Circulation

AHA SCIENTIFIC STATEMENT

Interventional Therapies for Acute Pulmonary Embolism: Current Status and Principles for the Development of Novel Evidence

A Scientific Statement From the American Heart Association

ABSTRACT: Pulmonary embolism (PE) represents the third leading cause of cardiovascular mortality. The technological landscape for management of acute intermediate- and high-risk PE is rapidly evolving. Two interventional devices using pharmacomechanical means to recanalize the pulmonary arteries have recently been cleared by the US Food and Drug Administration for marketing, and several others are in various stages of development. The purpose of this document is to clarify the current state of endovascular interventional therapy for acute PE and to provide considerations for evidence development for new devices that will define which patients with PE would derive the greatest net benefit from their use in various clinical settings. First, definitions and limitations of commonly used risk stratification tools for PE are reviewed. An adjudication of risks and benefits of available interventional therapies for PE follows. Next, considerations for optimal future evidence development in this field are presented in the context of the current US regulatory framework. Finally, the document concludes with a discussion of the pros and cons of the rapidly expanding PE response team model of care delivery.

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Pulmonary embolism (PE) represents the third leading cause of cardiovascular mortality.[1] Compared with the top 2 causes, myocardial infarction and stroke, comparatively little research has focused on novel technologies aimed at reducing morbidity and mortality from this disease. Over the past 5 years, this has begun to change as a result of a renewed interest in optimizing acute PE management, particularly among those patients presenting with severe disease. Signs of the shifting landscape for acute PE care can be seen in the rapid promulgation of the PE response team (PERT) concept[2] and the development of novel endovascular technologies to treat acute PE.[3,4]

This document seeks to clarify the current state of endovascular interventional therapy for acute PE and to provide considerations for evidence development for new devices that will define which patients with PE would derive the greatest net benefit from their use in various clinical settings. In this document, we first to define and discuss the limitations of current PE risk stratification that influence when endovascular therapies are used. Next, we review potential benefits and risks of endovascular PE intervention and then provide suggestions for which patient subgroups might benefit from various interventional therapies. Then, we offer considerations for interventional PE therapeutic evidence development (eg, trial designs, end points) and an assessment of the influence of the current US regulatory structure on this process. Finally, we assess the role of the PERT delivery-of-care model on the use of interventional PE therapies.

Key Words: AHA Scientific Statements ■ embolectomy ■ pulmonary embolism ■ thrombolytic therapy

https://www.ahajournals.org/journal/circ

PE RISK STRATIFICATION

PE presentation is heterogeneous, ranging from asymptomatic to sudden death. Therefore, it is important to assess the severity of PE at initial presentation, which is based on its acute hemodynamic effects and short-term prognosis (Table 1).[6–10]

Patients with a low risk of complications have been shown to do well when treated with anticoagulation alone.[11] Current evidence indicates that most patients with right ventricular (RV) dysfunction should also be treated with anticoagulation alone.[12–14] The benefits of active thrombus removal increase with the severity of PE. The harms of thrombolytic-based active thrombus removal strategies, particularly bleeding, increase with patient-specific risk factors for bleeding. The harms associated with catheter-based embolectomy and surgical embolectomy may be driven more by patient comorbidities than bleeding risk. The decision to use active thrombus removal is therefore driven primarily by the severity of the PE and is secondarily influenced by the presence of patient-specific risk factors for bleeding and comorbidities that might raise the risk of catheter-based embolectomy or surgery.

The most commonly used schemes for the classification of PE severity are those previously proposed by the American Heart Association (AHA)[12] and the European Society of Cardiology (ESC).[13] These 2 schemes, which have much in common, divide PE severity into 3 main categories.

- Massive (AHA) or high risk (ESC): Hypotension, defined as a systolic blood pressure <90 mm Hg, a drop of >40 mm Hg for at least 15 minutes (this latter criterion may be difficult to ascertain in some clinical circumstances), or need for vasopressor support, identifies these patients. They account for ≈5% of hospitalized patients with PE and have an average mortality of ≈30% within 1 month.[5,15–17]
- Submassive (AHA) or intermediate risk (ESC): RV strain without hypotension (see above) primarily identifies these patients. RV strain includes RV dysfunction on computed tomography pulmonary angiography or echocardiography (RV/left ventricular [LV] ratio >0.9)[6,7] or RV injury and pressure overload detected by an increase in cardiac biomarkers such as troponins or brain natriuretic hormone. There are differences in the patients that the AHA and ESC include in this risk category. The AHA criterion for submassive PE is RV strain without hypotension.[12] The ESC criteria for intermediate-risk PE are broader and include patients who have a simplified Pulmonary Embolism Severity Index (PESI) score ≥1 (ie, age >80 years; cancer, chronic respiratory disease, or cardiac disease; heart rate >110 bpm; systolic blood pressure <100 mm Hg; or oxygen saturation <90%), regardless of whether there is RV strain.[13] The ESC then subdivides intermediate-risk patients into 2 subgroups according to whether patients have both RV dysfunction and RV injury (intermediate risk–high) or only one or neither of these findings (intermediate risk–low). As a group, patients with submassive or intermediate-risk PE account for 35% to 55% of hospitalized patients with PE.[5,15–17] Data are conflicting on short- to intermediate-term mortality rates in these patients. In prospective randomized trials, patients treated with anticoagulation alone have 2% to 3% mortality rates over follow-up periods of ≈7 to 30 days.[18] Observational cohorts, both prospective and retrospective, have identified higher mortality rates in this population, with the range being 3% to 15% over a period of 7 to 90 days.[8,9,19–22] There are several potential reasons for the discrepancies in these mortality rates. Randomized trials may enroll selected populations, excluding patients with significant concomitant comorbidities and patients at the higher end of the intermediate-risk spectrum. In addition, observational studies, unlike most randomized trials, often include patients who sustain non–PE-related mortality, which may account for up to half of all deaths in these cohorts.[22]
- Low risk (ESC and AHA): These patients do not meet criteria for submassive (AHA) or intermediate-risk (ESC) PE. They account for 40% to 60% of hospitalized patients with PE and have an average mortality of ≈1% within 1 month.[23]

For simplicity, the remainder of this document uses the terms *high risk*, *intermediate risk*, and *low risk* when describing data on risk profiles of patients with PE. The term *intermediate risk* encompasses all patients meeting criteria for this designation by ESC guidelines and thus necessarily includes all patients classified as submassive in prior AHA scientific statements.

Distinctions Between the AHA/ESC and PESI Stratification Schemes

Although the AHA/ESC and the PESI stratification schemes assess risk in patients with acute PE, they assess somewhat different aspects of risk.[12,13,24,25] PESI (and its frequently used simplified version) estimates the risk of death resulting from any cause within 30 days, and its usual clinical application is to help identify patients with low-risk PE who can be treated without admission to the hospital. The AHA and ESC PE risk stratification schemes categorize patients as having a high, intermediate, or low risk of death within 1 month, with an emphasis on death resulting from PE, and their usual clinical application is to help identify higher-risk patients who may benefit from more intensive monitoring and treatment. Therefore, differences in risk stratifi-

Table 1. Current Factors Used for Categorizing PE Severity

Factor	Comment
History*	Age, cancer, heart and lung disease, dyspnea, shock,† mental confusion†
Physical examination*	
Heart rate†	
Elevated jugular venous pressure†	
Sao_2†	
Respiratory rate	
Hypotension†	Sustained hypotension (or need for inotropic/vasopressor support) denotes high-risk PE
Laboratory testing	
NT-BNP†	
Troponin†	Elevation is associated with RV dysfunction and with adverse short-term outcomes[5]
Serum lactate	
Imaging	
RV dilatation†	Can be assessed by CT or by echocardiography; care must be taken to choose the appropriate imaging plane[6,7]
RV dysfunction†	Associated with poor short- and long-term prognoses[8,9]

CT indicates computed tomography; NT-BNP, N-terminal pro-B-type natriuretic peptide; PE, pulmonary embolism; RV, right ventricular; and Sao_2, arterial oxygen saturation.

*History and physical examination findings make up the Pulmonary Embolism Severity Index score.

†Factors associated with PE-related death.

Table 2. Risk Factors for Bleeding With and Contraindications to Use of Thrombolytic Therapy (Both Systemic and Locally Administered)

Major contraindications
Structural intracranial disease
Previous ICH
Ischemic stroke within 3 mo
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
Relative contraindications
Systolic blood pressure >180 mm Hg
Diastolic bleed pressure >110 mm Hg
Recent bleeding (nonintracranial)
Recent surgery
Recent invasive procedure
Ischemic stroke >3 mo previously
Anticoagulated (eg, VKA therapy)
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age >65 y and particularly >75 y
Low body weight (eg, <60 kg)
Female
Black race

ICH indicates intracranial hemorrhage; and VKA, vitamin K antagonist.

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cation are to be expected when the AHA/ESC schemes and PESI are used in the same patients.[5] Studies that have assessed the prognostic value of these stratification schemes or have used them to guide practice have used in-hospital, 1-month, or 3-month time frames for follow-up.[12]

Qualifying Remarks Relating to PE Severity Classifications Schemes

First, PE severity is a continuum, and its separation into risk categories is an artificial construct.[19] Therefore, the risk of dying of PE varies within, as well as between, risk categories. For example, the risk will be higher in patients with high-risk PE who have more severe shock and in patients with intermediate-risk PE who have more severely compromised RV function and cardiac output.[12,13] Second, the risk of dying of PE may be influenced by factors other than those used by the risk models such as severe concomitant comorbidities, presence of deep vein thrombosis, or a history of syncope (see the Limitations of Current Risk Stratification Methods and Future Directions section).[12,13,26,27] Therefore, the risk of dying for an individual patient may not be accurately reflected by the risk category into which the patient falls. Third, the proportion of deaths attributable to PE is higher with shorter (eg, in hospital or 30 days) than with longer follow-up. At the 90-day follow-up, about half of observed deaths among patients hospitalized for PE are the result of causes other than PE.[5,15,16,28] Fourth, within risk categories, the risk of dying of PE may differ enough among patients to warrant different approaches to treatment. Fifth, patients may shift between risk categories over time. For these reasons, we suggest that risk stratification is a valuable aid to decision-making but should not dictate management separately from sound clinical assessment of the patient. Furthermore, treatment decisions will be influenced by a patient's risk of bleeding (Table 2; see the Risks of Interventional PE Therapies section), the extent and location of thrombus, operator expertise, and individual patient preferences.[12–14,29] Specifically, among patients with intermediate-risk PE, there is no set of clinical, physiological, or imaging criteria that, when assessed on a single occasion, can be used to decide whether a patient requires an advanced therapy. In addition, when a catheter-based intervention is selected, it may be appropriate to modify plans for interventional therapy after accessing the pulmonary arteries (PAs),

Table 3. Future Directions of Research for Risk Stratification

Assessment Modality	Current AHA/ESC Focus	Future Directions
Clinical assessment	Systolic blood pressure Syncope Cardiac arrest	Diastolic blood pressure Mean blood pressure Heart rate Oxygen saturation and partial pressure Respiratory rate Objective functional capacity Patient-reported distress Acute cognitive impairment
Biomarker assessment	Troponin Brain natriuretic peptide	Lactate Arterial pH Worsened glomerular filtration rate
Echocardiographic assessment	RV dysfunction	Tricuspid annular plane systolic excursion RV fractional area change RV cardiac performance index RV outflow track acceleration/deceleration times RV outflow track Doppler notching Cardiac stroke volume

AHA/ESC indicates American Heart Association/European Society of Cardiology; and RV, right ventricular.

either because catheter placement was difficult and is expected to increase the risks of complications or because hemodynamic measurements or imaging via PA catheterization reveals unexpected findings.

Limitations of Current Risk Stratification Methods and Future Directions

The shortcomings of current risk stratification schemes have the potential to be corrected by further rigorous study. Table 3 highlights a number of variables that we think have the potential to improve prediction models for death resulting from PE and warrant further study. These include variables associated with clinical, biomarker, and imaging assessments of the patient. Some have already been studied in a limited fashion.[10,25,30,31]

Summary

- Many schemes have been proposed for assessing the severity of PE and stratifying the patient's associated risk of hemodynamic decompensation and mortality.
- The goals of risk stratification schemes are not always the same; some focus on predicting all-cause mortality, whereas other focus on predicting death resulting from PE.
- All currently available risk stratification schemes have important limitations, including that their use for guiding clinical decision-making has not been shown to improve patient outcomes.
- Research dedicated to clarifying the patient-specific risks of decompensation within the population currently called submassive or intermediate risk is needed.

DEFINITION OF INTERVENTIONAL THERAPIES FOR PE

The cornerstone for treatment of PE is anticoagulation. However, adverse outcomes in patients with high-risk and intermediate-risk PE despite anticoagulation have prompted many physicians to consider therapeutic escalation through systemic thrombolysis, catheter-directed therapies, or surgical embolectomy. In patients with evidence of hemodynamic compromise, these techniques may be used in conjunction with invasive hemodynamic support devices such as extracorporeal membranous oxygenation or isolated percutaneous RV support.[32,33]

Percutaneous or catheter-based approaches have garnered interest because of the limitations of both anticoagulation and systemic thrombolysis and the complexity and risk associated with open surgical embolectomy in some patients with PE. However, the evidence supporting the effectiveness and safety of these approaches is much less robust than that examining systemic thrombolysis.[18,34] Broadly speaking, these devices attempt to rapidly decrease thrombus burden via pharmacomechanical means. They can be classified into 2 categories: catheter-directed thrombolysis (CDL) and catheter-based embolectomy. Current use of these therapies is predicated on thrombus burden, hemodynamics, overall patient condition, bleeding risk, and operator/institutional preferences and experience. In some instances, embolectomy may be performed concurrently or in series with CDL. Data on these techniques are limited. Tables 4 and 5 summarize technical characteristics of these devices as well as the most important studies assessing their use.

Catheter-Directed Thrombolysis

This refers to the administration of pharmacological thrombolysis via catheter-directed injection of a thrombolytic drug directly into the PA circulation (as opposed to via peripheral intravenous administration). The goals of CDL are to achieve similar or improved effectiveness compared with systemic thrombolysis and to decrease the rate of major and intracranial bleeding by delivering a significantly lower total dose of thrombolytic drug directly into the thrombus through a multi-sidehole infusion catheter. Most publications of CDL have reported a thrombolytic dose of approximately one-fourth that usually given systemically (for instance, 20–24 mg alteplase),[4,35] although the optimal dosing strategy is being actively investigated.[36] In addition, CDL aims to

Table 4. Characteristics of Interventional Pulmonary Embolism Devices

Device	Mechanism	Technical Considerations	Regulatory Status in United States
EKOSonic	USAT	5F catheter	510(k) Clearance for infusion for treatment of PE
Unifuse	CDL	4F–5F catheter	510(k) Clearance for treatment of peripheral vasculature
Cragg-McNamara	CDL	4F–5F catheter	510(k) Clearance for treatment of peripheral vasculature
Bashir Endovascular Catheter	Pharmacomechanical CDL	7F catheter with a nitinol-supported infusion basket that is expanded within the thrombus	510(k) Clearance for use in peripheral vasculature
AngioVac	Veno-veno bypass; funnel-shaped inflow tip to engage thrombi	26F access for inflow, 16F–20F access for outflow; requires perfusion team	510(k) Clearance for removal of undesirable intravascular material
FlowTreiver	Mechanical clot engagement with aspiration with adjunctive nitinol disks engage and mechanically retrieve clot	20F catheter; must manage blood loss associated with large-bore aspiration	510(k) Clearance for treatment of PE
Indigo System	Mechanical clot engagement with mechanized aspiration	8F catheter; large size of some proximal PE renders en bloc aspiration difficult with 8F device	510(k) Clearance for peripheral artery and venous systems
AngioJet	Rheolytic thrombectomy with option of thrombolytic vs saline spray	6F–8F catheters for venous thrombus; can cause hypotension and bradycardia	510(k) Clearance for peripheral thrombectomy; black-box warning against use in PAs
Aspire Max	Suction thrombectomy with specially designed handheld aspirator	5F–6F catheters	510(k) Clearance for removal of fresh, soft thrombi, and emboli from the peripheral and coronary vasculature

CDL indicates catheter-directed thrombolysis; PA, pulmonary artery; PE, pulmonary embolism; and USAT, ultrasound-assisted thrombolysis.

overcome a theoretical limitation of peripherally infused systemic thrombolysis in which blood may be shunted toward unobstructed PA segments rather than those with thrombus.[37] Two commonly used CDL catheters are Uni-Fuse (AngioDynamics Inc, Latham, NY) and Cragg-McNamara (ev3 Inc, Plymouth, MN) catheters. Both carry an indication from the US Food and Drug Administration (FDA) for infusion of thrombolytics into the peripheral vasculature without a specific indication for PE. Operators typically use 4F to 5F catheters with an infusion length of 5 to 10 cm, depending on thrombus burden.

An alternative to these simple infusion catheters is ultrasound-assisted thrombolysis (USAT) with the EKOSonic endovascular system (EKOS Corp, Bothell, WA), a specialized catheter with 2 lumens (Figure 1). One lumen houses a filament with multiple ultrasound transducers that emit high-frequency, low-energy ultrasound, whereas the other allows local thrombolytic delivery through multiple ports along its length. Low-energy ultrasound is claimed to facilitate the dissociation of fibrin strands, theoretically allowing more effective thrombolysis at lower doses by opening the thrombus ultrastructure to thrombolytic binding.[38] As with simple CDL catheters, these catheters may be placed in 1 or both PAs. This platform allows a gradual targeted infusion of thrombolytic typically over 12 hours, although more recent data suggest that as little as 2 to 4 hours may have comparable effectiveness.[36] The biggest theoretical advantage of USAT over standard CDL is more effective penetration of the thrombolytic agent over a shorter duration of time. There are no completed randomized comparison trials between standard CDL and USAT in the pulmonary circulation. A randomized trial of these 2 modalities in the iliofemoral venous circulation did not show differences in early venographic or 1-year disease-specific quality-of-life (QOL) measures.[39]

Although CDL, whether standard or USAT, offers theoretical benefits in patients with PE, there are important limitations. First, the risk of hemorrhagic complications inherent to thrombolytic administration is not obviated with the use of these modalities (see the Risks of Interventional PE Therapies section). Most important, although there is a fair amount of enthusiasm for CDL, the evidence base in support of its use is limited.[40]

CDL may be used in conjunction with mechanical thrombus fragmentation, aspiration, or maceration to further promote thrombus disaggregation by exposing a greater surface area of thrombus to endogenous or locally infused fibrinolytics. Complete thrombus removal is not the goal of these percutaneous methods; instead, downstaging from high-risk to intermediate-risk PE suffices. In intermediate-risk PE, mechanical debulking is unproven and is potentially risky because thrombus fragmentation may lead to distal embolization, resulting in an immediate increase in PA resistance and RV

Table 5. Summary of Key Studies

Trial	n	Randomized Treatment	Comparator	Major Bleeding Criteria	Follow-Up, d	Low-Risk PE, n (%)	Intermediate-Risk PE, n (%)	High-Risk PE, n (%)	Mean Age (Range or SD), y	Male, n (%)	Efficacy	Safety
ULTIMA,[20] 2013	59	tPA-USAT (20 mg)	Heparin	ICH, spinal, joint, retroperitoneal, pericardial, hemoglobin drop >2 g/dL with transfusion	90	0 (0)	59 (100)	0 (0)	63.01 (13.51)	28 (47.46)	RV/LV ratio reduced from 1.28±0.19 to 0.99±0.17 at 24 h (P<0.001)	1 Death, 0 major bleeds, 3 minor bleeds, 0 recurrent VTE
SEATTLE II,[54] 2015	150	tPA-USAT (24 mg)	Single arm	ICH, hemodynamic compromise, need for intervention	30	0 (0)	119 (79)	31 (21)	59 (16.1)	73 (48.7)	RV/LV ratio reduced from 1.55 to 1.13 at 48 h (P<0.0001), PASP 51.4 reduced to 36.9 mm Hg (P<0.0001) at 48 h	1 GUSTO major bleed, 16 GUSTO moderate bleed, 0 ICH/death
PERFECT,[56] 2015	101	tPA or urokinase, CDL (variable dosing; mean, 28 mg tPA)	Single arm	ICH, fatal bleed	30	0 (0)	73 (72)	28 (28)	60.3 (14.9)	53 (52.5)	PASP 51.17±14.06 to 37.23±15.81 mm Hg (P<0.0001)	0 Major procedure-related complications, major hemorrhages, or hemorrhagic strokes
OPTALYSE PE,[36] 2018	101	tPA-USAT (8–24 mg)	Compared 4 tPA protocols	Fatal, ICH, bleeding in critical organ, drop of 2 g hemoglobin or need for 2 U RBC treatment	3	0 (0)	101 (100)	0 (0)	60.0 (29–77)	53 (52.5)	RV/LV ratio reduced in all arms	4 Major bleeding, 1 recurrent PE, and 1 death at 30 d; 1 additional death at 1 y
FLARE,[3] 2018	106	FlowTriever	Single arm	VARC-2 definition	30	0 (0)	104 (100)	0 (0)	55.6 (13.6)	58 (54.7)	RV/LV ratio 1.53 to 1.15 in 48 h	1 Hemoptysis, 1 clinical deterioration, 1 cardiogenic shock, 1 ventricular fibrillation, 1 death
PEITHO,[46] 2014	1006	Tenecteplase, systemic (30–50 mg)	Heparin/LMWH/fondaparinux	ICH, life-threatening, fatal, need for transfusion	30	0 (0)	1005 (100)	0 (0)	66.15 (15.29)	473 (47.06)	Death/decompensation at 7 d: 2.6% tenecteplase vs 5.6% placebo (odds ratio, 0.44; 95% CI, 0.23–0.87; P=0.02)	Tenecteplase arm: 2% ICH, 6.3% extracranial bleeding

CDL indicates catheter-directed thrombolysis; FLARE, FlowTriever Pulmonary Embolectomy; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; OPTALYSE-PE, A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; PEITHO, Pulmonary Embolism International Thrombolysis Trial; PERFECT, Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis; RBC, red blood cell; RV/LV, right ventricular/left ventricular; SEATTLE II, A Prospective, Single-Arm, Multi-Center Trial of EkoSonic® Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (PE) II; tPA, tissue plasminogen activator; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism; USAT, ultrasound-assisted thrombolysis; VARC-2, Valve Academic Research Consortium; and VTE, venous thromboembolism.

afterload.[41,42] Notably, the advent of devices specifically designed for PE thrombus removal (addressed later in the current document) is intended to make these cruder debulking techniques obsolete.

Catheter-Based Embolectomy

Several techniques and catheters have been used for this purpose.[43] Only the more promising or commonly used techniques are discussed here. Although a preprocedural computed tomography angiogram is often the only guidance needed for placement of CDL catheters, selective pulmonary angiograms are typically used in embolectomy cases to carefully assess the location of thrombi, potential targets for treatment, choice of thrombectomy device, and best projection during angiography to optimize catheter navigation.

Catheter-Based Thrombus Maceration

Thrombus maceration may be performed with a modified pigtail catheter with a guide wire or, more commonly, with peripheral balloons, which are typically sized smaller than the true arterial lumen diameter. These techniques may be helpful in hypotensive pa-

Figure 1. EKOSonic ultrasound-assisted thrombolysis system.
Used with permission of EKOS Corporation, Bothell, WA.

tients with totally occluded proximal PA branches, in which maceration can establish some forward flow and partially decompress the RV until further treatment, for example, local thrombolysis, takes effect. However, distal embolization may inadvertently result in patient deterioration. Published evidence on these techniques is limited to case reports and series. The development of specific pulmonary embolectomy tools aims to make this technique obsolete.

Rheolytic Thrombectomy

Rheolytic thrombectomy with the AngioJet catheter (Boston Scientific, Marlborough, MA) has been used for PE thrombus removal with variable success. Technically, its use in the PA is similar to its use in the deep veins. High-speed saline jets travel backward from the tip of the catheter, creating vacuum and thrombus fragmentation effects. The catheter can also be used for intraprocedural pulse delivery of a low-dose thrombolytic agent (eg, alteplase 10–20 mg, reteplase 2.5–5 U, or tenecteplase 5–10 mg). Because of safety concerns, the AngioJet device should not be used as the initial treatment in patients with acute PE (see the Risks of Interventional PE Therapies section).

Large- and Small-Bore Embolectomy

Mechanical thrombectomy refers to actual extraction of thrombus from the pulmonary vasculature. Manual aspiration thrombectomy, a form of mechanical thrombectomy, can be performed by means of a large sheath or a straight guide catheter advanced directly into the thrombus or by way of specialized catheters that are designed to facilitate greater vacuum effects (eg, Pronto XL 14F Extraction Catheter, Vascular Solutions, Minneapolis, MN). It is often challenging to remove a significant amount of thrombus with manual aspiration alone because thrombi are frequently large and partially organized, making them hard to aspirate into a comparably small catheter/sheath. The Aspirex catheter (Straub Medical AG, Wangs, Switzerland) is an 11F device that aspirates thrombus through a flexible catheter tip. The catheter shaft contains a high-speed rotating coil that creates negative pressure for aspiration and serves to macerate thrombus that is brought into the catheter. There are limited data on the effectiveness and safety of this device, and it is not under current investigation for PE in the United States.[44] The FlowTriever system (Inari Medical, Irvine, CA) is a large-bore device that mechanically engages thrombus in the PAs through deployment of 3 self-expanding nitinol disks (Figure 2). The disks are retracted back into the catheter with entrapped thrombus while the large-bore guiding catheter is aspirated. In current practice, the device is often used as a simple large-bore suction catheter without the use of the associated nitinol disks. In either case, the device is designed to remove thrombus without the use of adjunctive thrombolytics. Results of the single-arm FLARE study (FlowTriever Pulmonary Embolectomy) were reported recently (Table 5).[3] The Indigo Thrombectomy System (Penumbra, Inc, Alameda, CA) is a smaller-bore aspiration catheter designed to engage thrombus and extract it with a continuous vacuum pump. Data on effectiveness are limited to retrospective case series, although a prospective single-arm study is ongoing (EXTRACT-PE [Evaluating the Safety and Efficacy of the Indigo® Aspiration System in Acute Pulmonary Embolism]; URL: ClinicalTrials.gov. Unique identifier: NCT03218566). The Aspire Max mechanical thrombectomy system (Control Medical Technology, Salt Lake City, UT) also aims to increase suction force through 5F to 6F catheters via a uniquely designed handheld aspirator. Although cleared by the FDA for removal of fresh, soft thrombi and emboli from the peripheral and coronary vasculature, the device has not been specifically evaluated in patients with PE. The AngioVac cannula (AngioDynamics, Inc) is a veno-veno bypass system designed to remove intravascular material via the application of suction. The veno-veno bypass circuit is initiated with a filter between the inflow (blood going from the patient to the extracorporeal pump) and outflow (blood going from the extracorporeal pump back to the patient) cannulas to trap unwanted intravascular

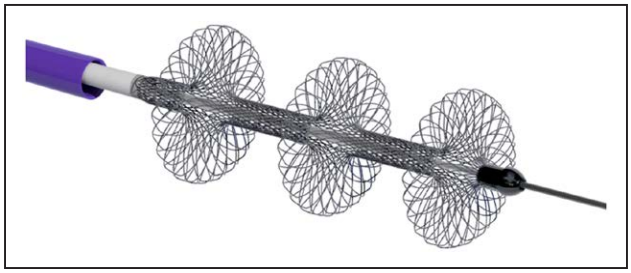

Figure 2. Flowtriever catheter-based embolectomy device.
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material. The inflow cannula is a 22F suction catheter, accessed via femoral or internal jugular veins, featuring a funnel tip to engage intravascular material, including thrombi. The outflow cannula (16F–20F, at the operator's discretion) returns blood to the body via a separate femoral or internal jugular vein. An oxygenator can be added to the circuit if needed. Data on effectiveness are limited, particularly in the pulmonary circulation.[45] Table 4 summarizes technical information on all interventional PE therapies.

Summary

- Current interventional therapies for acute PE include devices that facilitate CDL or catheter-based embolectomy.
- Two interventional devices, the EKOSonic endovascular system and the FlowTriever embolectomy device, have been cleared by the FDA for use in acute PE, with other devices pursuing clearance.

RATIONALE FOR INTERVENTIONAL THERAPIES FOR ACUTE PE

The rationale for interventional therapies for reperfusion in patients with PE depends on the severity of the presentation. In acute high-risk PE, the primary goal is to reduce acute PE–related mortality by rapidly reversing hemodynamic compromise and gas exchange abnormalities. In contrast, intermediate-risk PE is characterized by preserved hemodynamic status with evidence of RV dysfunction on imaging or cardiac biomarker determination. In these patients, the primary aims of advanced therapies are to avert possible hemodynamic collapse and death resulting from progressive right-sided heart failure and to expedite symptom resolution. Although these represent the rationale for device use, to date, no prospective study has demonstrated a mortality benefit associated with the use of any interventional therapy in any population of patients with PE.

Other potential but unproven benefits include prevention of recurrent PE by reducing thrombotic burden in the lower extremities via a systemic fibrinolytic effect and prevention of chronic thromboembolic pulmonary hypertension (CTEPH) and preservation of the normal hemodynamic response to exercise over the long term.

Prospective Studies of Systemic Thrombolysis

Much of the evidence supporting the use of interventional therapies for PE is extrapolated from clinical trials and meta-analyses of studies of systemic thrombolysis. The Europe-based PEITHO (Pulmonary Embolism International Thrombolysis Trial) is the largest randomized controlled trial of systemic thrombolysis in intermediate-risk PE, enrolling 1006 patients.[46] The study evaluated the impact of systemic thrombolysis with tenecteplase versus anticoagulation alone on all-cause mortality or hemodynamic collapse within 7 days of randomization. Thrombolysis decreased the frequency of the primary outcome (2.6% versus 5.6%; P=0.015), with the majority of the benefit driven by a lower incidence of hemodynamic collapse among patients treated with tenecteplase (1.6% versus 5.0%; P=0.002). However, the benefit of thrombolysis was incurred at the cost of increased major bleeding (6.3% versus 1.5%; P<0.001). Two percent of the tenecteplase-treated patients had intracranial hemorrhage (ICH) compared with 0.2% in the anticoagulation alone group. In addition, there was no impact on overall mortality at 7 days (2.4% in the tenecteplase group versus 3.2% in the placebo group; P=0.42). Long-term follow-up of the PEITHO trial among a selected subgroup of patients with information available (n=709) demonstrated no difference in 3-year mortality (20.3% versus 18.0%; P=0.43) or persistent symptoms or functional limitation (36.0% versus 30.1%; P=0.23), although no formal assessments of functional capacity or QOL were performed.[47] The frequency of CTEPH did not differ significantly among a more selected group of patients (n=290) with echocardiographic data available over variable follow-up time (2.1% versus 3.2%; P=0.79).

Meta-analyses of trials of systemic thrombolysis for acute PE have demonstrated both benefits and critical limitations of the therapy.[18,48] Chatterjee and colleagues[18] compared 1061 patients treated with thrombolytic therapy with 1054 patients treated with anticoagulation alone. Thrombolytic therapy was associated with a decrease in all-cause mortality (2.2% versus 3.9%; adjusted odds ratio [OR], 0.53 [95% CI, 0.32–0.88]; number needed to treat=59) and recurrent PE (1.2% versus 3.0%; adjusted OR, 0.40 [95% CI, 0.22–0.74]) compared with anticoagulation alone. The associated reduction in all-cause mortality with thrombolytic therapy was observed even when additional analysis was restricted to trials of patients with intermediate-risk PE (adjusted OR, 0.48 [95% CI, 0.25–0.92]. Similar to the findings of PEITHO, the benefit of systemic thrombolysis was offset by an increase in ICH (1.5% versus 0.2%; adjusted OR, 4.78 [95% CI, 1.78–12.04]). Another meta-analysis by Marti and colleagues[48] confirmed the finding of a reduction in all-cause mortality with thrombolytic therapy for acute PE (adjusted OR, 0.59 [95% CI, 0.36–0.96]). Similarly, increased major bleeding (adjusted OR, 2.91 [95% CI, 1.95–4.36]) and fatal hemorrhage or ICH (adjusted OR, 3.18 [95% CI, 1.25–8.11]) limited the benefit of thrombolysis. Persistent concern over the risk of ICH, which approaches

2% in clinical trials[46] and 3% to 5% outside of clinical trials,[15,49] has diminished enthusiasm for full-dose systemic thrombolysis and has driven the development of alternative systemic thrombolytic strategies with potentially lower bleeding risk.

One alternative strategy has focused on alteplase 50 mg IV over 2 hours compared with the FDA-approved regimen of 100 mg IV over 2 hours. This strategy has been investigated in 2 modest-sized randomized trials comparing its safety and effectiveness with anticoagulation alone (n=121) and full-dose thrombolysis (n=118), respectively.[50,51] Although neither study provides definitive evidence of the purported improved safety profile with this strategy, both studies demonstrated significant improvements in surrogate end points of RV performance. Most important, the studies demonstrated that the optimal dosing strategy for peripheral administration of thrombolysis remains unknown.

Summary

- Systemic thrombolysis has been studied against anticoagulation in several randomized trials, including studies focused on intermediate-risk patients.
- The risks and benefits of systemic thrombolysis are closely counterbalanced in the intermediate-risk PE population.
- The optimal dose and duration of systemic thrombolysis are unknown.

Interventional Therapies for PE: Theoretical Benefits

Interventional therapies for PE that use local thrombolysis offer the potential advantages of increased effectiveness of thrombus dissolution and the possibility of an enhanced safety profile with respect to systemic bleeding. Those that use mechanical thrombectomy offer direct and immediate mechanical relief of pulmonary obstruction without the need for thrombolytics. The data for catheter-based intervention for PE are restricted to small randomized controlled trials and single-arm prospective studies focused on the short-term surrogate end points of improvement in RV function, reduction in PA systolic pressure, and decreased angiographic thrombotic burden. To date, USAT is the most extensively studied of these techniques. The remainder of this section assesses the potential benefits of CDL and catheter-based embolectomy for the following outcomes: improving short-term surrogate outcomes, preventing recurrent PE, expediting symptom and return of functional status, and preventing CTEPH.

Improving Short-Term Surrogate Outcomes

Randomized trials of systemic thrombolysis carried out in intermediate-risk PE populations have demonstrated 3% to 4% rates of death over the short term (7–30 days) among patients treated with anticoagulation alone.[18] To date, no trials have been carried out that have had the power to assess potential benefits in short-term mortality or hemodynamic decompensation with the use of CDL or catheter-based embolectomy devices.

Given the difficulty with powering trials for these clinically important outcomes, the majority of trials of catheter-based interventional therapies have focused on surrogate markers. Most notably, prior observational studies have demonstrated that a computed tomography– or ultrasound-measured ratio of RV diameter to LV diameter >0.9 is independently associated with mortality at 30 days.[52–55] Hence, improvement in the RV/LV ratio has become an outcome of choice for assessing the effectiveness of interventional PE therapies.

In a randomized controlled trial of 59 patients with intermediate-risk PE and an RV/LV ratio >1.0 on transthoracic echocardiography (ULTIMA [Ultrasound Accelerated Thrombolysis of Pulmonary Embolism]), USAT (alteplase 20 mg total) plus anticoagulation reduced the RV/LV ratio from baseline to 24 hours to a greater extent than anticoagulation alone.[4] At 90 days, this difference was no longer significant. In a single-arm multicenter trial of 150 patients with acute high-risk (n=31) or intermediate-risk (n=119) PE undergoing USAT (SEATTLE II [A Prospective, Single-Arm, Multi-Center Trial of EKOSonic® Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (PE)]), the mean RV/LV ratio improved by 25% from before to 48 hours after the procedure (1.55 versus 1.13; mean difference, −0.42; $P<0.0001$).[35] A subsequent trial, OPTALYSE-PE (A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism), demonstrated a comparable reduction in the RV/LV ratio among patients with intermediate-risk PE randomized to 4 different infusion regimens of ultrasound-facilitated, catheter-directed fibrinolysis (8 mg/2 h, 8 mg/4 h, 12 mg/6 h, 24 mg/6 h).[36] A prospective, multicenter, single-arm study (FLARE) evaluated the FlowTriever System in 106 patients with acute PE.[3] Patients with proximal PE and RV/ ratio ≥0.9 were eligible for enrollment. The RV/LV ratio was reduced by 0.39 from baseline to 48 hours after the start of the procedure. The Penumbra device is a suction aspiration system initially developed for endovascular treatment of embolic stroke that is being actively studied in patients with PE and an RV/LV ratio >0.9 (EXTRACT-PE). Table 5 reviews key elements of completed studies.[3,4,36,46,54,56]

Summary

- Trials to date evaluating catheter-based approaches for treatment of acute PE have focused on the evaluation of imaging surrogates for improved short-term outcomes.

- CDL more rapidly reverses RV dysfunction in patients with acute PE than anticoagulation alone. The comparative effectiveness of CDL versus systemic thrombolysis for this end point is unknown.
- Limited available data on catheter-based embolectomy devices also demonstrate immediate improvements in RV dysfunction. The comparative effectiveness of these approaches versus any thrombolysis-based approach for this end point is unknown.
- Currently, no data support a short-term mortality benefit with catheter-based approaches for the treatment of PE.

Preventing Recurrent PE

The PEITHO trial was likely underpowered to detect a difference in recurrent PE between systemic fibrinolysis with tenecteplase and anticoagulation alone (0.2% versus 1%; *P*=0.12).[46] However, in a meta-analysis of systemic thrombolytic therapy for acute PE, thrombolysis was associated with a 60% reduction in recurrent PE compared with anticoagulation alone (OR, 0.4 [95% CI, 0.22–0.74]).[18] Lack of statistical power and single-arm trial design have limited the ability of trials to detect a difference in recurrent PE between CDL and anticoagulation alone.

Summary

- Currently, no data support a benefit in prevention of recurrent PE with catheter-based approaches.
- It is unclear whether CDL carries a similar magnitude of benefit for recurrent PE prevention as has been suggested by prior studies of systemic thrombolysis.
- Recurrent PE has not been an adequately evaluated end point in any published study of catheter-based embolectomy.

Expediting Symptom Resolution and Return of Functional Status

A subset of patients with PE will develop persistent symptoms, including chest pain and dyspnea, functional limitation, and exercise intolerance, which some have called the post-PE syndrome.[57] Several observational analyses and subanalyses of randomized trials have demonstrated elevated PA pressures (PAPs) among patients with PE treated with anticoagulation at 6 to 28 months of follow-up.[58,59] In a prospective observational study of 254 patients with PE, 29% had residual perfusion defects on a lung scan after a median of 12 months. Compared with those without perfusion defects, these patients were more often dyspneic (60% versus 36%; *P*=0.004) and had a shorter 6-minute walk distance (374 m versus 427 m; *P*=0.004). In a meta-analysis of long-term complications after PE, after a mean of 18 months, 33% of patients manifested New York Heart Association class II or greater dyspnea symptoms, and patients had a mean 6-minute walk distance of 415 m (95% CI, 372–458), which is at the fourth percentile compared with age- and sex-matched norms.[60] The relative contribution of deconditioning versus the role of persistent physiological abnormalities of the lungs and RV in explaining these findings remains an active area of investigation.[61,62]

Although reperfusion therapies in patients with PE may be hypothesized to be associated with expedited symptom resolution, existing data supporting the superiority of reperfusion over anticoagulation alone for restoring exercise capacity and QOL to pre-PE levels are mixed. In a study by Sharma et al,[63] subjects with acute PE (n=40) treated with systemic thrombolysis had higher pulmonary capillary blood volume (45 mm/m^2 versus 30 mm/m^2; *P*<0.001) and diffusion capacity (93% versus 72% predicted; *P*<0.001) after 1 year compared with those treated with anticoagulation alone. In the same study, after 7.4 years, subjects who received anticoagulation alone had higher PAPs and pulmonary vascular resistance both at rest and during exercise compared with those treated with systemic thrombolysis (PAP at rest: 22 mm Hg versus 17 mm Hg, *P*<0.02; PAP during exercise: 32 mm Hg versus 19 mm Hg, *P*<0.01; pulmonary vascular resistance: rest→exercise: 351→437 dynes·s^{-1}·cm^{-5} [*P*<0.01] versus 171→179 dynes·s^{-1}·cm^{-5} [*P*=NS]).[64] Three modest-sized randomized trials have demonstrated that RV dysfunction was less common at 3 to 6 months in patients treated with thrombolysis than in those treated with anticoagulation alone.[4,65,66] In contrast, the PEITHO long-term follow-up study did not find a difference in resting echocardiography between a select group of patients treated with systemic thrombolysis and those treated with placebo.[47] In addition, in long-term follow-up from PEITHO, systemic thrombolytic therapy did not result in reduced dyspnea or functional limitation (36% versus 30.1%; *P*=0.23).[47] In a systematic review of 26 studies including 3651 patients receiving at least 3 months of follow-up, those undergoing systemic thrombolytic therapy had no statistically significant difference in the risk of at least moderate functional impairment compared with those treated with anticoagulation alone (OR, 0.48 [95% CI, 0.15–1.49]; *P*=0.2).[60] No clinical trial data are available yet to suggest that CDL or catheter-based embolectomy has greater effectiveness than systemic thrombolytic therapy or anticoagulation alone in reducing long-term symptom burden or functional limitation.

Summary

- Observational data indicate that a substantial proportion of patients with PE develop persistent symptoms that include dyspnea on exertion and functional limitation after an incident PE. Similarly, a minority of patients demonstrate persistent clinical signs of their incident PE months to years after

diagnosis, including persistent lung perfusion defects and abnormal echocardiographic findings without frank pulmonary hypertension.
- It is uncertain whether systemic thrombolysis or interventional approaches to acute PE are associated with a decreased incidence of the post-PE syndrome.
- The relative contributions of deconditioning versus the role of persistent physiologic abnormalities of the lungs and RV in explaining the post-PE syndrome requires further research.

Preventing CTEPH

CTEPH, classified as World Health Organization group 4 pulmonary hypertension, is characterized by persistent macrovascular obstruction, pulmonary vasoconstriction, and a secondary small-vessel arteriopathy eventually resulting in right-sided heart failure.[67] The incidence of CTEPH after an acute PE at 2 years has been identified as 2% to 5% in various observational cohorts.[56,68] Although smaller studies suggested that systemic thrombolysis could reduce the risk of CTEPH,[50,59] 3-year follow-up data of a highly selected subset of patients from PEITHO demonstrated similar rates of CTEPH (2.1% versus 3.2%; *P*=0.79) in patients undergoing systemic thrombolysis compared with those receiving anticoagulation alone.[47]

Studies of CDL have demonstrated short-term reductions in PA systolic pressures with intervention.[4,35,69] In the ULTIMA trial, USAT resulted in a greater short-term reduction in the RV/right atrial pressure gradient (a surrogate for PA systolic pressure) than anticoagulation alone.[4] However, there was no difference in the RV/right atrial pressure gradient at 90 days between the 2 groups.

On the basis of these observations, there is inadequate evidence to suggest that systemic thrombolysis and interventional therapies reduce the risk of CTEPH in patients with acute PE compared with anticoagulant therapy alone.[58,59,61,62,70–72]

Summary

- It is unknown whether CDL or catheter-based embolectomy reduces the incidence of CTEPH in any population of patients presenting with acute PE.

RISKS OF INTERVENTIONAL PE THERAPIES

Clinicians must weigh the risk of potential harm of performing invasive PE therapies against the risk of omitting a potentially beneficial procedure. The greatest challenge in balancing these risks is a dearth of rigorously designed and adequately powered studies examining therapeutic safety. The current literature reporting interventional therapies largely comprises small, single-arm trials with significant heterogeneity in patient presentation characteristics, techniques of procedural performance, and reporting of outcomes. Hence, categorization of adverse events associated with interventional PE therapies must account for both known and predicted complications of invasive catheter-based therapies.

This section aims to describe specific risks associated with performing catheter-based interventions in the patient with acute intermediate- or high-risk PE. More general complications associated with catheter-based intervention, including access-related vascular complications, infection, and acute kidney injury, are not specifically addressed but also need to be considered when individual clinical decisions are made.

This section evaluates interventional PE therapies by examining the published literature and the FDA Manufacturer and User Facility Device Experience (MAUDE) database. MAUDE is a searchable online database of medical device reports received by the FDA. Medical device reports are submitted by both mandatory (manufacturers) and voluntary (physicians) reporters. These medical device reports serve as a passive surveillance tool to monitor device performance and to detect adverse events associated with device use. The information submitted by reporters has limitations, including the possibility of inaccurate or incomplete data. In addition, most reports are not verified through objective, independent assessment mechanisms. The prevalence and incidence of adverse events cannot be determined through the MAUDE database because events may be underreported and the total number of devices used in US practice is not known.

The following categories of adverse events as they relate to CDL and catheter-based embolectomy are summarized in the next sections: acute respiratory collapse, acute hemodynamic decompensation, pulmonary hemorrhage, ICH, and nonintracranial major bleeding.

Catheter-Directed Thrombolysis

With CDL, risks of hemodynamic decompensation triggered by rapid changes in RV afterload with passage of intrapulmonary wires and catheters exist, but the dearth of reported complications likely is a result of the small-bore nature of infusion catheters and the relative simplicity of wire and catheter navigation for placement. Additional theoretical causes of hemodynamic decompensation with isolated CDL include cardiac perforation and resultant tamponade or prolonged ventricular arrhythmias with catheter advancement through the RV. Both of these issues are not, to the best of our knowledge, reported in the literature. We found 3 total cases of hemodynamic compensation associated with CDL reported in the MAUDE database. Overall, this is a quite rare complication given the relatively atraumatic nature

of wires and catheters used for PA catheter placement. However, the most hemodynamically tenuous patients are probably at highest risk for it given their absence of hemodynamic reserve.

Acute respiratory collapse can theoretically be precipitated by sudden changes in ventilation/perfusion caused by disruption/distal embolization of thrombi with wires or catheters. It can also be caused by pulmonary hemorrhage resulting from PA rupture associated with the placement of CDL devices. One instance of pulmonary hemorrhage has been reported in the literature with USAT,[73] as well as 4 instances reported in the FDA MAUDE database (Table 6).[74] The largest retrospective study of pulmonary hemorrhage associated with PA catheter placement for hemodynamic monitoring (n=32 422) identified an incidence of 0.03%.[75] Although not widely reported in the literature, several aspects of the CDL procedure may predispose rare patients to experience this complication. These include the possibility of perforation of friable, smaller PAs with the wire used for catheter placement, the presence of pulmonary infarction in a subset of patients, and the use of thrombolytic therapy after placement.

The most commonly reported complications with isolated CDL involve bleeding. CDL aims to mitigate these risks through local drug delivery with lower total doses than systemic thrombolysis. There have been 566 patients treated in prospective studies of isolated CDL that have reported results over the past 5 years.[4,35,36,69,76,77] Before this era, there was a dearth of prospective studies of CDL, and when reported, thrombolytic dose and duration and outcome reporting were highly variable. Overall doses of CDL administered in the 6 recent prospective studies ranged from ≈8 to 25 mg alteplase, with the majority of studied patients receiving 20 to 24 mg of the drug. Among the 566 patients treated in these studies, in-hospital nonintracranial major bleeding occurred in 33 patients (5.8%). The definition of major bleeding in these studies was variable but largely included drops in hemoglobin of >2 g/dL, the need for transfusion, or the need for medical or procedural intervention. ICH occurred in 5 patients (0.9%) treated in these studies. In the MAUDE database, 1 patient has been reported to sustain fatal nonintracranial major bleeding in conjunction with the use of USAT, and 1 instance of ICH has been reported with CDL in MAUDE.

Figures 3 and 4 depict observational meta-analyses that demonstrate weighted point estimates and CIs for nonintracranial major bleeding and ICH among patients treated with isolated CDL. The weighted aggregate rate of nonintracranial major bleeding in these studies is 4.5% (95% CI, 1.1–7.4) with an ICH rate of 0.7% (95% CI, 0.0–1.3). In a meta-analysis of 15 prospective randomized controlled trials conducted between 1970 and 2014 of various systemic thrombolytic regimens (n=1061), nonintracranial major bleeding occurred in 9.2% of patients, and ICH occurred in 1.5% of patients.[18] Therefore, indirect comparisons suggest that CDL may be associated with about half the risk of nonintracranial and intracranial bleeding compared with systemic thrombolysis. However, no prospective comparative study of systemic versus catheter-directed thrombolytic approaches has been performed. Given the low numbers of patients with CDL analyzed prospectively thus far, the heterogeneity of study patients treated with systemic thrombolysis versus CDL, and observed rates and CIs of non-ICH major bleeding and ICH, it remains unclear whether this mode of therapy poses lower risks of major bleeding or ICH than systemic thrombolysis.

Summary

- Isolated CDL has not been associated with intraprocedural acute hemodynamic or respiratory decompensation in the published literature, although rare instances of these complications have been reported in the FDA MAUDE database.
- Pulmonary hemorrhage represents a rare, but important, intraprocedural complication associated with isolated CDL.
- ICH and non-ICH major bleeding are important complications of CDL. Although indirect evidence supports lower rates of these complications with CDL than systemic thrombolysis, currently available data do not allow clear delineation of the expected rates of these complications and whether they truly have a lower expected frequency than that associated with systemic thrombolysis.

Catheter-Based Embolectomy

As opposed to the passive thrombolytic infusion associated with CDL, thrombectomy devices seek to ac-

Table 6. FDA MAUDE-Reported Adverse Events of Interventional PE Therapies

	Events, n	Death, n	Hemodynamic Decompensation, n	Respiratory Decompensation, n	Pulmonary Hemorrhage, n	ICH, n	Major Bleeding, n
USAT	271	12	3	3	4	1	2
FlowTriever	11	5	6	1	4	0	1
Angiovac	52	22	36	15	0	1	3

FDA indicates US Food and Drug Administration; ICH, intracranial hemorrhage; MAUDE, Manufacturer and User Facility Device Experience; PE, pulmonary embolism; and USAT, ultrasound-assisted thrombolysis.

Source: US Food and Drug Administration MAUDE: Manufacturer and User Facility Device Experience.[74] Accessed February 26, 2019.

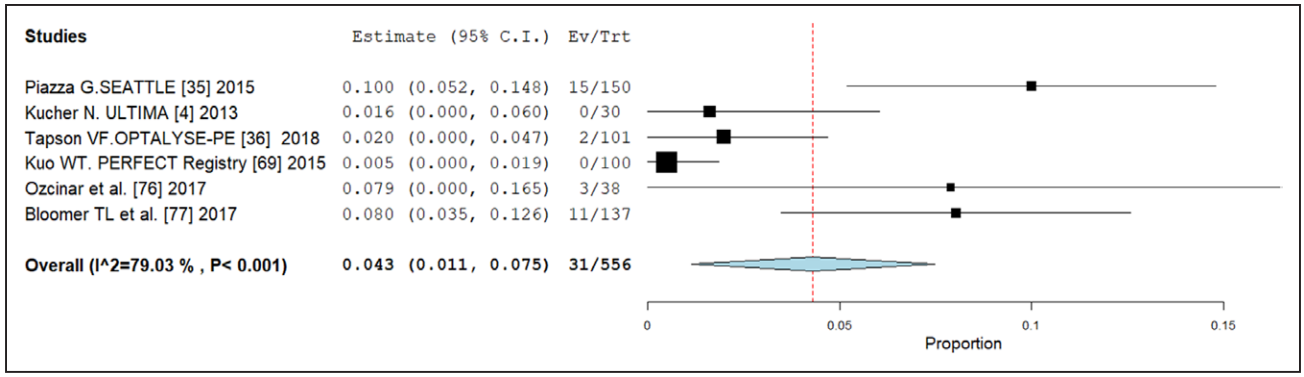

Figure 3. The figure depicts a random-effects observational meta-analysis of nonintracranial major bleeding in 6 prospective studies of catheter-directed thrombolysis.

The weighted pooled proportion of major bleeding events is 4.3% with a 95% confidence interval of 1.1% to 7.5%. The I-squared metric, the percentage of variation across studies that is attributable to heterogeneity rather than chance, demonstrates high heterogeneity across the studies for this outcome.[4,35,36,69,76,77] Ev/Trt indicates event/treatment; OPTALYSE-PE, A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism; PERFECT, Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis; SEATTLE, A Prospective, Single-Arm, Multi-Center Trial of EKOSonic® Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (PE); and ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism.

tively relieve obstruction of the PAs through a variety of mechanisms. Such devices can be used as a primary reperfusion therapy, in conjunction with systemic or localized thrombolysis approaches, or used after failed thrombolysis. It is likely that devices will be developed in the future that seek to more seamlessly use concomitant pharmacomechanical approaches to relieve PA obstruction. Unless otherwise specified, the remainder of this section describes the complication risks of existing thrombectomy devices when used without adjunctive thrombolysis.

Thrombectomy devices may carry a higher risk of intraprocedural complications than CDL. These devices are uniformly larger than infusion catheters, and their purpose is to engage and extract thrombus. Hence, there is potential for dislodging thrombi distally, thus worsening ventilation/perfusion mismatch or precipitating acute RV failure resulting from sudden changes in RV afterload. In addition, the wires and catheters needed to deliver these devices are often stiffer and less forgiving than those used for infusion catheter placement. This may increase the frequency of trauma to the pulmonary vasculature or cardiac structures.

Rheolytic Thrombectomy

Experience with rheolytic thrombectomy in PE is limited to case studies or series, with many patients treated with an adjunctive local thrombolytic. In the limited data reported, rheolytic thrombectomy has been associated with instances of profound bradyarrhythmia-induced hypotension, leading to hemodynamic collapse or death.[41,78] A proposed mechanism for these complications is the release of adenosine and bradykinin from sheared platelets. Other reported complications include hemoptysis from presumed pulmonary hemorrhage, worsening hypoxia, and major hemorrhage at access and nonaccess locations. One ICH event has been reported in a patient

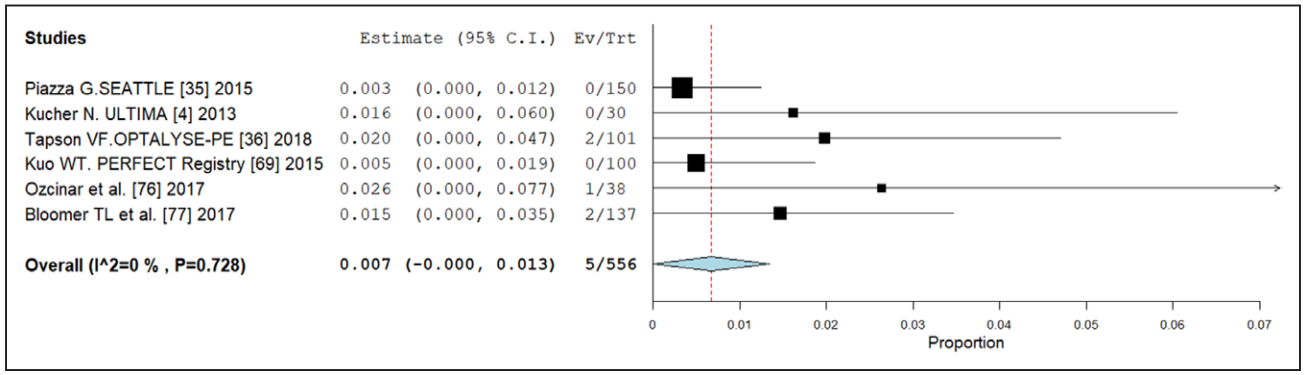

Figure 4. The figure depicts a random-effects observational meta-analysis of intracranial hemorrhage in 6 prospective studies of catheter-directed thrombolysis.

The weighted pooled proportion of major bleeding events is 0.7% with a 95% confidence interval of 0.0% to 1.3%. The I-squared metric, the percentage of variation across studies that is attributable to heterogeneity rather than chance, demonstrates no heterogeneity across the studies for this outcome. [4,35,36,69,76,77] Ev/Trt indicates event/treatment; OPTALYSE-PE, A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism; PERFECT, Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis; SEATTLE, A Prospective, Single-Arm, Multi-Center Trial of EKOSonic® Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (PE); and ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism.

treated with rheolytic thrombectomy who did not receive adjunctive thrombolysis. It is difficult to evaluate the comparative safety of rheolytic thrombectomy versus other management strategies for PE given the dissimilar baseline characteristics and differing techniques that may or may not use adjunctive thrombolysis. Regardless, on the basis of existing reports of adverse events, the labeling for these devices includes a black-box warning recommending against use in the PAs.

Large- and Small-Bore Embolectomy

Two large-bore thrombectomy devices have been used to date for PE. The FlowTriever has been evaluated in the single-arm prospective FLARE study.[3] The presented, but as yet unpublished, study reported that 3 of 108 patients had intraprocedural hemodynamic or respiratory decompensation. Our MAUDE database search revealed 4 additional reports of hemodynamic decompensation and 14 cases of respiratory decompensation related to the FlowTriever device (Table 6). Similarly, AngioVac thrombectomy in the PAs has been associated with hemodynamic collapse and RV free wall perforation that required surgical repair and surgical embolectomy.[79,80] The MAUDE database contained reports of an additional 34 cases of hemodynamic collapse related to the AngioVac.

In the FLARE study, no ICH or access-site major bleeding events were associated with FlowTriever use.[3] However, 1 patient experienced acute postprocedural hemoptysis and hemothorax resulting from either reperfusion injury or catheter-based trauma to the pulmonary circulation. The MAUDE database reported 3 cases of acute pulmonary hemorrhage associated with the FlowTriever device. The largest systematic review of AngioVac use (n=57) for various indications, including iliocaval thrombus, right atrial thrombus, and PE, described access-site hematomas in 6 patients, a fatal retroperitoneal bleed in 1 patient, and 1 case of ICH.[81]

Small-bore embolectomy device use in the literature is thus far limited to the Indigo aspiration system, which provides continuous suction thrombectomy. Current reported experience with this device is limited to 2 single-center case series totaling 24 patients.[82,83] There were no instances of intraprocedural respiratory or hemodynamic decompensation in these 2 studies. There were, however, 3 bleeding events: 1 intra-abdominal hemorrhage requiring coil embolization and 2 ICHs. Notably, all 3 bleeding events were seen in patients who also received 100 mg of systemically administered alteplase. It is anticipated that more safety data will be available after completion of the ongoing prospective trial of the device (EXTRACT-PE).

Summary

- Rheolytic thrombectomy has been associated with pulmonary hemorrhage and hemodynamic and respiratory collapse, leading to an FDA black-box warning related to its use for PE.
- Limited available data on large-bore thrombectomy devices have demonstrated instances of acute hemodynamic and respiratory collapse, as well as right-sided heart and PA injury.
- Rates of ICH and non–access-site bleeding are likely lower with devices designed for isolated large-bore embolectomy than with devices that use thrombolytic drugs, including CDL. Comparative rates of access-site major bleeding between CDL and large-bore thrombectomy are unknown.
- Safety data on small-bore embolectomy devices are too limited to draw conclusions.

PATIENT SELECTION FOR INTERVENTIONAL THERAPIES

All patients with PE should receive prompt therapeutic anticoagulation unless contraindicated.[12–14,84,85] More intensive therapies are most likely to benefit patients who are at the highest risk for dying of PE and at the lowest risk for bleeding (Table 7). Patients whose clinical presentation suggests low-risk PE should be treated with anticoagulation alone, and about half of patients with PE, in fact, can be treated as outpatients.[14,86,87] No further testing to stratify risk is required in these patients because there is little evidence that results should change management.[14,88] Selection of patients for home treatment can be aided by a number of clinical prediction rules, including PESI.[27] On the other end of the spectrum, patients presenting with hypotension need to be treated in a critical care setting and often require prompt aggressive measures such as systemic thrombolysis, catheter-based therapy, or mechanical circulatory support.[12,14,88,89]

Decisions about the treatment of patients who are in the intermediate-risk category are often the most difficult.[90] First, it is uncertain that short-term reperfusion therapies result in a mortality benefit or reduce long-term complications such as chronic breathlessness in these patients.[47] Second, it is difficult to identify which intermediate-risk patient will deteriorate and require active thrombus removal. Assessment of bleeding risk, including ICH risk, is also fundamental to decisions about administering thrombolysis to patients with PE. However, risk scores developed for other conditions such as atrial fibrillation have not proved translatable to patients with PE, and externally validated PE-specific scores to predict these complications are lacking.[12,14,18,29,88] Table 8 outlines knowledge gaps relevant to patient selection for reperfusion therapies.

In line with current guidelines, we discourage routine administration of thrombolytic therapy (either systemic or catheter directed) to patients with intermediate-risk PE. These patients should be promptly anticoagulated, receive supportive measures, and be closely moni-

Table 7. Factors Related to Treatment Allocation to Consider Beyond Risk Stratification

Factor	Explanation
Patient characteristics	
Bleeding risk	High bleeding risk is a contraindication to thrombolytic therapy. Inability to anticoagulate may also preclude other catheter-based therapies, surgical embolectomy, or ECMO.
Symptom severity	Severe breathlessness may encourage use of aggressive therapies for more rapid symptom resolution.
Respiratory status	Although not part of the formal risk stratification schemes based on hemodynamic criteria, deteriorating respiratory status may prompt an immediate intervention.
Functional status before PE	Impaired functional status before the PE may encourage more aggressive therapies in patients with otherwise less significant (eg, hemodynamically) clots. However, patients with very poor preexisting functional status may represent a group in which interventional therapies are futile.
Cancer and life expectancy	Cancer, especially metastatic cancer, is associated with increased bleeding risk and short life expectancy and may discourage the use of aggressive therapies. Other causes for short life expectancy should also be taken into account.
Clot characteristics	
Clot location (ie, distal vs proximal)	Endovascular therapy and surgical embolectomy are expected to be more effective with proximal clots.
Clot in transit	A clot in transit denotes high risk for a "second hit." Furthermore, if a patent foramen ovale is present, this type of clot increases the risk for systemic embolization (eg, stroke).

ECMO indicates extracorporeal membrane oxygenation; and PE, pulmonary embolism.

tored.[14,88] If patients deteriorate (hemodynamic, respiratory, or RV function), more intensive therapies, including thrombolysis, catheter-based or surgical embolectomy, and mechanical circulatory support, should be strongly considered. Among those who remain hemodynamically stable, a careful assessment for factors that elevate risk of decompensation should be undertaken, including elevated PESI or simplified PESI score, severe PE-related functional impairment, and objective signs of severely diminished end-organ perfusion or stroke volume. In those who meet these criteria and have nonprohibitive bleeding risk, systemic thrombolysis or CDL may be considered in order to achieve the goal of immediately improving RV performance. Catheter-based embolectomy represents an option for patients in this cohort with elevated bleeding risk, with the caveat that concerns for procedural hemodynamic or respiratory decompensation exist with these technologies.[4,12,35] Finally, clinicians must also be aware that the presence of markers of poor prognosis does not necessarily equate to improved long-term clinical outcomes with reperfusion therapy.[91]

Summary

- Systemic thrombolysis, surgical embolectomy, interventional PE therapy, and mechanical circulatory support should be strongly considered in patients with PE and hemodynamic instability.
- Among patients with intermediate-risk PE, a careful assessment for factors that elevate risk of

Table 8. Knowledge Gaps Related to Selection of Patients With PE for Treatment

Gap	Comment
Bleeding risk assessment	Bleeding risk is often extrapolated from patients without PE. Patient-specific bleeding risk and potential bleeding location are hard to predict.
Which nonhemodynamic clinical markers should promote intervention?	Although robust data support the need for aggressive therapy for hemodynamically unstable patients, it is unclear whether these interventions are indicated for reasons such as respiratory distress.
Prediction of short-term clinical deterioration in intermediate-risk PE	Some patients with intermediate-risk PE deteriorate, mandating more aggressive treatment. Close monitoring to detect and treat deterioration is advised; however, predicting deterioration and offering early preventive measures may be preferable.
What short- and long-term outcomes are improved by active thrombus removal at initial presentation?	Current evidence for aggressive therapies in intermediate-risk PE is confined to improvement of short-term surrogate outcomes (eg, RV dysfunction). Data on clinically important outcomes are lacking.
What is the value of new catheter-based therapies in intermediate-risk PE?	New interventional technologies are available for the treatment of PE; however, robust, clinically relevant data on their efficacy, safety, and indications are lacking.
CTEPH prediction and prevention	Most PE patients will not develop CTEPH. It is uncertain which patients will develop CTEPH and whether immediate intervention prevents it.
Post-PE syndrome prediction and prevention	Many patients have physical limitations long after the index PE. It is currently not known which patients will recover and whether immediate intervention prevents these long-term complications.
Which short- and long-term outcomes matter to patients?	Rare complications such as fatal hemorrhage and ICH must be weighed against the potential to prevent functional limitation.

CTEPH indicates chronic thromboembolic pulmonary hypertension; ICH, intracranial hemorrhage; PE, pulmonary embolism; and RV, right ventricular.

decompensation should be undertaken, including elevated PESI or simplified PESI score, severe PE-related functional impairment, and objective signs of severely diminished end-organ perfusion or stroke volume. In those who meet these criteria and have nonprohibitive bleeding risk, systemic thrombolysis or CDL may be considered. Catheter-based embolectomy represents an option for patients in this cohort with elevated bleeding risk, with the caveat that concerns for procedural hemodynamic or respiratory decompensation exist with these technologies.

- The use of either CDL or catheter-based embolectomy in patients with intermediate-risk PE has, thus far, been correlated only with more rapid improvement of RV dysfunction than anticoagulation alone, not short- or long-term clinical or functional outcomes.

Thrombus in Transit

In patients with PE and thrombus in transit, which may be found in the inferior vena cava, right atrium, or RV, there is an ≈5-fold increase in death resulting from PE.[92,93] Thrombus in transit is usually identified on surface echocardiography, occurs in ≈4% of patients with PE, and can appear to be adherent or free-floating.[92,94] Available treatments include anticoagulation, thrombolysis (either intravenous or CDT), catheter-based removal of the thrombus (eg, suction thrombectomy), and surgical embolectomy. No prospective data are available to guide therapy in such cases. An observational pooled analysis of 328 cases of right-sided heart thrombus in transit suggested that thrombolysis (OR, 4.8 [95% CI, 1.5–15.4]) and surgical embolectomy (OR, 2.6 [95% CI, 0.9–7.6]) were more often associated with a favorable outcome than anticoagulation alone.[95] Subsequent to this analysis, an adjusted comparison of 255 cases of thrombus in transit treated with anticoagulation and 70 cases treated with reperfusion did not find a convincing difference in all-cause (6.2% versus 14%; P=0.15) or PE-related (4.7% versus 7.8%; P=0.47) mortality.[94] Newer catheter-based techniques for treating thrombus in transit exist but have not been rigorously evaluated.[45] Although these findings appear to support active thrombus removal in patients with thrombus in transit, this decision is also influenced by the size and nature of the thrombus and the severity of the initial PE.

Figure 5 attempts to organize an evidence-based approach to intervention in PE, taking into account areas of clinical concern for which data are limited.

Summary

- Observational data support a role for active thrombus removal in patients with thrombus in transit, although this decision is also influenced by the size and nature of the thrombus and the severity of the initial PE.
- High-quality comparative effectiveness analyses of varying strategies for active thrombus removal, including systemic thrombolysis, surgical embolectomy, and interventional PE therapies, have not been performed in patients with thrombus in transit.
- Patients who have low cardiopulmonary reserve and larger thrombus in transit are expected to gain most from active thrombus removal.

EVALUATION OF INTERVENTIONAL PE THERAPIES

High-Risk PE

There is a paucity of data supporting a best interventional approach to manage high-risk PE. Ideally, high-risk PE studies would randomize patients to 2 active

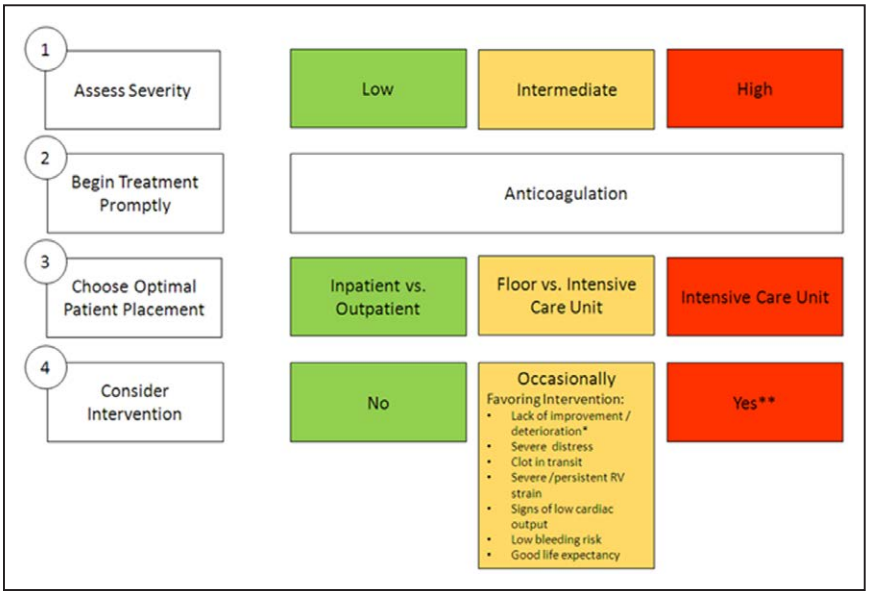

Figure 5. Suggested principles of management for hospitalized acute pulmonary embolism patients.
*A patient's status may change over time. Frequent reassessment is advised. **Do not delay prompt intervention while waiting for patient placement.

comparator therapies, with systemic thrombolytics (AHA Class IIa recommendation) being one of the comparators. However, a large proportion of patients with high-risk PE are not good candidates for systemic thrombolysis because of relative or absolute bleeding contraindications. In addition, no preliminary or pilot data convincingly show intravenous thrombolysis to be superior or inferior to endovascular interventions or open surgical techniques, posing a significant challenge to the estimation of effect size and power calculations. Moreover, these interventions are often made in tandem or in a serial fashion in this critically ill population. The need for flexibility in management of this patient population would likely lead to a large numbers of crossovers, biasing results to the null. Further complicating trial design is the need for emergent mechanical circulatory support in a proportion of these patients, which could confound the assessment of risks and benefits of an interventional PE device. In addition, the low incidence (5%) of high-risk PE may make enrollment impractical.[96] It should also be noted that enrollment of patients with life-threatening illnesses has unique challenges. A 1000-bed hospital may expect 10 to 15 high-risk PEs per year, and only a minority of these patients would likely enroll in an interventional study of PE therapy.

Hence, nonrandomized evaluations with prespecified performance goals for clinical effectiveness are reasonable in high-risk PE. Because conservatively managed high-risk PE is associated with high mortality, the best measure of clinical effectiveness in this population is short-term mortality. Although procedural safety should also be monitored in such analyses, the tolerance for procedure-related complications is high given the high short-term mortality associated with anticoagulation alone. Ideal studies of high-risk PE should prospectively examine all patients with high-risk PE, including those not treated with a device under evaluation at participating institutions, to provide greater insight into presenting populations and to maximize generalizability.

Summary

- Nonrandomized prospective studies of endovascular devices with prespecified performance goals for clinical effectiveness are reasonable for high-risk PE.
- The best primary measure of clinical effectiveness is short-term mortality.
- Prospective studies of high-risk PE should examine all patients with high-risk PE at participating institutions regardless of treatment strategy (anticoagulation alone, systemic lysis, interventional device, surgical embolectomy, mechanical support, or any combination of these). This can be accomplished by concurrent registries for high-risk patients not treated with a PE device under evaluation.

Intermediate-Risk PE

Determining the value of catheter-directed intervention for intermediate-risk PE involves a considerably different calculus. Short-term mortality rates are far lower than those observed for high-risk PE. In a meta-analysis of trials evaluating thrombolysis versus isolated anticoagulation, short-term mortality rates among patients treated with anticoagulation alone were <3%.[18] In the largest randomized trial of systemic thrombolysis versus anticoagulation alone evaluating intermediate-risk PE, 7-day mortality in the anticoagulation alone group was 1.8%.[46] Hence, anticoagulation alone prevents mortality for most patients with intermediate-risk PE. However, patients with intermediate-risk PE treated with anticoagulation alone have clinically significant rates of hemodynamic deterioration and high rates of longer-term decrements of exercise capacity and QOL.[46,61] Active thrombus removal positively affects the former, whereas its effects on the latter are unknown.[46,47]

Given the minimal short-term risk and low cost associated with anticoagulation alone, interventional therapies must prove safety and effectiveness compared with anticoagulation alone through randomized trials. Trial designs should demonstrate clinically meaningful differences in clinical or patient-centric end points. Assuming that effect sizes for interventional therapies are similar to those for systemic thrombolysis in this population, traditional approaches to powering randomized trials for mortality would require 1500 to 2000 patients to demonstrate superiority over a short time period (ie, 7 days). These sample size estimates presume enrollment of patients who fall into the ESC intermediate-high–risk category (ie, the population studied in PEITHO).[46] Modern mechanisms to overcome difficulties in enrollment in such a mega-trial include bayesian adaptive trial designs and embedding pragmatic randomized trials within a prospective registry.[97,98] Enriching the population with additional markers of disease severity such as marked tachycardia, relative hypotension, severe functional limitation, serum lactate elevation, or elevated PESI score may reduce sample size (with the tradeoff of narrowing the enrollable population). Composite end points that include short-term safety (eg, bleeding) and effectiveness could also be used to achieve a more practical sample size, with the caveat that both effectiveness and bleeding may be higher in the interventional arm, leading to a dilution of the effect size.

Patient-centric outcomes include objective measures of functional status and subjective patient-reported measures of QOL. Although CTEPH develops in only 2% to 5% of patients hospitalized with incident PE, up to 50% of patients with PE develop chronic anatomic and physiological abnormalities that have been correlated with diminished functional status and QOL.[99]

Although studies validating objective functional and subjective generic QOL measures in a PE population are limited, they should still be assessed in clinical trials. Several functional and QOL measures have been validated in a variety of cardiopulmonary conditions, and the Pulmonary Embolism Quality of Life has been validated in the PE population.[100,101]

Heart failure measures may also be translatable to the PE population given the similarities in symptomatology between the 2 diseases. Both the 6-minute walk distance and the New York Heart Association dyspnea class have been evaluated in several cohorts of patients with PE. A meta-analysis revealed that at a mean of 18 months after incident PE diagnosis, 33% of patients had New York Heart Association class II to IV symptoms, and patients had a mean 6-minute walk distance of 415 m (95% CI, 372–458), which is at the fourth percentile compared with age- and sex-matched norms.[60,102] Inclusion of these patient-centric end points in randomized trials ensures that outcomes meaningful to patients inform the risk/benefit discussion between physicians and patients.

Current prospective data evaluating interventional devices for PE have relied on surrogate outcomes for clinical effectiveness. The specific end point that has been most favored has been the short-term (24–48 hours) change in the RV/LV ratio as measured by serial CT angiography or echocardiography.[53] The outcome has become the surrogate of choice based on observational data indicating significantly elevated 30-day mortality rates when the RV/LV ratio >0.9. This and other observational data do not prove that rapid reduction of the RV/LV ratio through interventional means reduces mortality. Similar critiques can be leveled against other proposed surrogate end points such as radiographic PA obstruction scoring indexes and PAP changes. Table 9 summarizes known information about a host of clinical and surrogate end points for patients with intermediate-risk PE.

Ideally, device safety would be evaluated in the context of randomized controlled trials by rates of non-ICH major bleeding, ICH, hemodynamic decompensation, pulmonary decompensation, and cardiopulmonary injury. Major bleeding should be designated and categorized by a consensus, published bleeding scale. The universal BARC (Bleeding Academic Research Consortium) definitions, a well-validated tool that allows comparison with many prior interventional trials across various disease processes, is a potential option.[103] If BARC is used, major bleeding definitions should include BARC 2, 3a, 3b, and 5 categories. ICH (also known as BARC 3c bleeding) should be reported separately, given its outsized influence on decision-making for PE. Other bleeding tools that may

Table 9. Intermediate-Risk PE End Points

End Point	Time Assessed After Presentation	Value or Incidence With Anticoagulation Alone	Expected Value or Incidence With an Interventional Endovascular Therapy
Clinical end points			
PE-related death[18]	≈7 d	3%	1.5%
Hemodynamic decompensation[44]	7 d	5%	1.6%*
CTEPH[67]	1 y	4%	Unknown
Patient-centric end points			
6-min walk distance[59]	1 y	415 m	Unknown
Generic QOL (SF-36 physical component score)[100]	1 y	42	Unknown
Disease-specific QOL (PEmb-QOL score)[99]	1 y	13	Unknown
NYHA class >1[59]	1 y	33%	Unknown
Impaired CPET (Vo_2max <80%)[60]	1 y	46%	Unknown
Surrogate end points			
RV/LV ratio change[54,90]	24–48 h	24-h echocardiography: no change 48 h: unknown	24-h echocardiography: reduction of 0.3 48-h CTA: reduction of 0.4
Perfusion defects by V/Q scintigraphy[70]	6 mo	30%–50%	Unknown
Residual echocardiographic deficits[45]	2 y	36%	Unknown
Change in PASP[90]	90 d	11.6 (15.1) (ULTIMA)	12.3 (12.8)

CPET indicates cardiopulmonary exercise test; CTA, computed tomographic angiography; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PE, pulmonary embolism; PEmb-QOL, Pulmonary Embolism Quality of Life; QOL, quality-of-life; RV/LV, right ventricular/left ventricular; SF-36, Short Form-36; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism; Vo_2max, maximum oxygen consumption; and V/Q, ventilation/perfusion.

*Presumes equivalence between systemic thrombolytic therapy and endovascular thrombus removal.

be appropriate include those developed by the International Society of Thrombosis and Haemostasis and those used in prior cardiovascular trials such as the GUSTO trial (Global Utilization of Streptokinase and tPA for Occluded Arteries).[104–106]

Hemodynamic decompensation refers to an immediate need to initiate or escalate intravenous vasopressors, the initiation of mechanical circulatory support, or cardiac arrest. Cardiac arrest should be reported separately whenever possible. Pulmonary decompensation refers to the need for urgent positive pressure ventilation. In some cases, this may be caused by traumatic injury to the PA circulation with associated pulmonary hemorrhage. Rates of iatrogenic pulmonary hemorrhage should also be documented. In addition to these PE-specific complications, standard collection of data on endovascular complications such as vascular access-site complications, acute kidney injury, and trauma to the venous system or heart should be performed. Table 10[102–105] provides definitions for various safety end points for trials of intermediate-risk PE intervention.

Although randomized trials provide the most valid way to appropriately judge complication risk in a given population, there is significant complementary value in prospective registries that rigorously assess the end points above. Device-specific or disease-specific registries can actively survey complication rates and alert the medical community and regulators to early signals of harm, which is particularly valuable for relatively rare complications. Identifying potentially catastrophic events such as hemodynamic or pulmonary decompensation in patients treated with interventional devices is of particular importance given the rarity of these outcomes in patients treated with anticoagulation alone.

Table 10. Definitions of PE-Specific Safety End Points in Trials of Devices for Intermediate-Risk PE

Complication	Definition
ICH	Any new bleeding inside the cranium; BARC 3c bleeding
Non-ICH major bleeding	Consider use of validated bleeding assessment tools such as BARC, ISTH, or GUSTO; if using BARC, class 2, 3a, 3b, and 5 bleeding
Pulmonary decompensation	New initiation of positive pressure ventilation
Hemodynamic decompensation	Initiation/escalation of vasopressor therapy, initiation of mechanical circulatory support, or cardiac arrest
Pulmonary hemorrhage	Development of procedural or postprocedural hemoptysis or imaging study demonstrating intrapulmonary bleeding

BARC indicates Bleeding Academic Research Consortium[103]; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries[106]; ICH, intracranial hemorrhage; ISTH, International Society of Thrombosis and Haemostasis[104,105]; and PE, pulmonary embolism.

Summary

- Although single-arm studies have some value in establishing the preliminary safety and effectiveness of devices for the treatment of PE, these studies are not sufficient to stratify risks and guide clinical practice. Hence, data to support the use of interventional devices for intermediate-risk PE should come from randomized trials.
- Effectiveness outcomes should include traditional clinical outcomes (death, hemodynamic decompensation, development of CTEPH) and patient-centric functional or QOL outcomes.
- Functional or QOL outcomes may include the 6-minute walk distance, Pulmonary Embolism Quality of Life score, New York Heart Association classification, and Short Form-36 scores.
- Surrogate effectiveness end points, including the short-term reduction in RV/LV ratio, should not be a proxy for mortality or other clinical outcomes in studies of patients with intermediate-risk PE.
- Comparative safety evaluations of interventional devices in randomized trials should include major bleeding (consider the use of BARC or other consensus criteria), ICH, hemodynamic decompensation, and pulmonary decompensation. Complementary prospective registries should be encouraged to actively survey harms associated with relatively rare events.

Influence of the Current US Regulatory Environment on Evidence Development

The regulatory pathway strongly influences novel device development and evaluation. In the absence of clearance or approval for a specific indication, devices can be used only in an off-label fashion. Although off-label use of both drugs and devices at physician discretion remains a valuable option for selected cases, exclusively off-label treatment will reduce the incentive for industry to design devices specifically for the pulmonary circulation and to iteratively improve their technologies to optimize pulmonary performance.

The FDA designates novel devices into categories of low, moderate, or high risk to patients, with the 3 categories nominally designated as class I, II, and III, respectively.[107] All the classifications relate to clearance/approval of a device only for the specific indication under examination (ie, the evaluation of the safety and effectiveness of a device for the treatment of deep venous thrombosis would need to be separated from its evaluation for PE because of the disparate presentations, risks, and benefits of the device in the 2 different clinical scenarios). Class I devices are defined as low risk because they "are not purported or represented to be of substantial importance in preventing impairment of human health" and they "do not present a

potential unreasonable risk of illness or injury." Class II devices are designated as moderate risk because of the availability of "sufficient information to establish special controls to provide a reasonable assurance of the safety and effectiveness of the device." These special controls may include "promulgation of performance standards, post-market surveillance, patient registries…and other appropriate actions as FDA deems necessary to provide such assurance [of safety and effectiveness]." The FDA examines these special controls to "provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance." Finally, class III devices "present a potential unreasonable risk of illness or injury" and cannot be classified into class II because "insufficient information exists to determine that the special controls described above would provide reasonable assurance of its safety and effectiveness."[107]

Designation of a device as class III triggers the need for premarket approval by the FDA before device sales and marketing for the indication under consideration. Premarket approval represents the highest form of FDA device regulation and is a far more involved process than the 510(k) clearance pathway used for class I and II devices.[108] Although specific clinical study types and designs are not proscribed by the FDA for premarket approval, the FDA seeks a higher standard of evidence that ensures the safety and effectiveness of devices for which they would be less certain on the basis of the controls specified for class I and II devices. For invasive cardiovascular therapies, this has often, but not universally, taken the form of randomized controlled trials. Oftentimes, premarket approval applications are reviewed by advisory panels of expert clinicians and scientists who provide guidance to the FDA indicating the success of clinical studies to demonstrate a favorable profile for safety and effectiveness.

The FDA cites examples of class I devices as elastic bandages and enema kits. Class II devices include wheelchairs and some pregnancy test kits. Class III devices include many recently evaluated cardiovascular devices such as drug-coated balloons for peripheral artery disease and structural heart products such as transcatheter heart valves and left atrial appendage occlusion devices. The ultimate classification of a novel therapy is determined by the FDA. However, the FDA can rely on recommendations drafted by classification panels to assist in appropriate designations. Classification panels consist of members chosen for their expertise in clinical use, manufacturing, engineering, or administrative issues relevant to the device under evaluation. Each panel also has nonvoting members representing consumer and device manufacturing industry interests.

Thus far, 2 devices have been granted FDA clearance for the interventional treatment of PE: the EKOSonic USAT system and the FlowTriever embolectomy device. The Indigo embolectomy device is currently under evaluation. In all cases, the FDA designated the devices as class II. Clearance was based on clinical studies evaluating the safety and effectiveness of the devices for the treatment of PE, with assurance of effectiveness being demonstrated by short-term changes in the RV/LV ratio and safety based on results of single-arm 100- to 150-patient studies reviewed earlier in this document.

The above analyses were inadequately powered for and not designed to support clinical effectiveness (defined by mortality, recurrent venous thromboembolism, hemodynamic decompensation, QOL, or functional status at any time point) or to stratify risks and guide clinical practice. Although an argument can be made that procedural safety can be judged in a single-arm study, the above studies were not large enough to make clear judgments about the comparative safety of the interventional therapies against conservative therapy.

In summary, results of premarket evaluation studies for interventional devices thus far support effectiveness for surrogate end points: the short-term change in RV/LV ratio and reduction in PAPs. However, no rigorous evaluations of short-, intermediate-, or longer-term clinical or patient-centric end points have been performed in either the intermediate- or high-risk population. Procedural safety of the devices has been evaluated largely in intermediate-risk patients whose short-term risks with anticoagulation alone are low. Procedural safety of the devices has not been evaluated in a significant number of patients with high-risk PE.

Given the above, it is not expected that high-level evidence to justify the use of interventional devices for PE will be available before their widespread marketing. Generation of this high-level evidence must be driven by other mechanisms via interested stakeholders, including charitable organizations, professional societies, industry, and public funding sources.

Summary

- Thus far, interventional PE devices have been classified as moderate risk to patients, resulting in regulatory clearance via the 510(k) pathway.
- Level 1 evidence for the safety and effectiveness of interventional devices for PE will not be available before their widespread marketing.
- Generation of high-level evidence for PE devices will have to be driven by interested stakeholders, including charitable organizations, professional societies, industry, and public funding sources.

PE RESPONSE TEAMS

Despite all that has been outlined in the previous sections, data suggest that patients with massive PE are

Circulation. 2019;140:00–00. DOI: 10.1161/CIR.0000000000000707

actually being undertreated. Between 3% and 4.5% of patients with PE are hypotensive when they initially present to care.[20,109] Despite this, only a minority of these patients receive advanced therapies such as systemic intravenous thrombolysis, CDL, catheter-based embolectomy, or surgery.[109] The reasons for this treatment gap are unclear but are likely related to the perceived risks associated with these therapies and the unwillingness of individual clinicians to assume those risks on behalf of their patients. The rapidly evolving proliferation of therapeutic options and interventional devices makes choosing among different advanced therapeutic options challenging. As noted in this document, the development and promulgation of interventional devices for PE in particular will occur in the absence of Level 1 evidence evaluating safety or effectiveness. This knowledge gap means that specific therapeutic decisions are left to individual clinicians, who may be prone to their own biases and influenced by their previous experiences.

The PERT model was created to help address these treatment and knowledge gaps.[110–114] PERTs are like other rapid response teams (eg, stroke teams, trauma teams) in that they provide rapid assessment and treatment of patients with a life-threatening, time-sensitive illness. Typically, a PERT is activated by a clinical care team after a clinically significant PE is diagnosed.[2,115] Original descriptions of PERT focus on members of the PERT, representing different specialties that review the case in real time and provide a consensus recommendation to the care team. The PERT also serves as a mechanism to efficiently mobilize resources such as the catheterization laboratory or operating room when needed. PERTs are somewhat unique among rapid response teams in that interaction among multiple different specialties (eg, cardiology, emergency medicine, hematology, interventional radiology, pulmonary/critical care surgery, vascular medicine) is integral to this care model (Figure 6). This multidisciplinary approach ensures that clinicians with different perspectives on various therapeutic approaches participate in treatment decisions. In current clinical practice, real-time multiphysician review of all cases is not universal in existing PERTs, many of which function as more traditional consultancy services. However, the multispecialty involvement of providers within the teams at large remains a key characteristic in these hospitals as well.

The PERT model has several potential advantages. Engaging a multidisciplinary group of clinicians in discussions about individual patients and programmatic considerations about localized treatment guidelines may reduce individual and intraspecialty biases and conflicts of interest. Having representation from both interventional and noninterventional specialties may facilitate appropriate debate about the use of invasive therapeutic procedures, particularly in the absence of high-level evidence for their use. The fact that these debates are multidisciplinary is critically important so that the risks and benefits of specific interventions or procedures are not determined solely by clinicians who perform those procedures or do not perform those procedures. The PERT platform can serve as a mechanism for internal quality assessment and improvement at an institution. Engaging with the growing consortium of PERT programs may provide an infrastructure for the assessment of interventional devices both before and after approval. Research into the comparative effectiveness of these devices and interventions may take the form of clinical trials or observational outcomes research and cost-effectiveness studies. Both clinical trial and practice-based research designs may, in the future, be facilitated through a network of multidisciplinary collaborators associated with PERTs.

Similarly, representation among specialties that provide short-term care and long-term follow-up may help facilitate appropriate debate about which outcomes are most critical to consider during the determination of the initial treatment. It is extremely difficult to appropriately weight short-term outcomes such as PE-related mortality or thrombolysis-related hemorrhage alongside long-term outcomes such as cardiovascular disability, decreased QOL, and CTEPH. The relative im-

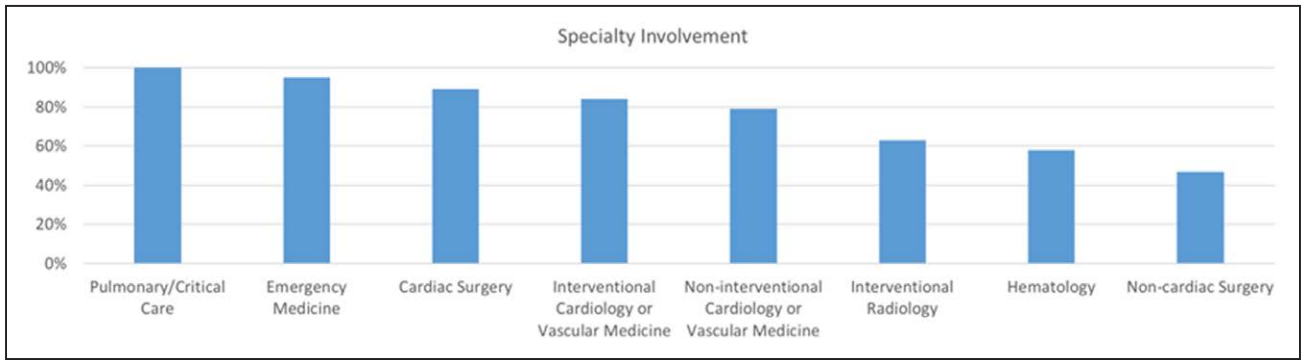

Figure 6. Specialty representation among US pulmonary embolism response teams (PERTs) according to information garnered from a survey of 39 initial institutions with PERTs.[2]

portance of these outcomes is an individual decision that varies across both clinicians and patients. In time, PERTs may generate outcome data that better inform treatment decisions. Until those data are available, the PERT approach enables various outcomes to be assessed and considered in a way that is both patient-centered and representative of the diversity of clinical experience.

Despite potential benefits of PERT programs, a number of well-founded criticisms exist. No robust data exist demonstrating superior clinical outcomes for hospitals using a PERT program compared with hospitals with usual care for patients with acute PE. However, the notion of rapid multidisciplinary care is not unique to PERT. In fact, the PERT model was based in part on the rapid response teams for shock, trauma, stroke, and cardiac arrest. Many of these programs are widely adopted and generally considered to improve care for acutely ill patients.[116–121] In the evaluation of the effect of PERT, studies will need to distinguish between evidence supporting (or refuting) this pathway of care from evidence supporting (or refuting) the use of individual therapies. Evidence in support of the PERT model of care must be distinguished from evidence in support of thrombolysis or catheter-based therapies, for example.

Although many have argued that there is no downside to rapid multidisciplinary evaluation and discussion for patients with complex medical conditions, others have raised concerns that the PERT model is costly and designed to increase the use of catheter-based interventional therapies. Initial data from individual centers demonstrate use of catheter-based therapies in a minority of patients with intermediate- and high-risk acute PE (Table 11).[113,122,123] Published reports from several academic centers suggest that CDL, for example, is used in 11% to 29% of PERT activations.[113,123,124] Although this represents a minority of patients presenting to these hospitals with PE, these rates of CDL use are substantially higher than that noted in general US practice.[125] In addition, within the PERT framework, catheter-based approaches may be supplanting systemic thrombolysis as the active thrombus removal strategy of choice for patients with intermediate- and high-risk PE. In each of the above institutions, the proportion of patients receiving PERT care undergoing CDL was far higher than that of patients receiving full-dose systemic thrombolysis (5%–6%). However, there appears to be substantial variation in the use of catheter-based therapies across institutions with a PERT. Unpublished data (C. Kabrhel, PERT Consortium Symposium, June 2018) demonstrate that the use of CDL varies from 0% to 20% across institutions and the use of any therapy more advanced than anticoagulation alone varies from 16% to 46%. This variation could be related to the local availability of resources, different specialty participation in the PERT, varying interpretations of and comfort with the data supporting different therapies, or other factors. Understanding the nature of the variation in the use of catheter-based procedures and how it affects treatments and outcomes of patients with PE is an important goal for future study. It will also be important to formally evaluate several other aspects of PERT. First, PERT may create a false sense of urgency in stable patients for whom urgent decision-making for symptomatic PE does not improve care. In addition, although the goal of PERT is to make consensus recommendations, this may not be possible in circumstances in which members of the team fundamentally disagree on the appropriate management strategy for a patient. Depending on the structure of the PERT, systematic mechanisms for adjudicating such disagreements may not exist. In addition, in the most emergent cases, there may be a downside in attempting to obtain multidisciplinary input on management rather than simply having a single experienced practitioner make rapid decisions. Finally, the current system of reimbursement does not easily allow compensation for the cognitive expertise and time spent by multiple different physicians on the same patient for a single diagnosis.

To properly address the knowledge gaps related to PERT and advanced therapies for acute PE, 2 types of studies are needed. The first should explore the impact of the PERT model on care delivery and clinical outcomes. The second should focus on comparing outcomes between various treatment strategies (eg, use

Table 11. Use of Active Thrombus Removal Therapies Among 3 Different PERTs

	MGH, n (%)		Cornell, n (%)		Cleveland Clinic, n (%)	
	High Risk (n=80)	Intermediate Risk (n=142)	High Risk (n=8)	Intermediate Risk (n=79)	High Risk (n=23)	Intermediate Risk (n=80)
Systemic full-dose thrombolysis	8 (10)	8 (6)	0 (0)	6 (8)	3 (14)	3 (4)
Systemic half-dose thrombolysis	0 (0)	0 (0)	0 (0)	0 (0)	4 (18)	13 (16)
CDL	6 (8)	19 (13)	4 (50)	21 (27)	7 (32)	7 (9)
Catheter-based embolectomy	0 (0)	1 (1)	0 (0)	0 (0)	3 (14)	1 (1)
Surgical embolectomy	4 (5)	3 (2)	0 (0)	0 (0)	2 (9)	4 (5)

CDL indicates catheter-directed thrombolysis; MGH, Massachusetts General Hospital; and PERT, pulmonary embolism response team.
Data derived from Reza and Dudzinski,[112] Carroll et al,[122] and Sista et al.[123]

of different devices versus noninterventional therapies). PERT programs can potentially offer significant benefits for both study types. Through the National PERT Consortium, many centers are actively entering their patients with intermediate- and high-risk acute PE into a centralized database. This infrastructure may initially allow postmarketing studies of devices and potentially serve as a platform for prospective device evaluation in the future, both ideally guided by principles articulated in earlier sections of this document.

The multidisciplinary PERT approach provides a model of cross-specialty collaboration that may aid in the investigation of novel devices for the treatment of PE. Like PERT, the assessment of novel interventions for PE should involve multiple clinical specialties, should focus on minimizing individual and specialty biases and conflicts of interest, and should consider the spectrum of clinical outcomes important to patients.

Summary

- PERTs universally involve multiple specialties that bring various experience and skills to the management of patients with acute PE.
- Published treatment patterns and clinical outcomes of PERTs are limited. Available data demonstrate the use of CDL in 10% to 20% of patients with intermediate-risk PE. The use of CDL in hospitals with PERTs appears to be more common than the use of systemic thrombolysis. Data on the influence of PERT on the use of catheter-directed embolectomy are limited.
- PERT may serve as a future platform for prospective observational and experimental research into technologies involved in the management of PE.
- It is unclear whether the PERT framework for acute PE care improves patient outcomes and is cost-effective. Formal health systems evaluation and implementation research on PERT have not yet been performed.

ARTICLE INFORMATION

The devices listed here serve only to illustrate examples of these types of devices. This is not intended to be an endorsement of any commercial product, process, service, or enterprise by the American Heart Association.

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on May 28, 2019, and the American Heart Association Executive Committee on June 19, 2019. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Giri J, Sista AK, Weinberg I, Kearon C, Kumbhani DJ, Desai ND, Piazza G, Gladwin MT, Chatterjee S, Kobayashi T, Kabrhel C, Barnes GD; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; and Council on Cardiovascular Surgery and Anesthesia. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e000–e000. doi: 10.1161/CIR.0000000000000707.

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Disclosures

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Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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(*Continued*)

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

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