Interventional Therapies in Acute Pulmonary Embolism

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KEYWORDS

• Pulmonary embolism • Catheter-directed thrombolysis • Catheter-directed embolectomy
• Cardiovascular mortality • Bleeding • Tissue plasminogen activator

KEY POINTS

- Catheter directed thrombolysis (CDL) and catheter-based embolectomy can be performed safely for patients presenting with intermediate or high-risk pulmonary embolism.
- CDL carries a 0.7% rate of intracranial hemorrhage and thus patient selection is paramount.
- While Catheter based embolectomy should carry a lower intracranial hemorrhage rate but is balanced by a higher risk of procedural respiratory or hemodynamic decompensation.
- Decisions regarding strategy of advanced therapies, timing, dosing of thrombolytics, patient selection can be facilitated by a multidisciplinary pulmonary embolism response team.

INTRODUCTION

Pulmonary embolism (PE) is the third leading cause of cardiovascular mortality among hospitalized patients.[1,2] It is estimated that 100,000 to 180,000 people die from PE annually in the United States.[3–5] Early risk stratification is critical to determine appropriate treatment and decrease morbidity and mortality. Patients with low-risk PE have excellent outcomes when treated with anticoagulation alone (<1% mortality at 1 month).[6] However, patients with intermediate-risk and high-risk PE have short-term mortality rates of 3% to 15% and greater than 30%, respectively.[7–10] The benefits of systemic thrombolysis in these populations are well-established, but accrue at the cost of life-threatening bleeding.[7,11] Concerns about the bleeding risks associated with systemic thrombolysis have prompted a growing interest in alternative options for management of this population, including catheter-directed thrombolysis (CDL) and catheter-directed embolectomy (CDE). This article discusses the current state of endovascular interventional therapy for acute PE, specific roles of CDL and CDE, and available technologies in this space.

PULMONARY EMBOLISM RISK STRATIFICATION

All major guidelines have used risk stratification to guide management. The American Heart Association classifies acute PE into 3 categories: massive, submassive, and low risk.[12] The European Society of Cardiology (ESC) has classified patients into analogous high-, intermediate-, and low-risk PE categories.[13] The main difference between these 2 PE classifications is within the intermediate or submassive category. The ESC acknowledges the complexity of the intermediate-risk category and further divides this into intermediate risk–high and intermediate risk–low.[13] In addition to using right heart strain to risk stratify the intermediate-risk group, the ESC guideline incorporates other clinical parameters such as the PE severity index and cardiac biomarkers in attempt to encompass a broader range of presentations. For the purposes of this review, risk categories will be described as high risk, intermediate risk, and low risk. Intermediate risk will encompass patients with PE and evidence of right heart strain without hypotension (ie, ESC criteria for intermediate risk/American Heart Association criteria for submassive).

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Although the American Heart Association/ESC classifications serve as a means to risk stratify patients with acute PE, treatment decisions are not always straightforward. Anticoagulation remains the cornerstone of acute PE management for low-risk patients and they do very well with this therapy alone. Although anticoagulation does not actively lyse thrombus, it allows endogenous thrombolysis to work unopposed, preventing further clot propagation and reducing thromboembolic burden.[1] In patients with high-risk PE, more intensive interventions are generally warranted given the higher likelihood of mortality, but are accompanied by a higher bleeding risk. Among patients with intermediate-risk PE, there is no simple algorithm to guide whether a patient requires advanced therapy. Many factors influence treatment decisions, including but not limited to institutional expertise, bleeding risk, extent and location of thrombus, and various patient factors. The uncertainty around optimal therapy for the intermediate risk group is also related to the paucity of data supporting the efficacy and safety of available catheter-based therapies. Catheter-directed therapies have garnered interest on the one hand because of limitations with anticoagulation for intermediate-risk patients and on the other owing to the risks associated with systemic thrombolysis and surgical embolectomy. The following sections discuss the rationale, evidence, and safety for catheter-directed therapies in acute PE.

RATIONALE FOR CATHETER-DIRECTED THROMBOLYSIS

The goal of thrombolytic therapy in high-risk patients is to rapidly improve hemodynamic instability. In contrast, thrombolytic therapy in intermediate-risk patients is used to prevent possible hemodynamic collapse in those with right ventricular (RV) dysfunction and to expedite symptom resolution. Other potential but unproven benefits include prevention of recurrent PE, chronic thromboembolic pulmonary hypertension (CTEPH) and post-PE–related functional impairment. Enthusiasm for CDL is fueled by the hope of similar efficacy to systemic thrombolysis, but with a decreased risk of major or intracranial bleeding. Most studies with CDL use a fraction of the total thrombolytic dose recommended for systemic thrombolysis with similar efficacy in surrogate outcomes. Catheter-directed therapies may also avoid the theoretic issue of thrombolytic agents being shunted away from regions with thrombus and toward unobstructed pulmonary arteries.[14] Theoretically, intrathrombus administration of thrombolytic therapy exposes a larger surface area of the clot to thrombolysis. This mechanism was described by Schmitz-Rode and colleagues,[14] who demonstrated that proximal vortex formation by obstructing emboli prevented a systemically administered drug from making effective contact with the thrombus. Given these theoretic benefits, a key clinical question is this: should catheter-directed lysis be used more often in high-risk patients and in selected patients with intermediate-risk PE?

SYSTEMIC THROMBOLYTIC THERAPY

Much of the evidence supporting CDL stems from studies of systemic thrombolysis. The Pulmonary Embolism International Thrombolysis (PEITHO) study was the largest randomized controlled trial (n = 1005) evaluating systemic thrombolysis in intermediate-risk PE. The study compared all-cause mortality and hemodynamic decompensation within 7 days of randomization between systemic thrombolysis and anticoagulation alone. Thrombolysis decreased the frequency of the primary endpoint (2.6% vs 5.6%; $P = .015$; number needed to treat, 33), but this was driven by a decrease in hemodynamic decompensation because the mortality rates were similar between the 2 arms.[11] These benefits were offset by increased rates of major extracranial bleeding (6.3% vs 1.5%; $P<.001$; number needed to harm [NNH], 20) and increased intracranial hemorrhage (ICH) in the tenecteplase group (2.0% vs 0.2%; $P = .003$; NNH, 45).[11]

In a meta-analyses of 16 randomized trials (n = 2115 patients) comparing thrombolysis with anticoagulation for acute PE (71% intermediate risk),[7] thrombolytic therapy was associated with decreased all-cause mortality (2.2% vs 3.9%; number needed to treat, 59) and recurrent PE (1.2% vs 3.0%; adjusted odds ratio [OR], 0.40; 95% confidence interval [CI], 0.22–0.74) at a mean follow-up of 82 days.[7] The decrease in all-cause mortality was observed even when the analysis was restricted to patients with intermediate risk PE (adjusted OR, 0.48; 95% CI, 0.25–0.92). However, this benefit was offset by an increase in ICH (1.5% vs 0.2%; adjusted OR, 4.78; 95% CI, 1.78–12.04; NNH, 79) and major bleeding (9.24% vs 3.42%; adjusted OR, 2.73; 95% CI, 1.91–3.91; NNH, 18).[7]

Current evidence does not support the routine use of thrombolytic therapy in unselected intermediate-risk patients with PE. However, studies evaluating CDL for

intermediate-risk PE have emerged in recent years given concerns over treatment efficacy with anticoagulation alone.

Catheter-Directed Thrombolysis to Prevent Short-Term Complications of Acute Pulmonary Embolism

The data supporting CDL are limited to a small randomized trial and several single-arm prospective studies. Because of the difficulty in powering trials for clinically important outcomes, the majority of these studies have focused on short-term surrogate outcomes. In prior observational studies, an RV to left ventricular (LV) diameter ratio of greater than 0.9 was associated with mortality at 30 days and has become accepted as a reproducible and well-validated tool for assessing patients with PE at risk for adverse outcomes.[15–17]

Ultrasound-Assisted, Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism (ULTIMA) was a randomized control trial that was able to demonstrate a greater reduction in RV/LV ratio in intermediate-risk patients when compared with anticoagulation alone without a difference in the complication rate.[18] The Pulmonary Embolism Response to Fragmentation, Embolectomy and Catheter Thrombolysis (PERFECT) and A prospective, Single arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (SEATTLE II) trials were 2 single-arm prospective studies that also demonstrated a similar reduction in RV/LV ratio as well as a significant reduction of pulmonary artery (PA) systolic pressures.[19,20] Both the PERFECT and SEATLE II trial included a small number of patients with high-risk PE. In the PERFECT trial, both ultrasound-assisted thrombolysis (USAT) and CDL were used and the study showed no difference in outcomes between the 2 devices. Although the PERFECT and ULTIMA trials had no major bleeding events, the SEATLE II trial had an 11% major bleeding rate with no catastrophic bleeding and with most of the bleeding events related to access site complications. SEATTLE II raised concerns about CDL and prompted Tapson and colleagues[21] to study even lower doses of tissue plasminogen activator (tPA) in relation to efficacy and safety. The OPTALYSE PE trial studied 101 patients that were divided into 4 arms of varying doses and infusion times of alteplase (4–24 mg) with no control arm and demonstrated a similar reduction in RV/LV ratio at 48 hours across all 4 arms. It also demonstrated that higher doses of alteplase were associated with increased thrombus clearance (5.5% [95% CI, 1.7%–9.3%] in the lowest dose arm vs 25.7% [95% CI, 12.8%–38.6%] in the highest dose arm). Four major bleeding events occurred that did not correlate with alteplase dosing, 2 of which were ICH. One ICH was in the setting of receiving systemic thrombolysis as a bailout for an inadequate clinical response after CDL.

These prior studies demonstrated an improvement in the RV/LV ratio with CDL, and recently more detailed invasive hemodynamic data in intermediate-risk PE were published. In this cohort of patients, the authors demonstrated that 40% had a low cardiac index defined as less than 1.8 L/min/m during the initial right heart catheterization.[22] Although the mean PA pressures and cardiac index improved regardless of initial cardiac index, the improvement was more pronounced in those starting with a lower cardiac index. After CDL treatment, the mean PA pressure and cardiac index improved significantly with CDL. This finding raises the possibility of using invasive and noninvasive functional hemodynamic assessments to select intermediate risk patients for CDL.

Although there are many methodologic limitations inherent in available studies, there are several key takeaways. Indirect comparisons demonstrate that CDL is significantly more effective in reducing the RV/LV ratio (Table 1) than anticoagulation alone. Given that several studies have shown CDL improves short-term surrogate outcomes in patients with intermediate-risk acute PE, CDL likely benefits carefully selected patients in this population, although larger randomized, controlled trials are needed to identify these patients.

Based on current limited evidence, there continues to be significant uncertainty regarding the safety of CDL; however, the key benefit of CDL is the profound decrease in amount of thrombolytic used. Based on the OPTALYSE-PE trial as well as prior studies such as Moderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) and a study by Wang and colleagues,[23,24] the current optimal dose of tPA is unknown and remains an area of active investigation. The OPTALYSE-PE trial suggests that higher doses of tPA are associated with faster thrombus resolution. The significance of this finding is unknown, but may be important given that many PE survivors have decreased exercise tolerance months and years after the event. These studies were also not designed to assess the long-term outcomes of CDL such as functional impairment, recurrent PE, CTEPH, and

Table 1
Comparison of studies assessing RV/LV ratio with use of advanced therapies versus anticoagulation

Study	N	Study Design	Mean Age (y)	Treatment	tPA Dose (mg)	Intermediate-Risk PE, n (%)	High-Risk PE, n (%)	Reduction in RV/LV Ratio
ULTIMA 2013[18]	30	RCT	63	USAT	20	30 (100%)	0 (0)	0.29 (22%) at 24 h
SEATTLE II 2015[19]	150	Single arm	59	USAT	24	119 (79.3)	31 (20.7)	0.42 (24%)
PERFECT 2015[20]	101	Single arm	60.3	USAT/CDL	28 (mean) variable	73 (72.3)	28 (27.7)	89.1% (95% CI, 76.8–94.4) had ↓ RV strain on echo
OPTALYSE PE 2018[21]	101	RCT	60	USAT	4–28	101 (100)	0 (0)	0.35–0.48 (22.6%–26.3%)
FLARE 2018[54]	106	Single arm	55.6	FlowTriever	0	106 (100)	0 (0)	0.39 (25%)
Fasullo et al,[57] 2011	37	RCT	72.1	Systemic tPA	50	37 (100)	0 (0)	0.38 (27%)
Becattini et al,[58] 2010	23	RCT	62.9	Systemic tPA	30–50	23 (100)	0 (0)	0.31 (24%) at 24 h
ULTIMA 2013[18]	29	RCT	63	AC	0	29 (100)	0 (0)	0.03 (2.5%)
Fasullo et al,[57] 2011	35	RCT	57	AC	0	35 (100)	0 (0)	0.2 (14%)
Becattini et al,[58] 2010	28	RCT	64.5	AC	0	28 (100)	0 (0)	0.1 (8%) at 24 h

Abbreviations: AC, anticoagulation; RCT, randomized control trial.

mortality. Last, there have been no data directly comparing the outcomes of systemic thrombolytic therapy to CDL and, thus, the differences in efficacy and safety between the 2 treatment modalities remain unknown.

Thrombolytic Therapy to Prevent Long-Term Complications of Acute Pulmonary Embolism

Post-PE syndrome and CTEPH are recognized long-term complications of acute PE. The pathophysiology of post-PE syndrome and CTEPH is thought to be multifactorial, including incomplete thrombus resolution, elevated PA pressures, and persistent RV dysfunction, as well as residual perfusion defects.[25–27] Some observational studies have demonstrated elevated PA pressures in patients with acute PE treated with anticoagulation alone at 6 to 28 months of follow-up.[25,26] A prospective observational analysis demonstrated 29% of patients who survive an acute PE will have persistent perfusion defects on V/Q scan at 12 months.[28] Patients with persistent perfusion defects were more likely to have dyspnea, higher PA pressures, and shorter distances on the 6-minute walk test. Additionally, the OPTALYSE PE study was able to demonstrate that higher doses of thrombolytic therapy was associated with faster clot resolution.[21] The clinical significance of this finding is unknown, but may be important given that incomplete clot resolution occurs in one-fourth to one-third of patients after acute PE.[29] Most thrombus resolution seems to plateau after 3 months owing to clot remodeling into a permanent fibrous scar.[29] This finding suggests that there may be a benefit to early clot resolution, although long-term follow-up in selected patients from the PEITHOs trial did not demonstrate a benefit in systemic thrombolytics over anticoagulation in the incidence of CTEPH or persistent functional limitation.[30] With currently available information, it is unclear whether upfront advanced therapy with CDL reduces long-term symptom burden. This topic remains an active area of investigation.

Devices for Catheter-Directed Lysis

The 2 most commonly used non–ultrasound-assisted catheters are the Uni-Fuse (Angiodynamics Inc, Latham, NY) and Cragg-McNamara (Covidien, Plymouth, MN) catheters. Both carry an indication from the US Food and Drug Administration for infusion of thrombolytics into the peripheral vasculature, without a specific indication for PE. Both are 4F to 5F multisidehole catheters. The most common ultrasound-assisted catheter is the EkoSonic Endovascular System (EKOS Corporation, Bothell, WA). The EKOS device (https://btgplc.com/en-US/EKOS/Home) uses multiple small ultrasound transducers inserted into the catheter to help facilitate thrombolytic delivery into the thrombus. The ultrasound energy is theorized to alter the local architecture of the fibrin clot by dissociating fibrin strands and increasing available receptor sites for tPA.[31] This technique may increase the efficacy of USAT and allows for shorter infusion times compared with standard CDL. There have been no randomized trials in acute PE comparing USAT versus traditional CDL in acute PE. In the PERFECT registry, there was no difference in technical or clinical success between the two.[20] Two retrospective studies also found no statistical differences in clinical and hemodynamic outcomes or complication rates between the 2 methods.[32,33] In a nonrandomized trial of 33 patients, USAT led to improved treatment outcome based on thrombus removal, decrease the duration of thrombolytic infusion time, and fewer treatment-related hemorrhagic complications.[34] A randomized trial comparing conventional CDL versus USAT in iliofemoral DVT found no difference between the modalities in clinical or ultrasound outcomes at 12 months.[35] Current available data do not suggest that USAT (which is associated with increased cost) improves thrombolytic efficacy when added to conventional CDL, but a current ongoing randomized head-to-head trial (SUNSET sPE NCT02758574) aims to address this question.[36] In this study, patients who have radiographic or biochemical evidence of submassive PE are randomized 1:1 to USAT or standard CDL. The primary outcome of this study is clearance of pulmonary thrombus burden assessed by postprocedure computed tomography angiography. Secondary outcomes include resolution of RV strain, improvement in PA pressures, and 3- and 12-month echocardiographic, functional, and quality-of-life measures.[36]

The Bashir Endovascular Catheter (Thrombolex Inc, Doylestown, PA) is an expandable nitinol basket with multiple sideholes that allow for thrombolytic agents to be infused directly into clot while also facilitating mechanical thrombus disruption. This device is currently being evaluated in a prospective single-arm study for PE. Technical considerations of CDL and a summary of devices can be found in Table 2.

Safety of Catheter-Directed Lysis

As expected, the most commonly reported complications with CDL involve bleeding. The

Table 2
Devices used in catheter directed therapies

Device	Mechanism	Technical Considerations	Associated Prospective Studies
EkoSonic	USAT	5F catheter. Remain on full dose anticoagulation during the procedure with goal ACT of >200 s. Subtherapeutic heparin dose after thrombolytic infusion is initiated. Fibrinogen/PTT levels checked every 4–6 h, consider reducing or stopping infusion if fibrinogen <100–150. May need cardiac anesthesiologist if anesthesia is required. Caution in patients with LBBB to avoid iatrogenic CHB.	ULTIMA, SEATTLE II, OPTALYSE PE
Cragg-McNamara	CDL		
Unifuse	CDL		
AngioVac	Venoveno bypass with large filter in between to catch/remove thrombus	Two access sites. 26F access for inflow, 22F for outflow. Requires a perfusionist.	
FlowTreiver	Mechanical aspiration with 3 nitinol self-expanding disks to help to remove the thrombus	20F catheter. Continuous aspiration may lead to blood loss.	FLARE
Penumbra Indigo	Mechanical aspiration	8F catheter. Continuous aspiration may result in blood loss.	EXTRACT-PE (under investigation)
AngioJet	High flow saline jet producing negative pressure allowing aspiration of thrombus	8F catheter. Bradycardia, hypotension.	

Abbreviations: ACT, activated clotting time; CHB, complete heart block; LBBB, left bundle branch block; PTT, partial thromboplastin time.

definition of major and minor bleeding often varies between trials, which makes it difficult to directly compare studies or combine bleeding rates. Given that the optimal dose of tPA remains under active investigation, the thrombolytic dosage and duration used in previous studies is also highly variable. In the 6 largest and most recent prospective trials consisting of 556 patients that underwent USAT (PERFECT, OPTALYSE, ULTIMA, SEATTLE II, Bloomer and colleagues,[37] and Ozcinar and colleagues[38]), the pooled estimate for major bleeding was 4.3% (95% CI, 1.1%–7.5%) and the estimated ICH rate was 0.7% (95% CI, 0.0%–1.3%).[39] These rates seem to be lower than those observed in a meta-analysis of systemic thrombolytic therapy (n = 1061), where major bleeding and ICH occurred in 9.2% and 1.5% of patients, respectively.[7] It is important to note that the average age of patients the 6 largest prospective studies evaluating CDL was 62 years old, whereas the majority of major bleeding in the meta-analysis of systemic thrombolysis occurred in patients aged more than 65 years. The younger age in the catheter-based studies may exaggerate the safety profile of CDL and this technology needs to be studied more extensively in the older population. Additionally, early studies in a controlled environment often underestimate true complication rates and higher rates of major bleeding should be expected in general use. Although indirect evidence may suggest lower rates of bleeding complications with CDL compared with systemic therapy, additional prospective

comparative studies are needed to confirm this finding.

Other potential complications of CDL include cardiac tamponade from cardiac perforation, ventricular arrhythmias with catheter advancement through the RV, papillary muscle/tricuspid valve trauma with the use of stiff wires, worsening hemodynamics owing to distal embolization of proximal nonocclusive thrombi, and transient complete heart block in those with a baseline left bundle branch block.[40] These complications are rare given the low profile of these catheters in comparison with larger embolectomy devices and, to our knowledge, have not been reported in the literature. Pulmonary hemorrhage from PA rupture is also a potential complication but it has been rarely reported. The largest retrospective analysis of pulmonary hemorrhage associated with PA catheter placement (n = 32,422) identified an incidence of 0.03%.[41] A summary of bleeding events in recent trials involving CDL are listed in Table 3.

Patient Selection for Catheter-Directed Lysis

All patients with acute PE should receive prompt anticoagulation unless contraindicated.[12] Patients with low-risk PE should be treated with anticoagulation alone with many eligible for outpatient therapy.[42–44] The use of thrombolysis is not recommended in low-risk patients because their short-term mortality rates are 1% with anticoagulation.[12] At the other extreme, patients with hemodynamic instability warrant strong consideration of advanced treatment options, including systemic or catheter-based therapy because they have a high incidence of adverse outcomes.[12] There is a paucity of data supporting the best interventional approach in these patients and head-to-head randomized, controlled trials in this patient population are difficult for a number of reasons. Only 5% of PEs are high risk, which makes recruiting a study powered to detect clinically meaningful outcomes challenging. Many patients have relative or absolute contraindications (Table 4) to systemic thrombolysis (47% in 1 study), limiting the ability to randomize patients.[9] Based on available evidence, it is reasonable for patients with high-risk PE with contraindications to systemic thrombolytics or failed thrombolysis to undergo CDL or be considered for surgical or catheter-based thrombectomy, assuming clinical expertise is available. Therapeutic options in the high-risk category should be individualized with the help of a multidisciplinary team.

Management of intermediate-risk patients is controversial. Traditionally, anticoagulation alone has been sufficient to prevent further morbidity in these patients, but some studies suggest that a subset of these patients with RV dysfunction may be at risk for early decompensation despite initial stability.[12] Recognizing that clinical progression from intermediate-risk to high-risk PE can occur rapidly, patients with intermediate-risk PE should be monitored closely for deterioration with escalation of therapy if needed.

In view of the equivocal data presented, it is prudent to rigorously examine the risks and benefits of thrombolytic therapy in each patient in the intermediate-risk category. PE-related functional impairment and objective signs of impaired end organ perfusion (such as elevated lactate), elevated heart rates, relative hypotension, and severity of hypoxia should also be taken into consideration when deciding on thrombolysis. Owing to the equivocal data of advanced therapies in acute PE in the intermediate-risk group along with rapidly evolving therapeutic options, multidisciplinary PE response teams have been created to help with immediate risk stratification and rapid triaging.[45,46] At present, the available literature is insufficient to support the routine use of CDL for intermediate risk patients. However, it is important to recognize that there may be a subset of intermediate-risk PE patients that may benefit from CDL and ongoing research efforts should work to better identify this group.

CATHETER-BASED EMBOLECTOMY

Catheter-based embolectomy refers to nonlytic, nonsurgical, catheter-based therapies for acute PE that seek to remove thrombus and relieve obstruction of the pulmonary arteries. The data behind catheter-based embolectomy are relatively sparse, but growing. Furthermore, the variety of devices in catheter-based embolectomy make it more difficulty to study. We next focus on the general indications and considerations of catheter-based embolectomy, the risks and benefits of these therapies, and then review specific devices.

Rationale and Indications for Catheter-Based Embolectomy

At least one-third of patients with acute PE have some contraindications to systemic thrombolytics and up to 10% of patients who receive thrombolytic therapy remain in shock.[47,48] For these patients, surgical embolectomy may be considered, but surgical expertise is often limited to selected centers and surgical

Table 3
Complication rates with catheter-directed lysis

Study[REF]	N	Mean Age (y)	Study Design	tPA Dose (mg)	No. of High-Risk PE Patients	No. of Intermediate-Risk PE Patients	Major Bleeding Rate, n (%)	ICH, n (%)
ULTIMA 2013[18]	59	63	Randomized controlled trial	20	0	30[a]	0 (0) CDL vs 0 (0) AC	0 (0)
SEATTLE II 2015[19]	150	59	Prospective single arm	24	31	119	15 (10)	0 (0)
PERFECT 2015[20]	101	60.3	Prospective single arm	28 (mean), variable	28	73	0 (0)	0 (0)
Bloomer et al,[37] 2017	137	59	Prospective single arm	17 (median), 2–48	16	121	13 (9.4)	2 (1.4)
OPTALYSE PE 2018[21]	101	60	Randomized controlled trial	4–24	0	101	4 (4)	2 (2)
Total	519 treated with CDL				75	444 treated with CDL	31 (6.0)	4 (0.77)

[a] Twenty-nine patients were treated with anticoagulation.

Table 4
Contraindications to systemic thrombolysis

Absolute Contraindications	Relative Contraindications
Prior intracranial hemorrhage	Systolic blood pressure >180 or diastolic >110
Known structural cerebral lesion	History of ischemic stroke >3 mo
Known malignant neoplasm	Major surgery within the last 3 wk, recent invasive procedure
Ischemic stroke within 3 mo	Trauma or prolonged cardiopulmonary resuscitation >10 min
Suspected aortic dissection	Recent extracranial bleeding (2–4 wk)
Active bleeding (excluding menses)	Age >75
Recent head trauma or brain injury	Pregnancy, active peptic ulcer, pericarditis, diabetic retinopathy

embolectomy can have high morbidity and mortality, especially in patients who have failed thrombolytic therapy. Percutaneous pulmonary embolectomy may be an attractive option for these patients and should be considered in those with persistent hemodynamic instability despite thrombolytic therapy or in those who have contraindications to thrombolytics.[12,13] An important adjunctive therapy in these cases is mechanical circulatory support, either extracorporeal membranous oxygenation or isolated percutaneous RV support.[49,50] Mechanical circulatory support can be used to buy time for a patient's RV to recover while on anticoagulation, serving as a bridge to more definitive treatment (CDL, CDE, surgical embolectomy), or as a bail-out in the case of intraprocedural hemodynamic decompensation.

As with CDL, catheter-based embolectomy in patients with intermediate-risk acute PE remains controversial. Patients that should be considered are those with a higher risk of developing hemodynamic instability and those with significant symptoms, persistent desaturation, or significant functional limitation despite adequate anticoagulation. In general, patients also must meet anatomic criteria when considering percutaneous pulmonary embolectomy. Thrombus in the central, lobar, or interlobar arteries should be the targets of emboli, and anything more distal is unlikely to benefit owing to anatomic restrictions of the catheter navigating into smaller vessels.[51] Given the paucity of data and lack of standard approach regarding catheter-based embolectomy, patient selection should involve a multidisciplinary discussion among specialists with expertise in each therapeutic option.

Specific Catheters and Techniques

Catheter-based thrombus maceration

Clot maceration can be performed using a modified pigtail catheter with a guidewire that exits from a side hole of the pigtail loop. Manual rotation attempts to break down fresh thrombus into smaller fragments that can embolize downstream and allow forward flow. Peripheral balloons can also be used for this purpose. These techniques may be helpful in hypotensive patients with totally occluded proximal branches to allow forward flow and partially decompress the right ventricle until further treatment, such as local thrombolysis takes effect.[52] It is not clear if maceration is helpful by itself because the majority of reported cases have been performed in conjunction with thrombolytic therapy.[52] In the current era with dedicated embolectomy devices available, this technique has been rendered largely obsolete (see Table 2).

Rheolytic thrombectomy

This technology uses high-speed saline jets that travel backward from the tip of the catheter creating a vacuum and thrombus fragmentation effects. While embedded in the thrombus, it can also provide pulse delivery of thrombolytic agents. This device has been associated with profound bradycardia and a high incidence of procedure-related complications (hemoptysis from presumed pulmonary hemorrhage, major hemorrhage at access and non-access site locations) when used in PE patients.[53] The US Food and Drug Administration has issued a Black Box warning regarding its use in PE treatment.

FlowTriever

Currently there is only 1 prospective, multicenter, single arm study (FLARE) that evaluated the FlowTriever system (Inari Medical, Irvine, CA) in 106 patients with acute PE.[54] Patients with proximal PE and RV/LV ratio of 0.9 or higher

were eligible for enrollment and, notably, the study excluded patients who had recent thrombolytic use. The primary endpoint was change in RV/LV ratio at 48 hours, which was significantly reduced by 0.39 (25%) (95% CI, 1.53–1.15; $P<.0001$) from baseline. To put these results into context, the change in RV/LV ratio with FlowTriever embolectomy was similar to trials evaluating CDL and significantly better than anticoagulation alone at the 24- to 48-hour timepoint (see Table 1). Notably, there was no ICH or access site major bleeding. Four patients had clinical deterioration, which included 1 intraprocedural pulmonary hemorrhage requiring lower lobectomy. Two patients had minimal thrombus removal during thrombectomy and experienced respiratory deterioration during or immediately after the procedure, requiring intubation. One patient arrested in the setting of periprocedural agitation, requiring increasing sedation. These major adverse events emphasize the tradeoff between CDL and CDE, bleeding on one side and risk of decompensation in the other.

The FlowTriever (Inari Medical) is the only CDE device cleared by the US Food and Drug Administration and features a 20F aspiration guide catheter (termed AGC or Triever 20) and a restoration catheter that is advanced inside the catheter over a wire and placed near the thrombus (https://www.inarimedical.com/flowtriever/). The device has undergone several iterations over the past few years and the latest version has significantly more suction power (104 mL/s) than the first version. The AGC is typically placed near the clot and owing to the large suction force created will often remove large pieces of thrombus. There is now a 16F device for more distal clots in subsegmental vessels and also a larger 24F device to extract larger proximal clots en bloc. The second component of this system consists of 3 self-expanding nitonol mesh disks that are advanced through the larger AGC or Triever catheter to engage, disrupt, and retract the clot back into the AGC. This technique is typically used when the clot is adherent to the vessel wall or more distal. The discs come in different sizes to target varying sizes and locations of the pulmonary arterial circulation. Once the clot is loosened, it can be aspirated through the AGC. Given the need for continuous aspiration through a large-bore device, careful attention should be paid to blood loss during the procedure. At the conclusion of the case, the 20F to 26F venous sheath is removed and a mattress suture is applied. Patients remain on heparin throughout the procedure and can remain on heparin immediately afterward as well. The initial FLARE Trial was in intermediate-risk patients, but there are growing data for use even in massive pulmonary emboli.

AngioVac

The AngioVac catheter (AngioDynamics) is a 22F catheter with a funnel shaped, balloon-expandable layered tip that can remove thrombus through a centrifugal pump (https://www.angiodynamics.com/products/3/AngioVac/). It also has an 18F reinfusion canula that creates a venovenous bypass circuit with a large filter in between to remove aspirated thrombus. This procedure requires 2 access points and usually requires a perfusionist to be present to set up and operate the system. The major benefit of this system is that it can suction large amounts of blood and thrombus without significant blood loss. The major limitation of this device in treatment of acute PE are its large size, inflexibility, and the need for procedural support from a perfusion team. This makes it difficult to steer through the tortuous anatomy to get to the PA. The data on the use of AngioVac for pulmonary emboli are sparse. There are no randomized controlled trials or large retrospective analyses on the use of this device in acute PE. Much of the data have been extrapolated from use for iliocaval vein thrombosis. Published experiences in acute PE are limited to case reports and small case series.[55] The largest systematic review of AngioVac providing safety data included 57 patients in whom the device as used for various indications (iliocaval thrombus, right atrial thrombus, and PE); there were 6 access site hematomas, 1 fatal retroperitoneal bleed, and 1 ICH.[56]

Penumbra Indigo

The Indigo system (Penumbra Inc, Alameda, CA) device is a smaller bore suction aspiration device that has been used in the peripheral arterial and venous circulations as well as in neurovascular cases. The Indigo embolectomy system (Penumbra, Inc) is a flexible 8F small-bore aspiration catheter that is connected to a continuous suction vacuum system (https://www.penumbrainc.com/peripheral-device/indigo-system/). A wire separator is moved back and forth at the tip of the catheter to clear clot and improve aspiration of thrombus. The major benefit of the Indigo system is the small size and ease of delivery to the pulmonary arteries. The major drawbacks of the system are that it requires aspiration, which can result in substantial blood loss, and that the catheter caliber may not be large enough to

effectively perform embolectomy on larger, central thrombi. To minimize blood loss, the catheter is usually placed more distally closer to the clot and aspiration is performed by slowing pulling back while visualizing the amount of blood flowing into the cannister. If a significant amount of blood is returning into the cannister, the catheter likely disengaged the thrombus and then the operator should reposition the catheter to reengage the thrombus. The device was studied in a prospective, single-arm, multicenter trial in patients with PE and an RV/LV ratio of greater than 0.9 (EXTRACT-PE; NCT03218566). Preliminary results from EXTRACT-PE showed that the use of the Indigo aspiration system in acute PE resulted in an RV/LV reduction of 0.43 and a major adverse event rate (pulmonary hemorrhage) of 1.7% at 48 hours.

Safety of Catheter-Based Embolectomy

Many of the same procedural-related complications that occur with CDL also exist with catheter-based embolectomy. However, nonaccess site bleeding risk with catheter-based embolectomy is typically lower than CDL as no thrombolytic therapy must be concomitantly administered. This was consistent with the 0.9% (1/104) rate of major bleeding events in the FLARE trial. However, thrombectomy devices may carry an increased risk of intraprocedural complications compared with CDL given that the catheters and devices are much larger and stiffer wires used to guide advancement of larger devices into the pulmonary vasculature may result in structural damage to the heart or pulmonary vessels.

SUMMARY

Historically, there have been 2 main treatment modalities for acute PE: systemic thrombolysis and anticoagulation. Although anticoagulation remains the cornerstone of acute PE therapy, the role of catheter-based therapies is rapidly evolving to fill an unmet clinical need in PE treatment. Although systemic thrombolysis is effective in acute PE, the benefits are often offset by the high risk of bleeding. CDL may offer a potentially lower bleeding profile despite similar efficacy, although there are no available head-to-head randomized, controlled trials. Optimal tPA dosing remains an area of active investigation. Patients with absolute contraindications to thrombolytic therapy or those who require rapid thrombus removal may be candidates for catheter-based embolectomy.

The current evidence does not support the routine use of catheter-directed therapy in preference to anticoagulation alone in intermediate-risk patients. A select subgroup of these patients may benefit from catheter-based therapies and decision making in this setting may be facilitated by the use of a multidisciplinary PE response teams.

DISCLOSURE

Dr S. Khandhar has served as a primary investigator for Inari Medical. Dr J. Giri reports Board of Directors of PERT Consortium, advisory board of Astra Zeneca, consulting fees from Phillips Medical. Drs R. Zhang, T. Kobayashi, and S. Pugliese have nothing to report.

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