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Expert Review

Evolving Management Trends and Outcomes in Catheter Management of Acute Pulmonary Embolism

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Background

Venous thromboembolism (VTE) and its resulting sequelae (pulmonary embolism [PE], chronic thromboembolic pulmonary hypertension [CTEPH], postthrombotic syndrome) are responsible for a significant number of hospitalizations in the United States, with annual estimates of VTE affecting as many as 900,000 Americans .[1,2] PE constitutes a large proportion of complications of VTE, having an incidence of 0.95 per 1000 persons per year hospitalized in developed countries prior to the coronavirus disease 2019 (COVID-19) epidemic. There are nearly 600,000 acute PE cases annually in the United States.[3,4] Many reports underestimate the concomitant increasing burden from patients with COVID-19 in addition to subclinical cases.[5] The optimal management of PE treatment is based primarily on risk stratification and the given PE subtypes. Patients with a high bleeding risk or those with hemodynamic compromise lack a consensus treatment protocol despite recently published guidelines that highlighted specific patients within this high-risk population.[6] Despite rapid advances in VTE treatment technology over the past decades, PE outcomes and mortality have remained relatively unchanged.[7] Furthermore, multiple studies continue to report a greater than 65% morbidity and mortality in many VTE scenarios, especially when stratified by age.[8-10] Depending on the classification of the PE, mortality ranges from 1% for submassive PEs to more than 65% for massive PEs.[11,12] Limited guidance of the management provided for acute interventional therapy of PE in part corroborates the controversial nature of the available and evolving therapies. Individual institutional guidelines and protocols further convolute the VTE and PE management consensus.[13,14] This article examines the most contemporary trials and studies centered on the advanced management, specifically catheter-directed therapies, of acute PE.

Pulmonary Embolism Classification

The term PE denotes mechanical (clot, air, tumor, or fat) obstruction to pulmonary blood flow by material originating from a distal location. PE has a broad clinical presentation, ranging from asymptomatic to hemodynamic instability to sudden death.[13] Identifying the severity of PE based on the right ventricular (RV) ventriculoarterial compliance, hemodynamic instability, and RV strain, using imaging and clinical symptoms, is crucial for determining necessary therapeutic interventions and prognostication.[13] See Table 1[13,15,16] for the PE classification schema. Right heart failure due to acute

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Table 1
Pulmonary Embolism Classification Schema[13,15,16]

Severity	Hemodynamics	Anatomic Site
Massive (high-risk)	• Defined by hemodynamic instability. • Highest risk of early mortality. • Necessitates early and aggressive treatment.	Saddle • 3%-6% of all PE. • Embolic material at the bifurcation of main PA.
Submassive	• Without systemic hypotension (SBP ≥90 mmHg) but with either RV dysfunction or myocardial necrosis • 2 subtypes: a) Intermediate-high: • RV dysfunction by echocardiography or CTPA • Abnormal cardiac troponins. b) Intermediate-low: • No RV strain and/or dysfunction (minimal to no rise in cardiac enzymes)	RV dysfunction means the presence of at least 1 of the following: • RV dilation (RV/LV diameter >0.9) or RV systolic dysfunction on echocardiography • RV dilation (RV/LV >0.9) on CT • Elevation of BNP (>90 pg/mL) • Elevation of N-terminal pro-BNP (>500 pg/mL); or • Electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion) • Myocardial necrosis is defined as either of the following: • Elevation of troponin I (>0.4 ng/mL) or • Elevation of troponin T (>0.1 ng/mL)
Low-risk PE	• Hemodynamic stability without evidence of RV strain.	Segmental • Higher rates of pulmonary infarction leading to alveolar hemorrhage, pleural effusion, and pleuritis. • Typically, minimal effect on gas exchange except in pre-existing cardiopulmonary disease.

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; PA, pulmonary artery; PE, pulmonary embolus; PESI, Pulmonary Embolism Severity Index; RV, right ventricular; s/s, signs and symptoms; sPESI, simplified Pulmonary Embolism Severity Index.

increases in RV pressure is the primary cause of death in massive PE and frequently occurs within the first few hours after presentation.[17] Massive PE is distinguished by the presence of hemodynamic instability defined by one of the following: cardiac arrest, persistent hypotension (systolic blood pressure [SBP] <90 mmHg, ≥40 mmHg decrease in SBP from baseline for >15 minutes and not due to other etiology), or obstructive shock (either SBP <90 mmHg or the need for vasoactive drug support to achieve SBP ≥90 mmHg, along with signs of end-organ ischemia [eg, oliguria, lactic acidosis, altered mental status]).[17] Moreover, in massive PE, especially with signs or symptoms of RV failure, there is an increased risk of early death that persists up to 30 days after initial presentation.[17] Hence, patients presenting with massive PE necessitate a more aggressive treatment plan as compared to less-severe forms of acute PE.

Submassive PE, associated with an intermediate-risk level of early mortality reported as high as 14%, is further subdivided into intermediate-high and intermediate-low subgroups.[18-20] In those with a confirmed PE but without hemodynamic instability (submassive), progressive RV dysfunction remains extant and requires a further assessment as a means of determining needed management strategies and risk levels.[17] It is important to highlight that a massive PE may not be limited only to central anatomic locations, but may be due to a high clot burden that is peripherally located (ie, subsegmental). In addition, in patients with significant preexisting cardiovascular disease, known history of chronic thromboembolic pulmonary hypertension, pulmonary hypertension from other causes, lower clot burdens may precipitate hemodynamic instability as well. Hence, the evaluation of patients with submassive PE should take into consideration signs of RV dysfunction, RV strain, and patients' cardiopulmonary reserve, emphasizing the upsurge in PERTs (Pulmonary Embolism Response Teams) to ensure adequate risk stratification and treatment pathways.

Treatment Modalities for Acute PE

The initial pharmacologic treatment of acute PE includes therapeutic anticoagulation using unfractionated heparin or subcutaneous low-molecular-weight heparin, followed by direct oral anticoagulants.[21] Massive PE and certain submassive PE subtypes (those with clinical deterioration causing worsening RV failure) traditionally have been treated with systemic thrombolysis (STT). However, major bleeding is one of the primary contraindications to using STT. The Pulmonary Embolism Thrombolysis (PEITHO) trial commonly is used to define hemodynamic collapse, moderate bleeding, and severe bleeding, as described in Table 2.[22-24] The rate of major bleeding (intracranial hemorrhage [ICH], extracranial bleeding needing transfusions and/or interventions) associated with STT has been estimated as high as 20%, with a 2%-to-3% risk of ICH.[25,26]

Predictors of bleeding include age, weight, gender, patients with end-organ damage, low hematocrit, previous ICH, and stroke.[27] Surgical pulmonary thrombectomy is an option for massive PE and submassive PE subtypes with a high risk for hemodynamic collapse, those who cannot receive STT, those unstable after STT administration, or have failed therapy, and in those with right-heart thrombus at risk for left-sided embolization.[28] Surgical pulmonary thrombectomy, while previously

Table 2
Definition of Bleeding and Risk Stratification[22,23,24]

Hemodynamic Collapse	Moderate Bleeding	Severe Bleeding
Initiation of CPR and/or Systolic blood pressure <90 mm Hg >15 minutes duration; and/or Systolic blood pressure drop >40 mmHg for >15 minutes; and/or Cold extremities or low urinary output <30 mL/h; and/or Need for vasopressors to maintain perfusion	Bleeding resulting in the requirement of a blood transfusion, but did not lead to hemodynamic compromise requiring fluid replacement, inotropic support, or interventional treatment.	Bleeding leading to hemodynamic compromise requiring fluid and/or blood products, inotropic support, or surgical treatment.

Abbreviation: CPR, cardiopulmonary resuscitation.

Table 3
Comparison of Systemic, Surgical, and Catheter-directed Therapies[29-31]

Therapy Type	Summary of Therapy	Indications / Contraindications
Systemic thrombolytic therapy	Unfractionated heparin, subcutaneous low-molecular-weight heparin, or fondaparinux.	Initial therapy in hemodynamically stable patients. Contraindicated in severe bleeding, signs or symptoms of bleeding, patients at risk of bleeding including intracranial hemorrhage.
Surgical embolectomy	Surgical exposure and removal of thrombus.	In cases of failure or contraindications to thrombolytic therapy, hemodynamic collapse, or those patients who cannot receive fibrinolysis. Contraindicated in patients unable to receive anticoagulation, poor surgical candidate, increased small clot burden.
Catheter-directed therapy	Thrombolytics directly into the affected pulmonary artery/arteries to deliver higher effective concentration of drug near the clot as opposed to delivering it systemically.	In cases of hemodynamic instability in which bleeding risk is elevated, and surgical embolectomy contraindicated. Contraindicated in facilities without capabilities, inaccessible to percutaneous placement of catheter.

thought to have been associated with high mortality, has been shown to have improved mortality due to advances in surgical technique and shorter durations of cardiopulmonary bypass.[28] See Table 3[29-31] for a description of current PE therapies. Limited utilization of surgical embolectomy has led to an interest in less-invasive yet effective therapies in reducing clot burden in the pulmonary circulation.

Catheter-directed interventions have become an alternative to STT as an evolving therapy for acute PE patients, while being able to mitigate the prohibitive bleeding risks with STT. The first catheter-based intervention to be approved in the United States was the Greenfield suction catheter (Medi-Tech/Boston Scientific, Watertown, MA), which utilized suction to aspirate thrombus from the pulmonary arteries.[32] It was, however, quick to fall out of common use due to the bulky nature of the catheter necessitating a venous cutdown for its use.

Acute Interventional PE Therapy: Mechanical Thrombectomy and Embolectomy

Interventional therapies for acute PE can be classified into two major groups:

A. Mechanical thrombectomy and/or embolectomy
   a. Direct thrombectomy
   b. Suction and/or aspiration embolectomy

B. Catheter-directed thrombolysis (CDT)
   a. Ultrasound-assisted catheters
   b. Nonultrasound-assisted catheters

Mechanical embolectomy refers to mechanical thrombus disruption using devices to reduce clot burden without the infusion of lytic medications. This can be accomplished by direct thrombectomy, suction embolectomy, and aspiration embolectomy. Mechanical embolectomy commonly is performed with the Amplatz thrombectomy device (Microvena, White Bear Lake, MN), which consists of a 6-Fr or 8-Fr catheter with a 1-cm long metallic capsule at its end. The capsule houses an impeller that is driven coaxially up to 150,000 rotations per minute by high air pressure (50-100 PSI). Negative pressure at the catheter tip draws adjacent thrombus into the end port of the capsule, where it becomes fragmented by the rotating blades. The fragmented thrombus then is expelled radially through two sideports, and cleaved particles repeatedly are aspirated, further macerating the thrombus. The thrombus is broken down into small particles, less than 13 μm in size.[33] Although characterized by good success rates in improving thrombus burden, the lack of adequate directionality made this a less popular option in the management of acute PE.[34]

Suction or aspiration embolectomy is accomplished by several different catheter systems:

A. Aspirex catheter (Straub Medical, Switzerland): Is an 11-Fr device that aspirates thrombus through a flexible catheter tip. The catheter shaft contains a high-speed rotating coil, which creates negative pressure for aspiration and also serves to macerate a clot that is brought into the catheter.[35]

B. Angiovac system (Angiodynamics Inc., Latham, NY): The Angiovac cannula is a 22-Fr nitinol-reinforced cannula with a length of 90 cm, an expandable funnel-shaped distal tip, and a variable angulation of the tip. The expanded funnel-shaped tip aids in the suction aspiration of a clot while being able to reinfuse suctioned blood after passing through a filter, serving as an extracorporeal bypass circuit. The disadvantages with the Angiovac apparatus include the large cannula size, hemodynamic perturbations from blood loss, the need for an extracorporeal circulation, and the risk of right-heart perforation due to the device's limited maneuverability.[36,37]

C. Penumbra Indigo System (Penumbra Inc., Alameda, CA)[38,39]: The Penumbra system is a suction aspirator device that has a proprietary "smart" catheter tubing system that can adjust the suction applied across the catheter to establish suction. Sista et al evaluated the Penumbra system in a multicenter single-arm study that enrolled 119 patients with acute submassive PE in the EXTRACT-PE study.[40] The primary safety endpoint was the rate of major adverse events (composite of device-related: death, major bleeding, and serious adverse events) at 48 hours. The authors found a mean reduction in the RV/left ventricle (LV) ratio of 0.43 between baseline and at 48 hours postintervention (95% confidence interval [CI]: 0.38-0.47; $p < 0.0001$).[40] Rates of cardiac injury, pulmonary vascular injury, clinical deterioration, major bleeding, and device-related death at 48 hours were 0%, 1.7%, 1.7%, 1.7%, and 0.8%, respectively.

D. Flowtriever system (Inari Medical, Irvine, CA)[41]: The Flowtriever system is a combined aspiration and mechanical thrombectomy device. It is comprised of a set of distal nitinol- mesh discs that are retracted after deployment distal to the clot, carrying with it an inherent advantage of being able to combine clot aspiration with mechanical removal. Newer iterations of this device with a longer catheter segment (up to 120 cm length) to clear distal clots also are made available by the manufacturer. The Flowtriever Pulmonary Embolectomy Clinical Study, a prospective, multicenter, single-arm study evaluating the Flowtriever system in 106 patients with acute PE and right-heart strain, demonstrated that a percutaneously introduced catheter used in patients with intermediate-risk PE had significant improvement in RV strain, with minimal bleeding complications. The primary outcome, a change in the RV/LV ratio at 48 hours postintervention, was 0.38 (25.1%; $p < 0.0001$); there were four patients (3.8%) who experienced six major adverse events (all judged as procedure-related and not device-related), one of which was major pulmonary bleeding deemed secondary to pulmonary infarction and reperfusion injury.[42]

E. Angiojet catheter (Boston Scientific, Marlborough, Massachusetts, USA): The Angiojet catheter is a 6-Fr rheolytic embolectomy device that utilizes the Bernoulli principle of enabling clot fragmentation and aspiration by using a high-velocity saline jet. The inherent advantage of this device is the ability of the Bernoulli effect to initiate thrombus fragmentation and aspiration with minimal vessel damage. Complications of the Angiojet system, such as instances of bradycardia, hypotension, and hemodynamic collapse, purported to be from the release of vasoactive mediators, have been reported, which led to the issue of a black box warning on the Angiojet systems.[43]

Acute Interventional PE Therapy: Catheter-Directed Thrombolysis (CDT)

CDT is a technique of directing thrombolytic agents directly to affected pulmonary arteries to deliver a higher effective concentration of the thrombolytic drug in close proximity to the thrombus as opposed to systemic drug delivery. The benefit of CDT is the enhanced local drug delivery at the target site, as a systemically administered drug could be maldistributed to unintended sites, such as the systemic circulation or the nondiseased pulmonary artery in cases of unilateral pulmonary emboli. See Table 4[44-49] for a description of various CDT modalities.

A. CDT without concomitant ultrasound: CDT without ultrasound is a technique that involves using a 4-to-5-Fr catheter, such as the Uni-Fuse (AngioDynamics Inc., Latham, NY) or Cragg-McNamara catheter (Medtronic, Minneapolis, MN), which are advanced within a pulmonary thrombus under fluoroscopic guidance. The thrombolytic drug is typically infused at a rate of 1-to-2 mg/hour over a period of 12-to-24 hours, and is monitored by serial coagulation testing during therapy. The drug dosing regimen and duration are variable among studies, and a clear consensus still is lacking at the present time.

B. Ultrasound-assisted catheter-directed thrombolysis (US-CDT): The EKOS system is an ultrasound-facilitated catheter and directed-fibrinolytic device approved in the United States for the treatment of PE in 2014.[35] The EKOS system consists of a 5.4-Fr dual-lumen infusion catheter with side-ports. The inner lumen emits a high-frequency, low-intensity ultrasound signal (US), while the outer lumen has a side channel for the infusion of thrombolytic agents. The ultrasound waves are purported to aid dissociation of fibrin strands, aiding better penetration of thrombolytic drugs.

Table 4
CDT Modalities, Subtypes, and Contraindications[44-49]

Subtype	Mechanism of Action
Mechanical embolectomy	Mechanical thrombus disruption using devices to reduce clot burden without an infusion of any lytic medications.
Rheolytic embolectomy	Employs the venturi effect in enabling clot fragmentation and aspiration using a saline jet directed at the thrombus.
Suction embolectomy	The catheter itself has an aspiration guide that can suction clots using negative pressure.
Aspiration embolectomy	An 8-Fr device with the flexibility for placement in segmental branches of the pulmonary arteries.
Catheter-directed thrombolysis	A technique of directing thrombolytics directly into the affected pulmonary artery/arteries as a means to deliver higher effective concentration of drug in close proximity to the clot as opposed to systemically delivering it.
Catheter-directed therapy without ultrasound	This technique involves using 4/5-Fr catheters, such as Uni-Fuse, that are advanced within a pulmonary thrombus under fluoroscopic guidance.
Ultrasound-assisted catheter-directed therapy	Ultrasound-assisted catheter-directed thrombolysis (EKOS) A 5.4-Fr dual-lumen infusion catheter with side holes. The inner lumen emits high-frequency, low-intensity ultrasound while the outer lumen has slits that can infuse lytic medication. The catheter has a lumen for infusion of saline to serve as the coolant fluid to prevent overheating of the catheter from ultrasound wave emanation.

Abbreviation: CDT, Catheter-directed thrombolysis.

The EKOS catheter also has a separate lumen for infusion of saline to serve as a coolant to prevent overheating of the catheter from US wave emanation.

There have been four completed prospective trials involving the EKOS catheter; the ULTIMA trial (The European-based Ultrasound Accelerated Thrombolysis of Pulmonary Embolism), the SEATTLE II trial (A Prospective, Single-arm, Multicenter Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism), the PERFECT trial (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) and the OPTALYSE trial (Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism), all of which demonstrated rapid improvement and restoration in RV function.[34,40,50,51]

The ULTIMA trial was a multicenter randomized controlled trial that enrolled 59 patients with submassive PE to heparin alone (n = 29) versus US-CDT (n = 30). The primary outcome, a change in the RV/LV ratio after 24 hours of therapy, was reduced in the ultrasound-assisted thrombolysis utilizing tPA (tissue plasminogen activator) (brand name Activase) group from 1.28 ± 0.19 to 0.99 ± 0.17 ($p < 0.001$), but not in the systemic heparin group (1.20 ± 0.14 to 1.17 ± 0.20, [$p = 0.31$]). At 90 days, bleeding events were not different between the heparin and US-CDT groups (three in the US-CDT group and one in the heparin group; $p = 0.61$). The ULTIMA trial reported three non-ICHs, defined as minor bleeds in the total study population.

The SEATTLE-II trial was a prospective, single-arm, multicenter trial that evaluated the efficacy of US-CDT using the EKOS system in 31 patients with massive PE and 119 patients with submassive PE using either 1 mg/h for 24 hours by a single catheter or 1 mg/h/catheter for 12 hours with bilateral catheters (both groups received 24 mg total tPA).[40] The primary outcome was a change in the RV/LV ratio from baseline to 48 hours, and the primary safety outcome was major bleeding within 72 hours of intervention. The trial found improved RV/LV ratios in all 150 patients (1.55 *v* 1.13; $p < 0.0001$), improved mean pulmonary artery systolic pressures (51.4 mmHg *v* 36.9 mmHg; $p < 0.0001$), and improved Miller index scores (22.5 *v* 15.8; $p < 0.0001$). The Miller index is composed of a score for arterial obstruction (objective score with three points for total occlusion and zero points for no occlusion) and a score for reduction of the peripheral perfusion of the lungs (subjective evaluation).[52] The modified Miller score adds scoring for the location of PE within the pulmonary artery, with one point for periphery vasculature and a maximal score of 16 for central vasculature (ie, saddle emboli). SEATTLE-II bleeding rates were lower than the previous PEITHO trial, reporting extracranial bleeding occurring in 32 patients (6.3%) in the Tenecteplase group; the SEATTLE-II had the upper boundary of the 95% CI on this estimate and was 2.4% for full-dose STT with a single serious bleeding event reported (groin hematoma associated with hypotension), along with 15 patients experiencing a moderate bleeding event; there were no ICHs.[22,53]

The PERFECT trial was a prospective, multicenter, international registry in which the investigators examined the efficacy of CDT versus mechanical thrombectomy for patients with massive PE (n = 28) and submassive (n = 73) PE. The primary outcome, described as 'clinical success,' included meeting the following three endpoints: (1) stabilized hemodynamics (SBP >90 mmHg without chemical support); (2) improved pulmonary hypertension (systolic pulmonary artery pressure < baseline at presentation), right heart strain (as determined by qualitative echocardiography), or both; and (3) survival to hospital discharge. The primary safety outcomes were procedure complications and major bleeding. All patients except one with submassive PE (who underwent mechanical thrombectomy) received CDT with a mixture of both non-US-CDT (64%) and US-CDT (36%). Clinical success was achieved in 86% (95% CI: 67.3%-96.0%) of patients with massive PE and

97% (95% CI: 90.5%-99.7%) of patients with submassive PE. Among those who underwent CDT, there were no reported major bleeding events and a 5.9% in-hospital mortality rate.[51]

The OPTALYSE trial was a small, randomized, multicenter trial that examined the efficacy of lower thrombolysis dosing during US-CDT in 101 patients with submassive PE compared to STT in patients with PE using the RV/LV ratio as a primary outcome.[50,54] Patients were randomized to one of four arms of varying tPA dosing: (1) 4 mg per lung/two hours; (2) 4 mg/lung/four hours; (3) 6 mg/lung/six hours; (4) 12 mg/lung/six hours. The trial found a significant 25% improvement in the RV/LV diameter ratio from baseline to 24 hours, as well as reduced clot burden as measured by the modified Miller score in all four arms when using lower doses (4-12 mg/lung) and with shorter infusion times of two-six hours).[55] The bleeding risk was noted to be about 4%, with two patients developing ICH in the trial group. Improvement in Miller scores also was seen in all groups. Additionally, of two ICH events, one was attributed to tPA delivered by US-CDT.[54] The trial had the drawback of not having a control group with heparin alone to compare these findings with a group that did not receive US-CDT. Notably, low-dose heparin (300-500 U/h) was continued during the treatment period with tPA via the US-CDT catheter.

In all four of the aforementioned trials, ULTIMA, SEATTLE II, PERFECT and OPTALYSE, there were no reported fatal ICHs, an improvement over the previous systemic therapy trials: PEITHO, MAPPET, MOPETT, and TOPCOAT (Table 5).[22,42,51,54,56-64] Only the SEATTLE II trial reported a complication of transfusion for extracranial bleeding.[40] All four of these studies were limited to a 90-day or fewer outcome period, and none of these trials provided clear data on long-term outcomes of CDT compared to STT in these outcome periods.

Recent and Ongoing CDT Trials

Much of the current PE-related therapeutic investigations, particularly those involving CDTs, are focused on submassive PE therapies. In contrast to massive acute PE (mortality of >50% without intervention), as well as low-risk PE scenarios that also require anticoagulation, patients with submassive PE present a gray area with enough clinical equipoise in terms of enabling the study as to what the optimal intervention is in this context. Avgerinos et al recently published their SUN-SET sPE (Standard versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism) trial findings, which was one of the first trials to directly compare US-CDT against conventional CDT in patients with acute submassive (intermediate-risk) PE. In a multicenter, randomized, single-blinded trial, 81 patients were compared in a parallel head-to-head design, with the primary outcome being computed tomography angiography-determined thrombus load reduction (modified Miller score) at 48 hours, and key secondary outcomes included the RV/LV ratio, major and minor bleeding, and adverse events up to 90 days.[65] Although the dose and duration of therapy were left to the clinicians' discretion, the mean total tPA dose (19 ± 7 mg for US-CDT *v* 18 ± 7 mg for CDT [p = 0.53]), and the duration of therapy (14 ± six hours for US-CDT and 14 ± five hours for CDT [p = 0.99]) were similar. The mean reduction in the thrombus score was 31 ± 4 at baseline to 22 ± 7 (p < 0.001) in the US-CDT group *v* 33 ± 4 to 23 ± 7 (p < 0.001) in the CDT group, and the difference between the groups was not significant (p = 0.76). The mean difference in the RV/LV ratio from baseline to 48 hours was superior in the US-CDT group (1.54 ± 0.3 to 0.37 ± 0.34 US-CDT group *v* 1.69 ± 0.44 to 0.59 ± 0.42 CDT group [p = 0.01]) in the CDT group. Major bleeding was reported in two patients who were both in the US-CDT arm (one patient with hemorrhagic stroke, a second patient with both epistaxis and vaginal bleeding requiring transfusion); relatively higher tPA doses were used in both of these patients (~28 mg total). In the context of submassive PEs, as compared to a bleeding rate of more than 11% in STT groups as reported in the PEITHO trial, the SUN-SET sPE trial bleeding rate of 2.5% supported CDT therapies as being associated with an overall lower bleeding risk.[22] One in-hospital death occurred on day 58 in a patient in the US-CDT arm attributed to hypersensitivity pneumonitis.[65] Criticisms of SUN-SET sPE include a lack of protocol standardization concerning confounders affecting the primary outcome and its relatively small sample size and attendant low study power.[66]

Various trials assessing CDT use in acute PE currently are underway that address prior trials' lack of randomization, lack of specific and meaningful clinical endpoints (eg, long-term cardiopulmonary health as measured by a six-minute walk distance or development of CTEPH), as well as risk-benefit ratios.[67] Completed in September 2020, the KNOCOUT-PE (An International Pulmonary Embolism Registry Using EKOS) trial included 1,500 subjects from 80 study locations to examine both retrospective data (those who had received US-CDT for PE) and prospective data (de novo patients with PE who ultimately received US-CDT as part of their therapy), in which the EKOS system was chosen as the modality to treat both submassive and massive PE. KNOCOUT-PE included a variety of primary outcome measures; in part, RV/LV ratio change at 24 and 48 hours, persistent pulmonary hypertension at three months, other urgent interventions for index PE following US-CDT, the need for US-CDT as an adjunct, serious adverse events (eg, major bleeding), all-cause mortality, and various quality-of-life assessments. KNOCOUT-PE findings still are pending.[68]

The USAT-CDT (Standard versus Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism) trial completed its enrollment in December 2020, which included 18 patients in a randomized, controlled, parallel design to compare US-CDT versus non–US-CDT in acute submassive PE patients. USAT-CDT's primary outcome was a reduction in thrombus as determined by a computed tomography angiography from baseline to 72 hours, along with 17 various secondary outcomes (ie, early and late mortality, major and minor bleeding, RV/LV ratios, echocardiographic markers of RV dysfunction, six-minute walk tests at three and six months, cost analyses, and various quality-of-life assessments). Results still are pending for USAT-CDT.[69]

Table 5
Acute PE Trials

Name of Trial	Year	Design	Primary Outcome	Findings	Summary
PEITHO [59] (Pulmonary Embolism Thrombolysis)	2014	MCT, DB, N = 1005, ITT	All-cause mortality or hemodynamic decompensation at seven days.	Tenecteplase is associated with increased extracranial bleeding at seven days (6.4% *v* 1.2%; p < 0.001 NNH 20) and stroke (2.4% *v* 0.2% with NNH 45).	Patients with submassive PE treated with UFH; does Tenecteplase reduce primary outcome compared to placebo; results were Tenecteplase is associated with increased rate of bleeding.
MAPPET-3[60]	2002	Single-center, unblinded, N = 121, unknown	Pulmonary HTN, recurrent PE	pHTN 16% *v* 63% (p < 0.001, NNT2) or recurrent PE 0% *v* 5% p = 0.08	Low-dose tPA with anticoagulation reduced the incidence of pHTN and recurrent PE in a specific cohort of patients.
MOPETT[57] (Moderate Pulmonary Embolism Treated with Thrombolysis)	2013	Single-center, unblinded, non-placebo, N = 121	pHTN incidence	pHTN 16% *v* 63% (p < 0.001, NNT2) or recurrent PE 0% *v* 5% p = 0.08	Low dose tPA with anticoagulation reduced incidence of pHTN and recurrent PE in specific cohort of patients
TOPCOAT[58]	2014	Randomized, single weight-based bolus of Tenecteplase or placebo, double-blinded fashion	Death, circulatory shock, intubation, or major bleeding within five days or (ii) recurrent PE, poor functional capacity (RV dysfunction with either dyspnea at rest or exercise intolerance) or an SF36(®) Physical Component Summary (PCS) score <30 at 90-day follow-up.	Sixteen (37%) placebo-treated and six (15%) Tenecteplase-treated patients had at least one adverse outcome (exact two-sided p = 0.017).	Tenecteplase associated with adverse outcome.
OPTALYSE[54] (Optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk PE)	2018	MCT, parallel-group, N = 100	Optimal tPA dose for US-CDT of acute intermediate-risk PE for a reduction in the RV-LV diameter ratio.	Arm one (4 mg/lung/two hours), 0.40 (24%; p = 0.0001); arm two (4 mg/lung/four hours), 0.35 (22.6%; p = 0.0001); arm three (6 mg/lung/six hours), 0.42 (26.3%; p = 0.0001); and arm four (12 mg/lung/six hours), 0.48 (25.5%; p = 0.0001).	US-CDT with shorter delivery duration and lower dose tPA demonstrated improved with RV function and reduced clot burden.
BETULA[56] (Low dose CDT for acute PE)	2020	Ongoing, single-center, outcome-blinded, randomized, parallel group	Improvement in the RV-LV ratio	Pending	Sixty patients with acute intermediary high-risk PE randomized 1:1 to UFH or CDT.
FLARE[42] (Flowtriever Pulmonary Embolectomy Clinical Study) study	2016	Ongoing, Prospective, multicenter, single-arm study	Flowtriever system in 106 patients with acute PE and right heart strain.	Pending	Evaluate the safety and effectiveness of the Flowtriever System for use in the removal of emboli from the pulmonary arteries in the treatment of patients with acute pulmonary embolism.
EXTRACT-PE[61] (Evaluating the Safety	2017	Ongoing, multicenter, randomized	Change in the RV/LV ratio per CTA.	Pending	

(*continued*)

Table 5 (*continued*)

Name of Trial	Year	Design	Primary Outcome	Findings	Summary
and Efficacy of the Indigo Aspiration System in Acute *Pulmonary Embolism*) Trial					Indigo aspiration system in patients with submassive PE.
SUNSET-PE[62] (Standard vs ultrasound-assisted catheter thrombolysis for submassive PE)	2016	Ongoing, randomized, parallel-design	Compare standard CDT to USAT for the treatment of patients with acute submassive PE.	Interim results: The mean RV/LV ratio was reduced from 1.59 ± 0.29 at baseline to 1.11 ± 0.23 within 48 hours. One (2.2%) major (hemorrhagic stroke) with no neurologic deficits by discharge and 2 (4.4%). At 30 and 90 days, there were no deaths and no recurrent venous thromboembolism.	Subjects will be randomized to, either standard CDT or USAT.
USAT-CDT[63] (Standard vs Ultrasound-assisted Catheter Thrombolysis for Submassive Pulmonary Embolism)	2016	Ongoing, randomized, controlled study.	To see if USAT adds any benefit in the outcomes and costs of CDT s for patients with acute submassive PE.	Pending	Compare standard CDT to USAT for the treatment of acute submassive (PE).
KNOCOUT PE[64] (International Pulmonary Embolism Registry Using EKOS)	2018	Retrospective data and prospective data where an EKOS device has been chosen as the modality to treat submassive and massive PE.	Change in the ratio of the measurement of the right ventricular to left ventricular diameters (RV/LV) as measured by echocardiogram or CTA persistence of pulmonary hypertension defined as mean pulmonary artery pressure greater than 25 mmHg by echocardiogram (three months).	Pending	Understand acoustic pulse thrombolysis (APT) treatment regimens used as standard of care globally for pulmonary embolism. The registry will include individuals who have already received the APT treatment and those that will undergo APT treatment
PERFECT[51] (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis)	2010	Prospective observational	Capture high-quality patient safety and effectiveness data on CDT use for acute PE. The goal will be achieved by capturing a concise set of immediate and short-term functional and clinical outcome data for PE patients undergoing CDT.	High-risk (n = 28) and intermediate-risk (n = 73) patients utilizing registry data. Non–US-CDT (64%) and ultrasound-assisted thrombolysis (USAT) (36%). Among those who underwent CDT, there were no reported major bleeding events and a 5.9% in-hospital mortality rate.	CDT versus mechanical thrombectomy for high-risk (n = 28) and intermediate-risk (n = 73) patients utilizing registry data.

Abbreviations: CDT, catheter-directed thrombolysis; CT, computed tomography; CTPA, computed tomographic pulmonary arteriography; DB, double-blinded; LV, left ventricular; MCT, multicenter trial; PAP, pulmonary artery pressure; pHTN, pulmonary hypertension; PE, pulmonary embolism; rtPA, recombinant tissue plasminogen activator; tPA, tissue plasminogen activator; UFH, unfractionated heparin; US, ultrasonography; US-CDT, ultrasound-directed catheter directed thrombolysis; USAT, ultrasound-accelerated thrombolysis.

Current Societal Guidelines

See Table 6[6,17,70,71] for the current societal recommendations on the use of CDTs in the context of acute PE. Of note, the most current of these guidelines came from the European Society of Cardiology, published in 2019. As this present review has in part highlighted, a significant amount of new research has emerged addressing CDT use in PE; hence, even the most currently published PE-related guidelines lag and have yet to assimilate the most recent data into their respective

Table 6
Society and/or Organization and Most Recent Year of Publication for Catheter-Directed Therapy Recommendations in Acute PE

Acute PE Subtype	2016 ACCP[70]	2011 AHA[6]	2019 ESC[17]	2019 PERT Consortium[71]
Intermediate- or Intermediate-high risk	If hypotension is present and: (a) the patient is a high-bleeding risk; (b) the patient has failed STT; or (c) patient death is likely before STT effects (hours), catheter-assisted thrombus extraction is suggested *with or without catheter-directed thrombolysis.*	No recommendation given regarding catheter-directed thrombolysis.	Consider catheter-directed treatment in those patients with hemodynamic deterioration already receiving anticoagulation therapy. (Class IIa recommendation/LOE C)	*Consider catheter-directed thrombolysis* if: (1) The risk of clinical deterioration based on hemodynamics, degree of RV dysfunction, end-organ ischemia, gas exchange. (2) No absolute contraindications to STT.
High-risk	See above.	No recommendation given regarding catheter-directed thrombolysis.	(a) Catheter therapies should be considered when STT is contraindicated or has failed. (Class IIa recommendation/LOE C) (b) Catheter therapies may be used in conjunction with ECMO in those with refractory circulatory collapse or cardiac arrest. (Class IIa recommendation/LOE C)	*Consider catheter-directed thrombolysis* if relative contraindications to STT.

Abbreviations: ACCP, American College of Chest Physicians; AHA, American Heart Association; ECMO, extracorporeal membrane oxygenation; ESC, European Society of Cardiology; LOE, level of evidence; PE, pulmonary embolism; PERT, Pulmonary Embolism Response Team; RV, right ventricle; STT, systemic thrombolysis.

advanced PE treatment recommendations. Moreover, significant variation and ambiguity exist between the varying societal guidelines, in part due to insufficient robust clinical trials examining key clinical endpoints as related to catheter-based therapies.

Improving Acute PE Management by a Team Approach

Current societal guidelines recommend STT in addition to anticoagulation, but there is no single unified guideline or specific accepted set of guidelines for the treatment of submassive PE, and there is no expert consensus on the role of endovascular therapy in these clinical situations. This ambiguity has led to hospitals creating PERTs responsible for the identification and risk stratification of patients presenting with PE.[72,73] Although the exact constituents of PERTs vary, the ultimate goal is to have an expert multidisciplinary team able to rapidly evaluate patients with PE for medical, surgical, and endovascular therapies. Several recent studies analyzing the efficacy of PERTs have shown significant increases in the utilization of STT and CDTs in massive PE, a decrease in the ICU length of stay time, and a decrease in the elapsed time from diagnosis to therapeutic anticoagulation following the creation of a PERT, without a change in major bleeding or overall cost.[25,54,73-77] PERTs also demonstrated a significant decrease in 30-day inpatient mortality when compared to hospitals without such teams (8.5% *v* 4.7%, p = 0.03).[74-76] Many hospitals do not have the comprehensive surgical or endovascular facilities to implement the therapy indicated by a PERT compared to technically simpler STT and anticoagulation.[78] Due to system limitations, many facilities elect to use a bridging therapy to transfer patients with acute PE to a referral center with capabilities of CDT and or surgical thrombectomy.

Role of Venoarterial Extracorporeal Membrane Oxygenation (VA ECMO) in the Management of Acute PE

Extracorporeal membrane oxygenation (ECMO) has been used as a bridging therapy between failed STT and the need for advanced intervention.[79] By using ECMO, the RV can recover while the patient is transferred or prepared for definitive therapy, such as CDT or surgical embolectomy. Venoarterial (VA) ECMO used in the context of acute PE provides hemodynamic support, oxygenation, and is a temporizing means during the treatment of the underlying clot burden in parallel with RV function recovery. Nonetheless, and in part due to a lack of controlled trials, the 2019 European Society of Cardiology guidelines give VA ECMO use in acute PE a low-grade (IIb, level of evidence C) recommendation and should be considered for select high-risk, hemodynamically unstable, or arrest patients with PE.[17] Similarly, in the 2011 American Heart Association PE management guideline paper, ECMO was not recommended; however, as part of the 2020 American Heart Association 'Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,' ECMO use was given a '2b' recommendation and stated that although there is evidence lacking for the routine use of ECMO-assisted cardiopulmonary resuscitation, its use should be considered for select cardiac arrest patients, especially if for reversible causes requiring limited durations of mechanical support.[80] A recent

systematic review of VA ECMO for cardiac arrest due to massive PE that included 301 patients from 77 publications reported that the use of VA ECMO led to improved outcomes, with an overall survival rate of 61%; however, no descriptions of the combined use of VA ECMO with CDT were noted in the cohort.[81] A second contemporary systematic review of ECMO use in high-risk PE scenarios (associated cardiac arrest or obstructive shock) included 635 patients from 21 studies in whom a variety of reperfusion strategies were used, including 30 (7.2%) patients treated with concurrent CDT and 20 (4.8%) patients treated with US-CDT. Although the total pooled estimate for the primary outcome (all-cause death) was 41.1% (95% CI: 27.7%-54.5%), with no significant association among the varying reperfusion strategies ($p = 0.061$), there were no specific subgroup analyses for the catheter-therapy groups.[82] The role of the combined use of CDT with VA ECMO is a promising therapeutic option. However, there is a paucity of investigation into this tandem therapeutic option for PE management, with only limited information from case series and reports.

The recent reported case series involving the combined use of VA ECMO and CDT by Tran et al involved a single-center series of 49 patients, all cannulated for massive PE, in which six (12%) patients were treated with US-CDT using the EKOS system.[83] Their primary outcome was in-hospital death and 90-day survival. Among the six patients in their ECMO + CDT cohort, the median ICU length of stay was six days (interquartile range five-six), the hospital length of stay was nine days (interquartile range seven-11), and all patients survived to hospital discharge.[83] In a similar series, a single-center report from George et al on 32 patients with similar baseline characteristics placed on VA ECMO for massive PE over a three-year period noted 21 patients (66%) survived to decannulation and 17 (53%) survived to hospital discharge.[84] Eleven of 15 patients in their series who received CDT using the EKOS system survived to discharge, in contrast to all five patients in the systemic thrombolysis group who died. ECMO was utilized beforehand in the CDT group, in contrast to those receiving systemic thrombolytics who had ECMO initiation afterwards. Overall, the only baseline feature associated with nonsurvivors was a history of malignancy ($p = 0.038$). A pre-ECMO lactate level of ≤ 6 mmol/L had the greatest combined sensitivity (76.2%) and specificity (100%) for predicting the ability to successfully wean from ECMO and survive to discharge (sensitivity = 82.4% and specificity = 84.6%).[84]

In a 2019 single-center case series, Al-Bawardy et al reported on 13 patients undergoing VA ECMO for massive acute PE.[79] All 13 patients were in cardiac arrest upon presentation or had an in-hospital arrest prior to ECMO institution. Three patients (23%) received CDT therapy with the EKOS system, eight received systemic thrombolysis, one patient received both systemic thrombolysis and CDT, and four patients ultimately underwent surgical embolectomy (none of whom were in the CDT group). For the entire cohort, 30-day mortality was 31% and one-year mortality 54%. In a single case report, combined VA ECMO and CDT were utilized in a 27-year-old pregnant patient at 31 weeks' gestation with pre-existing CTEPH presenting with RV failure secondary to an acute massive PE.[85] Urgent cesarean section was performed under general anesthesia with only vasoactive drug support. Immediately after delivery, the patient's hemodynamic status deteriorated, and VA ECMO support was instituted, followed by CDT and localized suction embolectomy. The patient was separated successfully from ECMO on day four and was discharged from the ICU on day 23.[85]

In select PE scenarios, the use of VA ECMO and CDT in combination appears to be beneficial in terms of providing needed circulatory support while simultaneously treating the underlying pathophysiology.[86] Based on the available series and reports, these combined interventions appear safe, are associated with few complications, and may enable an optimal means with which to enable RV recovery after massive PE. However, until further investigation occurs on the use of this combined modality, it remains unclear in exactly which patients and in which PE scenarios that combined ECMO and CDT therapies should be the treatment of choice.

Summary

There has been tremendous research into the pathophysiology of acute PE, including risk stratification and treatment modalities. Early intervention of acute PE with classical STTs is not always feasible or possible. STT, nonetheless, remains the mainstay of therapy given its rapid effect on clot burden if decompensation, patient hemodynamics, or bleeding risk allows. Catheter-directed interventions (mechanical embolectomy and CDT) or surgical embolectomy are options in patients with a high bleeding risk. These interventions require a multidisciplinary approach (ie, PERTs) to identify appropriate patients, risk-stratify these patients, and provide appropriate therapies to these patients. PERTs facilitate the careful assessment of factors that elevate the risk of decompensation, including signs of reduced organ perfusion, severe RV strain and dysfunction, and respiratory insufficiency. In patients without the above signs of hemodynamic deterioration or RV strain, there is no clear consensus for the use of catheter-directed interventions such as CDT. CDT has distinct advantages; however, it can be expensive, time-consuming, and the response to therapy is often nonuniform among stratified patient cohorts.

In patients with submassive PE with clinical deterioration and signs of RV strain with elevated bleeding risk, CDT may be considered.[13] Given the wide spectrum of catheter-therapy devices, the various mechanisms of action, and clinical indications, the decision to use advanced therapies must be decided on a case-by-case basis.[87] PERTs may serve as the platform in weighing the risk of endothelial injury, hemolysis, major and minor bleeding, intracranial hemorrhage, and inherent procedural risk. Though CDT usage has increased, the EKOS system remains the only United States-approved device for the treatment of acute PE. Robust, high-powered, prospective random controlled trials are needed to prove a benefit in submassive PE, and the results of current trials and studies are anticipated to aid in further treatment guidance. Study

outcomes are needed that transcend the analysis of initial RV/LV dimension improvements to also include insight into various long-term clinical outcomes (six-minute walk test, mortality at 30, 90, 365 days) and whether the risks associated with a given treatment modality outweigh the potential benefit. It is imperative that CDT be considered with sound clinical judgment and risk stratification in equal stance to classic interventions.

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Conflict of Interest

The authors have no conflict of interest or financial involvement with this manuscript.

References

1 Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2011 update: A report from the American Heart Association. Circulation 2011;123:e18–e209.
2 Lamba M, Pickering J, Than M, et al. Long-term outcomes in patients with pulmonary embolism: Results from a longitudinal cohort study. Intern Med J 2021;51:699–704.
3 Ranka S, Mohananey D, Agarwal N, et al. Chronic thromboembolic pulmonary hypertension-management strategies and outcomes. J Cardiothorac Vasc Anesth 2020;34:2513–23.
4 Tapson VF, Humbert M. Incidence and prevalence of chronic thromboembolic pulmonary hypertension: From acute to chronic pulmonary embolism. Proc Am Thorac Soc 2006;3:564–7.
5 Rali P, O'Corragain O, Oresanya L, et al. Incidence of venous thromboembolism in coronavirus disease 2019: An experience from a single large academic center. J Vasc Surg Venous Lymphat Disord 2021;9:585–91.
6 Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. Circulation 2011;123:1788–830.
7 Anderson FA, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: The Worcester DVT Study. Arch Intern Med 1991;151:933–8.
8 Widimský J, Malý J, Eliáš P. Doporučení pro diagnostiku a léčbu akutní plicní embolie. Vnitř Lék 2008;54;1S25-21S72.
9 Belohlavek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol 2013;18:129–38.
10 Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: An analysis using multiple-cause mortality data. Arch Intern Med 2003;163:1711–7.
11 Iaccarino A, Frati G, Schirone L, et al. Surgical embolectomy for acute massive pulmonary embolism: State of the art. J Thorac Dis 2018;10:5154–61.
12 Lilienfeld DE, Godbold JH, Burke GL, et al. Hospitalization and case fatality for pulmonary embolism in the twin cities: 1979–1984. Am Heart J 1990;120(2):392–5.
13 Giri J, Sista AK, Weinberg I, et al. 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(20):e774–801.
14 Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up: JACC State-Of-The-Art Review. J Am Coll Cardiol 2020;75:2950–73.
15 Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019;54(3).
16 Barrios D, Rosa-Salazar V, Morillo R, et al. Prognostic significance of right heart thrombi in patients with acute symptomatic pulmonary embolism: Systematic review and meta-analysis. Chest 2017;151(2):409–16.
17 Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543–603.
18 Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: Initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). J Am Coll Cardiol 2011;57:700–6.
19 Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: Results of a multicenter registry. Circulation 1997;96:882–8.
20 Jimenez D, de Miguel-Diez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism: Analysis from the RIETE registry. J Am Coll Cardiol 2016;67:162–70.
21 Righini M, Le Gal G, Aujesky D, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: A randomised non-inferiority trial. Lancet 2008;371:1343–52.
22 Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402–11.
23 Steering C. Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Am Heart J 2012;163:33–8.
24 Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the S, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
25 Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: A meta-analysis. JAMA 2014;311:2414–21.
26 de Winter MA, Vlachojannis GJ, Ruigrok D, et al. Rationale for catheter-based therapies in acute pulmonary embolism. Eur Heart J Suppl 2019;21:I16–22.
27 Klok FA, Kooiman J, Huisman MV, et al. Predicting anticoagulant-related bleeding in patients with venous thromboembolism: A clinically oriented review. Eur Respir J 2015;45:201–10.
28 Yavuz S, Toktas F, Goncu T, et al. Surgical embolectomy for acute massive pulmonary embolism. Int J Clin Exp Med 2014;7:5362.
29 Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: A systematic review and meta-analysis. Eur Heart J 2015;36:605–14.
30 Martinez Licha CR, McCurdy CM, Maldonado SM, et al. Current management of acute pulmonary embolism. Ann Thorac Cardiovasc Surg 2020;26:65–71.
31 Taslakian B, Sista AK. Catheter-directed therapy for pulmonary embolism: Patient selection and technical considerations. Interv Cardiol Clin 2018;7:81–90.
32 Greenfield LJ, Kimmell GO, McCurdy WC 3rd. Transvenous removal of pulmonary emboli by vacuum-cup catheter technique. J Surg Res 1969;9:347–52.
33 Gandini R, Maspes F, Sodani G, et al. Percutaneous ilio-caval thrombectomy with the Amplatz device: Preliminary results. Eur Radiol 1999;9:951–8.

34 Tafur AJ, Shamoun FE, Patel SI, et al. Catheter-directed treatment of pulmonary embolism: A systematic review and meta-analysis of modern literature. Clin Appl Thromb Hemost 2017;23:821–9.
35 Dumantepe M, Teymen B, Akturk U, et al. Efficacy of rotational thrombectomy on the mortality of patients with massive and submassive pulmonary embolism. J Card Surg 2015;30:324–32.
36 Al-Hakim R, Park J, Bansal A, et al. Early experience with angiovac aspiration in the pulmonary arteries. J Vasc Interv Radiol 2016;27:730–4.
37 Worku B, Salemi A, D'Ayala MD, et al. The AngioVac device: Understanding the failures on the road to success. Innovations (Phila) 2016;11:430–3.
38 Farhat-Sabet AA, Tolaymat B, Voit A, et al. Successful treatment of acute limb ischemia secondary to iatrogenic distal embolization using catheter directed aspiration thrombectomy. Front Surg 2020;7:22.
39 Inc P. Accessed. https://www.penumbrainc.com/peripheral-device/indigo-system/; July 10, 2021. Accessed.
40 Piazza G, Hohlfelder B, Jaff MR, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. JACC Cardiovasc Interv 2015;8(10):1382–92.
41 Medical I. Inari Medical. Available at: https://www.inarimedical.com/; Accessed July 10, 2021.
42 Tu T, Toma C, Tapson VF, et al. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: The FLARE study. JACC Cardiovasc Interv 2019;12:859–69.
43 Lin PH, Okada T, Steinberg JL, et al. Rheolytic pharmacomechanical thrombectomy in experimental chronic deep vein thrombosis: Effect of L-arginine on thrombogenicity and endothelial vasomotor function. World J Surg 2007;31:664–75.
44 Piazza G. Advanced management of intermediate- and high-risk pulmonary embolism: JACC focus seminar. J Am Coll Cardiol 2020;76:2117–27.
45 Ferrigno L, Bloch R, Threlkeld J, et al. Management of pulmonary embolism with rheolytic thrombectomy. Can Respir J 2011;18:e52–8.
46 Chopard R, Ecarnot F, Meneveau N. Catheter-directed therapy for acute pulmonary embolism: Navigating gaps in the evidence. Eur Heart J Suppl 2019;21:I23–30.
47 Heberlein WE, Meek ME, Saleh O, et al. New generation aspiration catheter: Feasibility in the treatment of pulmonary embolism. World J Radiol 2013;5:430–5.
48 Furfaro D, Stephens RS, Streiff MB, et al. Catheter-directed thrombolysis for intermediate-risk pulmonary embolism. Ann Am Thorac Soc 2018;15:134–44.
49 Pei DT, Liu J, Yaqoob M, et al. Meta-analysis of catheter directed ultrasound-assisted thrombolysis in pulmonary embolism. Am J Cardiol 2019;124:1470–7.
50 Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479–86.
51 Kuo WT, Banerjee A, Kim PS, et al. Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial results from a prospective multicenter registry. Chest 2015;148:667–73.
52 Miller GA, Sutton GC, Kerr IH, et al. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. Br Heart J 1971;33:616.
53 Sista AK, Kearon C. Catheter-directed thrombolysis for pulmonary embolism: Where do we stand? JACC Cardiovasc Interv 2015;8:1393–5.
54 Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: The OPTALYSE PE trial. JACC Cardiovasc Interv 2018;11:1401–10.
55 Bankier AA, Janata K, Fleischmann D, et al. Severity assessment of acute pulmonary embolism with spiral CT: Evaluation of two modified angiographic scores and comparison with clinical data. J Thorac Imaging 1997;12:150–8.
56 Zuo Z, Yue J, Dong BR, et al. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev 2021;4:CD004437.
57 Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013;111:273–7.
58 Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: Multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost 2014;12:459–68.
59 Barco S, Russo M, Vicaut E, et al. Incomplete echocardiographic recovery at 6 months predicts long-term sequelae after intermediate-risk pulmonary embolism. A post-hoc analysis of the Pulmonary Embolism Thrombolysis (PEITHO) trial. Clin Res Cardiol 2019;108:772–8.
60 Meyer M, Fink C, Roeger S, et al. Benefit of combining quantitative cardiac CT parameters with troponin I for predicting right ventricular dysfunction and adverse clinical events in patients with acute pulmonary embolism. Eur J Radiol 2012;81:3294–9.
61 Sista AK, Horowitz JM, Tapson VF, et al. Indigo aspiration system for treatment of pulmonary embolism: Results of the EXTRACT-PE Trial. JACC Cardiovasc Interv 2021;14:319–29.
62 Avgerinos ED, Mohapatra A, Rivera-Lebron B, et al. Design and rationale of a randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism. J Vasc Surg Venous Lymphat Disord 2018;6:126–32.
63 Engelberger RP, Stuck A, Spirk D, et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis: 1-year follow-up data of a randomized-controlled trial. J Thromb Haemost 2017;15:1351–60.
64 Piazza G, Sterling KM, Tapson VF, et al. One-year echocardiographic, functional, and quality of life outcomes after ultrasound-facilitated catheter-based fibrinolysis for pulmonary embolism. Circ Cardiovasc Interv 2020;13:e009012.
65 Avgerinos ED, Jaber W, Lacomis J, et al. Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: The SUNSET sPE trial. JACC Cardiovasc Interv 2021;14:1364–73.
66 Sista AK. Is it Time to sunset ultrasound-assisted catheter-directed thrombolysis for submassive PE? JACC Cardiovasc Interv 2021;14:1374–5.
67 Aggarwal V, Giri J, Nallamothu BK. Catheter-based therapies in acute pulmonary embolism: The good, the bad, and the ugly. Circ Cardiovasc Interv 2020;13:e009353.
68 Corporation E. Retrospective and prospective international EkoSonic® registry of the treatment and clinical OUTcomes of patients with pulmonary embolism 2020.
69 Standard vs Ultrasound-assisted Catheter Thrombolysis for Submassive Pulmonary Embolism. ClinicalTrials.gov indentifer: NCT03086317. Available at; https://clinicaltrials.gov/ct2/show/NCT03086317. Accessed July 17, 2021.
70 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315–52.
71 Rivera-Lebron B, McDaniel M, Ahrar K, et al. Diagnosis, treatment and follow up of acute pulmonary embolism: Consensus practice from the PERT consortium. Clin Appl Thromb Hemost 2019;25:1076029619853037.
72 Barnes GD, Kabrhel C, Courtney DM, et al. Diversity in the pulmonary embolism response team model: An organizational survey of the national PERT consortium members. Chest 2016;150:1414–7.
73 Romano KR, Cory JM, Ronco JJ, et al. Vancouver General Hospital Pulmonary Embolism Response Team (VGH PERT): Initial three-year experience. Can J Anaesth 2020;67:1806–13.
74 Xenos ES, Davis GA, He Q, et al. The implementation of a pulmonary embolism response team in the management of intermediate- or high-risk pulmonary embolism. J Vasc Surg Venous Lymphat Disord 2019;7:493–500.
75 Rosovsky R, Chang Y, Rosenfield K, et al. Changes in treatment and outcomes after creation of a pulmonary embolism response team (PERT), a 10-year analysis. J Thromb Thrombolysis 2019;47:31–40.

76 Jen WY, Kristanto W, Teo L, et al. Assessing the impact of a pulmonary embolism response team and treatment protocol on patients presenting with acute pulmonary embolism. Heart Lung Circ 2020;29:345–53.
77 Chaudhury P, Gadre SK, Schneider E, et al. Impact of multidisciplinary pulmonary embolism response team availability on management and outcomes. Am J Cardiol 2019;124:1465–9.
78 Meneveau N. Unmet needs in the management of pulmonary embolism: Catheter-directed therapy looks set to fill the void. Eur Heart J Suppl 2019;21:I14–5.
79 Al-Bawardy R, Rosenfield K, Borges J, et al. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: A case series and review of the literature. Perfusion 2019;34:22–8.
80 Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: Adult basic and advanced life support: 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020;142:S366–468.
81 Scott JH, Gordon M, Vender R, et al. Venoarterial extracorporeal membrane oxygenation in massive pulmonary embolism-related cardiac arrest: A systematic review. Crit Care Med 2021;49:760–9.
82 Baldetti L, Beneduce A, Cianfanelli L, et al. Use of extracorporeal membrane oxygenation in high-risk acute pulmonary embolism: A systematic review and meta-analysis. Artif Organs 2021;45:569–76.
83 Tran D, Hays N, Shah A, et al. Ultrasound-assisted catheter directed thrombolysis for pulmonary embolus during extracorporeal membrane oxygenation. J Card Surg 2021;36:2685–91.
84 George B, Parazino M, Omar HR, et al. A retrospective comparison of survivors and non-survivors of massive pulmonary embolism receiving veno-arterial extracorporeal membrane oxygenation support. Resuscitation 2018;122:1–5.
85 Weinberg L, Kay C, Liskaser F, et al. Successful treatment of peripartum massive pulmonary embolism with extracorporeal membrane oxygenation and catheter-directed pulmonary thrombolytic therapy. Anaesth Intensive Care 2011;39:486–91.
86 Guliani S, Das Gupta J, Osofsky R, et al. Venoarterial extracorporeal membrane oxygenation is an effective management strategy for massive pulmonary embolism patients. J Vasc Surg Venous Lymphat Disord 2021;9:307–14.
87 Reza N, Dudzinski DM. Pulmonary embolism response teams. Curr Treat Options Cardiovasc Med 2015;17:387.