Invasive Strategies for the Treatment of Pulmonary Embolism. Where Are We in 2020?

Miguel A. Maturana, MD, Michael P. Seitz, MD, Issa Pour-Ghaz, MD, Uzoma N. Ibebuogu, MD, FACC, FSCAI, and Rami N. Khouzam, MD, FACC, FACP, FASNC, FASE, FSCAI

Abstract: Pulmonary Embolism (PE) is the third most common cause of cardiovascular mortality in the United States, with 60,000-100,000 deaths per year following myocardial infarction and stroke. During the past 5 years, there has been an introduction of novel interventions as a result of a renewed interest in optimizing PE management, particularly among those individuals with more severe disease of hemodynamic significance. The cornerstone treatment for PE is anticoagulation. More aggressive alternatives have been considered for patients with intermediate and high-risk PE. In general, these options can be grouped into 3 different categories: systemic thrombolysis, catheter-directed interventions, and surgical embolectomy. Systemic thrombolysis has shown statistical benefit in several randomized trials for intermediate- and high-risk PE, however, this benefit has been offset by an elevated risk of major bleeding and intracerebral hemorrhage, limiting their use in clinical practice. Catheter-directed thrombolysis refers to catheter-directed injection of a thrombolytic drug directly into the pulmonary artery. Three interventional devices (EKOSonic endovascular system, FlowTriever embolectomy

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device and the Indigo thrombectomy system) have recently been cleared by the US Food and Drug Administration for marketing, and several others are in various stages of development. As of today, catheter-based interventions are limited to small randomized trials and single arm-prospective studies focused on short-term surrogate endpoints. Although single arm studies carry some value establishing the preliminary safety and effectiveness of these devices, they are not sufficient to stratify risk and guide clinical practice. Furthermore, no trials have been performed with enough power to assess potential mortality benefit with the use of catheter-directed thrombolysis or catheter-based embolectomy devices, hence treatment decisions continue to be influenced by individual risk of bleeding, the location of thrombus and operator expertise until additional evidence becomes available. (Curr Probl Cardiol 2021;46:100650.)

Introduction

Pulmonary Embolism (PE) is the third most common cause of cardiovascular mortality worldwide, following myocardial infarction and stroke, with 60,000-100,000 deaths-per-year in the United States.[1] Over the years, research has focused in surrogate studies on systemic thrombolysis, extrapolating data from clinical trials and meta-analysis aiming to reduce morbidity and mortality from this condition. During the past 5 years however, this approach has started to change with the introduction of novel interventions as a result of a renewed interest in optimizing acute PE management, particularly among those individuals presenting with more severe disease.[2] Despite advances in research and access to sensitive diagnostic testing, the morbidity and mortality related to this entity continues to cause a tremendous economic burden to the US healthcare system. Today, venous thromboembolism has an annual cost of $7-10 billion per year, and these expenses continue to rise.[3]

PE presentation is heterogenous, ranging from benign to serious and life-threatening disease. The upfront management of PE is guided by the initial presentation, therefore early recognition, group stratification and access to treatment are major determinants for prognosis. While current stratification models attempt to group patients in low-, intermediate-, or high-risk based on hemodynamic status, right ventricular (RV) strain and

cardiac stress biomarkers,[4,5] the individual risk of mortality is difficult to predict as about 50% of observed deaths are from non-PE related causes and patients may transition from mild (40%-60% of hospitalized patients), to severe disease (≈5% of patients) at any given point during their course.[6] RV strain, a surrogate mortality endpoint, is widely used in clinical practice as a marker for severity and is defined as RV dysfunction on computed tomography (CT) pulmonary angiography or echocardiography (RV/left ventricular ratio (LV) >0.9) or RV injury and pressure overload detected by an increase in cardiac biomarkers such as troponin or brain natriuretic hormone.[7,8] The Pulmonary Embolism Severity Index score (and its frequently simplified version) estimates the risk of death from any cause at 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.[9] The cornerstone for treatment of PE is anticoagulation. Consequently, for patients who present with low-risk PE, anticoagulation alone is recommended.[10] More aggressive alternatives have been considered for patients presenting with intermediate and high-risk PE. In general, these options can be grouped into 3 different categories: systemic thrombolysis, catheter-directed interventions and surgical embolectomy. Current ongoing research studies on the use of systemic thrombolysis or more invasive strategies in this subgroup of patients are under investigation. The European Society of Cardiology (ESC) and the American College of Chest Physicians (CHEST) published specific guidelines, in 2014 and 2016 respectively, for the management of PE in intermediate and high-risk patients. In intermediate-risk PE, both organizations stated that use of primary systemic thrombolysis is not recommended.[11] In high-risk PE patients, however, both the 2014 ESC and 2016 CHEST guidelines recommend systemic thrombolytic therapy. The ESC guidelines also recommend surgical pulmonary embolectomy and catheter directed interventions for high-risk patients in whom full-dose thrombolysis is contraindicated or has failed.

Systemic Thrombolysis

The largest trial on systemic thrombolysis performed to date is the Pulmonary Embolism International Thrombolysis trial in which 1006 patients presenting with intermediate-risk PE were randomized to receive systemic tenecteplase versus anticoagulation alone.[12] In this study, administration of systemic thrombolysis (Tenecteplase 30-50 mg) showed benefit for the combined endpoint of mortality or hemodynamic collapse at 7 days of randomization. Thrombolysis decreased the

frequency of the primary outcome (2.6% vs 5.6%; P= 0.015) with most of the benefit preceded by a lower incidence of hemodynamic collapse (1.6% vs 5.0%; P = 0.002). However, this came with the cost of increased major bleeding (6.3% vs 1.5%; $P < 0.001$), specifically intracranial hemorrhage (ICH; 2.0% vs 0.2%). In addition, there was no statistical difference on overall mortality at 7 days (2.4% in the Tenecteplase group vs 3.2% in the placebo group; P= 0.42). As such, thrombolysis has demonstrated statistical benefit in several randomized trials for intermediate- and high-risk PE, however this benefit has been offset by persistently elevated risk of major bleeding, fatal hemorrhage and ICH, all of which limit their use in clinical practice.[13,14] Given the significant side-effects of systemic thrombolysis therapy, catheter-directed approaches have been developed to reduce the dose of thrombolytics or to avoid thrombolysis altogether.

Catheter-Directed Thrombolysis

Catheter-directed thrombolysis (CDL) refers to the administration of pharmacological thrombolysis via catheter-directed injection of a thrombolytic drug directly into the pulmonary artery (PA) circulation. In comparison to systemic thrombolysis trials, CDL investigations have been limited. Most publications have reported a thrombolytic dose of approximately one-fourth of that which is usually given systemically, with the hope of reducing the risk of major bleeding and hemorrhagic complications previously observed with systemic thrombolysis. Two commonly used CDL catheters are the Unifuse (AngioDynamics Inc, Latham, NY) and the Cragg-McNamara (ev3 Inc, Plymouth, MN) catheters. These catheters have been approved by the US Food and Drug Administration (FDA) for infusion of thrombolytics into peripheral circulation. Operators typically use 4F-5F catheters with an infusion length of 5-10 cm, depending on thrombus burden as visualized on concurrent pulmonary angiography or preprocedural CT. Bashir Endovascular Catheter, a pharmacochemical 7F catheter with a nitinol-supported infusion basket that expands within the thrombus has also been cleared by FDA for use in peripheral vasculature. The promise of CDL lies in a potential increase in thrombolytic effectiveness, coupled with improved safety profile and reduced off-target major and intracranial hemorrhage, because of the local administration and potential for reduced thrombolytic dosing compared with systemic thrombolysis. Unfortunately, no controlled studies have been performed comparing CDL to systemic thrombolysis in PE, and CDL has been compared with isolated anticoagulation in limited studies.[2,6] As of today, 3 interventional devices (EKOSonic endovascular system, FlowTriever

embolectomy device and most recently the Indigo thrombectomy system) using pharmaco-mechanical strategies to recanalize an occluded PA, have been cleared by the US FDA for marketing, and several others are in various stages of development.

Ultrasound-Assisted Thrombolysis

Ultrasound assisted thrombolysis (USAT) technology with the EKOSonic endovascular system (EKOS Corp, Bothell, WA) offers an alternative to simple infusion catheters. EKOS is a specialized 5F catheter with 2 lumens that simultaneously deliver thrombolytics and emit high-frequency, low-energy ultrasound. The ultrasound theoretically disrupts fibrin cross-linking to allow for improved thrombolytic penetration at lower doses by opening the thrombus ultrastructure to thrombolytic binding.[15] As with simple CDL catheters, EKOS can be placed in one or both PAs. Typically, thrombolysis is infused over a 12-hour period, however, most recent data suggests that 2-4 hours of thrombolytic infusion is not inferior to standard therapy.[16] The biggest theoretical advantage of USAT over standard CDL is more effective penetration of the thrombolytic agent over a shorter duration of time, however there are no completed randomized comparison trials between standard CDL and USAT in the pulmonary circulation. Prior observational studies have shown a direct and independent correlation between RV/LV ratio >0.9 and mortality at 30 days.[17-19] In Ultrasound Accelerated Thrombolysis of Pulmonary Embolism, a randomized controlled trial of 59 patients with intermediate-risk PE and RV/LV ratio >1.0 on echocardiogram, USAT plus anticoagulation reduced the RV/LV ratio from baseline to 24-hours to a greater extent than anticoagulation alone.[20] In SEATTLE II (A Prospective, Single-Arm, Multicenter Trial of EKOSonic endovascular System and Activase for Treatment of Acute Pulmonary Embolism), a single-arm, multicenter trial of 150 patients with acute, high-risk or intermediate-risk PE, USAT improved RV/LV ratio by 25% within 48 hours after the procedure (1.55 vs 1.13; mean difference, -0.42; $P < 0.0001$).[21] In OPTALYSE PE (2018), another randomized controlled trial studying USAT, 101 patients with intermediate-risk PE were divided into 4 treatment arms of varying doses and infusion times of alteplase (4-24 mg) with no control arm, and the results demonstrated a similar reduction in RV/LV ratio at 48 hours across all 4 arms.[22] CDL catheters, whether standard or USAT, more rapidly reverse RV dysfunction in patients with acute PE compared to anticoagulation alone and may be used in combination to other interventional strategies such as mechanical thrombus

fragmentation, rheolytic thrombectomy and mechanical thrombectomy (Table 1).

Thrombus Maceration

Mechanical thrombus fragmentation consists of a pigtail-catheter with a wire or a peripheral balloon and has been used in patients with a totally occluded proximal PA branch. Advancing this catheter allows forward flow through the PA and subsequent decompression of the RV, until further treatment, for example, CDL takes place. Rheolytic thrombectomy with the AngioJet catheter (Boston Scientific, Marlborough, MA) utilizes high-speed saline jets which travel backward from the tip of the catheter, creating vacuum and thrombus fragmentation effects. This catheter can also deliver low dose thrombolytics and has shown variable success.

Mechanical Thrombectomy

This form of intervention consists of specialized different sized catheters that are designed to generate greater vacuum effects in the absence of thrombolysis administration (as in Pronto XL 14F Extraction Catheter, Vascular Solutions, Minneapolis, MN). The Aspirex catheter (Straub Medical AG, Wangs, Switzerland), a 11F device can aspirate a thrombus with a flexible catheter tip. This catheter creates negative pressure in the area of the thrombus through high-speed rotation coils macerating and aspirating the clot into the catheter. The FlowTriever system (Inari Medical, Irvine, CA) FDA approved in 2018, is a large bore 20F catheter that is advanced through the occluded PA and retracted back mechanically engaging and retrieving the thrombus by deploying 3 self-expanding nitinol disks while the large-bore catheter creates vacuum effect and aspirates the clot. The single-arm FLARE study (FlowTriever Pulmonary Embolectomy), a prospective, multicenter, single-arm trial evaluated 106 patients with acute PE at 18 sites in the United States.[23] FLARE included patients with proximal PE and right heart strain (RV/LV ratio ≥ 0.9). At 48 hours following the procedure, the mean RV/LV ratio in the study decreased from a baseline of 1.53 to 1.15, a difference of 0.39 ($P < 0.0001$). Indigo Thrombectomy System (Penumbra, Inc, Alameda, CA) a suction device initially developed for endovascular treatment of embolic stroke, is a smaller 8F bore aspiration catheter and functions as a continuous vacuum pump. The EXTRACT-PE (Evaluating the Safety and Efficacy of the Indigo Aspiration System in Acute Pulmonary Embolism), a prospective single-arm study of 119 patients at 22 study centers in the

TABLE 1. Summary of key trials

Trial	Device and/or thrombolytic, and dose	Comparator	Study design	n	Intermediate-risk PE, *n* (%)	High-risk PE, *n* (%)	Reduction in RV/LV ratio	Major adverse events
PEITHO 2014	Tenecteplase, systemic (30-50 mg)	Heparin/LMWH/ fondaparinux	RCT	1006	1005 (100)	0 (0)		Tenecteplase arm: 2% ICH, 6.3% extracranial bleeding
ULTIMA 2013	EkoSonic (20 mg tPA-USAT)	Heparin	RCT	59	59 (100)	0 (0)	0.29 (22%) at 24 h	1 Death, 0 major bleeds, 3 minor bleeds, 0 recurrent VTE
SEATTLE II 2015	EkoSonic (24 mg tPA-USAT)	Single arm	Single arm	150	119 (79)	31[21]	0.42 (24%)	1 GUSTO major bleed, 16 GUSTO moderate bleed, 0 ICH/death
OPTALYSE PE 2018	EkoSonic (8-24 mg tPA-USAT)	Compared 4 tPA protocols	RCT	101	101 (100)	0 (0)	0.35-0.48 (22.6%-26.3%)	4 Major bleeding, 1 recurrent PE, and 1 death at 30 d; 1 additional death at 1 y
FLARE 2018	FlowTriever (0 mg tPA)	Single arm	Single arm	106	104 (100)	0 (0)	0.39 (25%)	1 Hemoptysis, 1 clinical deterioration, 1 cardiogenic shock, 1 ventricular fibrillation, 1 death
EXTRACT- PE 2019	Penumbra Indigo (0 mg tPA)	Single arm	Single arm	119			0.43 (27.3%) at 48 h	1.7% major adverse event rate

GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial; ICH, Intracranial Hemorrhage.

United States, has been Indigo's strongest evidence for advancing their use in PE. This trial was conducted under an investigational device exemption from the FDA. In early November 2019, Penumbra announced that the primary efficacy endpoint of the EXTRACT-PE trial was met with a significant mean reduction in RV/LV ratio of 0.43, corresponding to a 27.3% reduction, at 48 hours after intervention.[24] The primary safety endpoint was reached as well with a major adverse event composite rate (including device-related death, major bleeding, and device-related serious adverse events) of 1.7% within 48 hours. Compared to other trials which have tested for similar efficacy and safety endpoints, the results of EXTRACT-PE were similar to SEATTLE II and FLARE in terms of efficacy, but superior to SEATTLE II and FLARE in terms the percentage of major adverse events within 48 hours.[25] Additionally, there was a 37-minute Indigo procedure time, and intraprocedural thrombolytic drugs were not used in over 98% of the patients enrolled in this trial. Shortly thereafter, on December 20, 2019, US FDA granted approval for Indigo for an expanded indication for treatment of PE.[26] The Indigo aspiration system is also indicated for the removal of fresh, soft emboli, and thrombi from vessels of the peripheral arterial and venous systems. Aspire Max mechanical thrombectomy system (Control Medical Technology, Salt Lake City, UT) is a 5F-6F catheter and utilizes a unique manual aspirator. The AngioVac cannula (AngioDynamics, Inc) is a veno-veno bypass system designed to remove intravascular material via suction, and consists of a funnel-shaped 26F inflow tip accessed via femoral or internal jugular veins that engages the thrombi, while an outflow 16F-20F catheter returns blood to the body via a separate femoral or internal jugular vein catheter (Table 2).

Regardless of the classification or treatment modality, all patients with PE should receive prompt therapeutic anticoagulation unless contraindicated. Invasive strategies are preferred for high-risk PE patients and low risk for bleeding. Low-risk PE should be treated with anticoagulation alone, and about half of these patients in fact can be safely treated as outpatients.[27] Defining treatment for intermediate-risk category is often complex. These patients should be anticoagulated and closely monitored given the dynamic nature of the condition. If patients deteriorate (hemodynamic, respiratory of RV function), more invasive therapies, including thrombolysis, catheter-based or surgical embolectomy and mechanical support, should be strongly considered.[28,29]

TABLE 2. Comparison of interventional PE devices

Device	Mechanism	Size and technical considerations	US FDA-approved treatment indications
EkoSonic	USAT	5F catheter	Clearance for treatment of PE
Unifuse	CDL	4F-5F catheter	Clearance for use in peripheral vasculature
Cragg-McNamara	CDL	4F-5F catheter	Clearance for use in peripheral vasculature
Bashir Endovascular Catheter	Pharmacochemical CDL	7F catheter with a nitinol-supported basket that expands within the thrombus	Clearance for use in peripheral vasculature
AngioVac	Veno-veno bypass with large filter to catch and remove thrombus	2 Access sites: 26F access for inflow; 22F access for outflow; requires perfusion team	Removal of undesirable intravascular material
FlowTriever	Mechanical aspiration with 3 nitinol self-expanding disks to help remove thrombus	20F catheter; must manage blood loss associated with large-bore aspiration	Clearance for treatment of PE
Penumbra Indigo System	Mechanical aspiration	8F catheter; large size of some proximal PE makes en bloc aspiration difficult; continuous aspiration may result in blood loss	PE and peripheral artery and venous systems
AngioJet	Rheolytic thrombectomy with option of either thrombolytic or saline spray	6F-8F catheters for venous thrombus; can cause hypotension and bradycardia	Peripheral thrombectomy; black-box warning against use in PAs
Aspire Max	Suction thrombectomy with specially designed handheld aspirator	5F-6F catheters	Clearance for removal of fresh, soft thrombi, and emboli from the peripheral and coronary vasculature

Conclusion

To date, catheter-based interventions are limited to small randomized controlled trials and single arm-prospective studies focused on short-term surrogate endpoints of improvement in RV function, RV to LV diameter (RV/LV ratio) and reduction in PA systolic pressure, with USAT being the most extensively studied of these techniques. CDL are not exempted of complications as major bleeding, ICH and pulmonary hemorrhage, a

rare but important complication with CDL along with thrombi dislodging and precipitation of RV failure with thrombectomy devices. Promising results recently released in EXTRACT-PE and the recent FDA approval for the treatment of PE are conveying Indigo Thrombectomy System to the eyes of the scientific community. Its small size, ease of delivery to the pulmonary arteries, the low adverse event rate in the EXTRACT-PE trial could make it the superior device. Although single arm studies have some value establishing the preliminary safety and effectiveness of devices for the treatment of PE, these studies are not sufficient to stratify risk and guide clinical practice. Hence, data to support the use of interventional devices for intermediate-risk PE should come from randomized trials. As of today, no trials have been carried out that have the power to assess potential benefits in short-term mortality or hemodynamic decompression with the use of CDL or catheter-based embolectomy devices, hence treatment decisions will continue to be influenced by patient's risk of bleeding, the extent and location of thrombus, operator expertise, and individual patient preferences until further evidence becomes available.

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