another. CDE and CDT each have advantages, but there is a possible trend toward first-line use of an embolectomy strategy.
- Intermediate-risk PE patients represent a true contemporary management challenge. Most of these patients will do well, and exposing these patients to the risks of advanced therapies is not justified on a large scale. However, some of these intermediate-risk patients will experience clinical deterioration, and require definitive PE therapy early.
- PERTs are essential in to individualize care and decision-making, by marshaling the combined experience of clinicians with expertise in PE, to help match patient risk to appropriate treatment. PERTs can also help with diagnosis.

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