When should we involve interventional radiology in the management of acute pulmonary embolism?

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Shareable abstract (@ERSpublications)
In patients with high-risk PE with risk of bleeding, active bleeding or when systemic thrombolysis fails, percutaneous catheter-directed therapy (CDT) should be considered. Ongoing trials will analyse role of CDT in acute intermediate–high-risk PE. https://bit.ly/3JIc0mA

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Abstract

Pulmonary embolism (PE) is a common disease associated with high morbidity and mortality. Currently, guidelines recommend systemic thrombolysis in patients with haemodynamic instability (high-risk PE) or patients with intermediate–high-risk PE with haemodynamic deterioration. Nevertheless, more than half of high-risk PE patients do not receive systemic thrombolysis due to a perceived increased risk of bleeding. In these cases, percutaneous catheter-directed therapy (CDT) or surgical embolectomy should be considered. CDT has emerged and appears to be an effective alternative in treating PE, with a hypothetical lower risk of bleeding than systemic thrombolysis, acting directly in the thrombus with a much lower dose of thrombolytic drug or even without thrombolytic therapy. CDT techniques include catheter-directed clot aspiration or fragmentation, mechanical embolectomy, local thrombolysis, and combined pharmaco-mechanical approaches. A few observational prospective studies have demonstrated that CDT improves right ventricular function with a low rate of haemorrhage. Nevertheless, the evidence from randomised controlled trials is scarce. Here we review different scenarios where CDT may be useful and trials ongoing in this field. These results may change the upcoming guidelines for management and treatment of PE, establishing CDT as a recommended treatment in patients with acute intermediate–high-risk PE.

Introduction

Pulmonary embolism (PE) is a common disease associated with high morbidity and mortality worldwide [1]. The clinical presentation of PE ranges from asymptomatic to cardiogenic shock or sudden death [2, 3]. Although anticoagulant treatment is the cornerstone of therapy, risk stratification is essential to determine the most appropriate therapeutic strategy and the most proper location for the patient (*i.e.* intensive care unit, hospital ward or home) [4]. Stratification of acute PE comprises high-risk PE, intermediate-risk PE (intermediate–high or intermediate–low) and low-risk PE. High-risk PE involves haemodynamic instability, which is defined using any of the following criteria.

1) Cardiac arrest: need for cardiopulmonary resuscitation.
2) Obstructive shock: systolic blood pressure (BP) <90 mmHg or vasopressors required to achieve a BP ⩾90 mmHg despite adequate filling status and end-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate).
3) Persistent hypotension: systolic BP <90 mmHg or systolic BP drop ⩾40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia or sepsis.

To differentiate low-risk *versus* intermediate-risk PE we need to evaluate clinical signs of PE severity, serious comorbidity, and right ventricle (RV) dysfunction on transthoracic echocardiogram (TTE) or computed tomography pulmonary angiography (CTPA). Intermediate-risk PE contains pulmonary embolism severity index (PESI) ⩾III, simplified PESI (sPESI) ⩾1, Hestia criteria ⩾1 or RV dysfunction on TTE or CTPA. By contrast, if PESI class risk <III, sPESI=0, no Hestia criteria and no findings of RV

dysfunction, the patient is stratified as low-risk PE [4]. In low-risk PE, early discharge or outpatient management with standard anticoagulant therapy should be considered [4]. Intermediate-risk PE can be divided into intermediate–low-risk and intermediate–high-risk PE. Intermediate–high-risk PE is characterised by both RV dysfunction and elevated cardiac troponin, while intermediate–low-risk PE is confirmed if only one or none of those criteria are present [4]. Figure 1 shows risk stratification of acute PE.

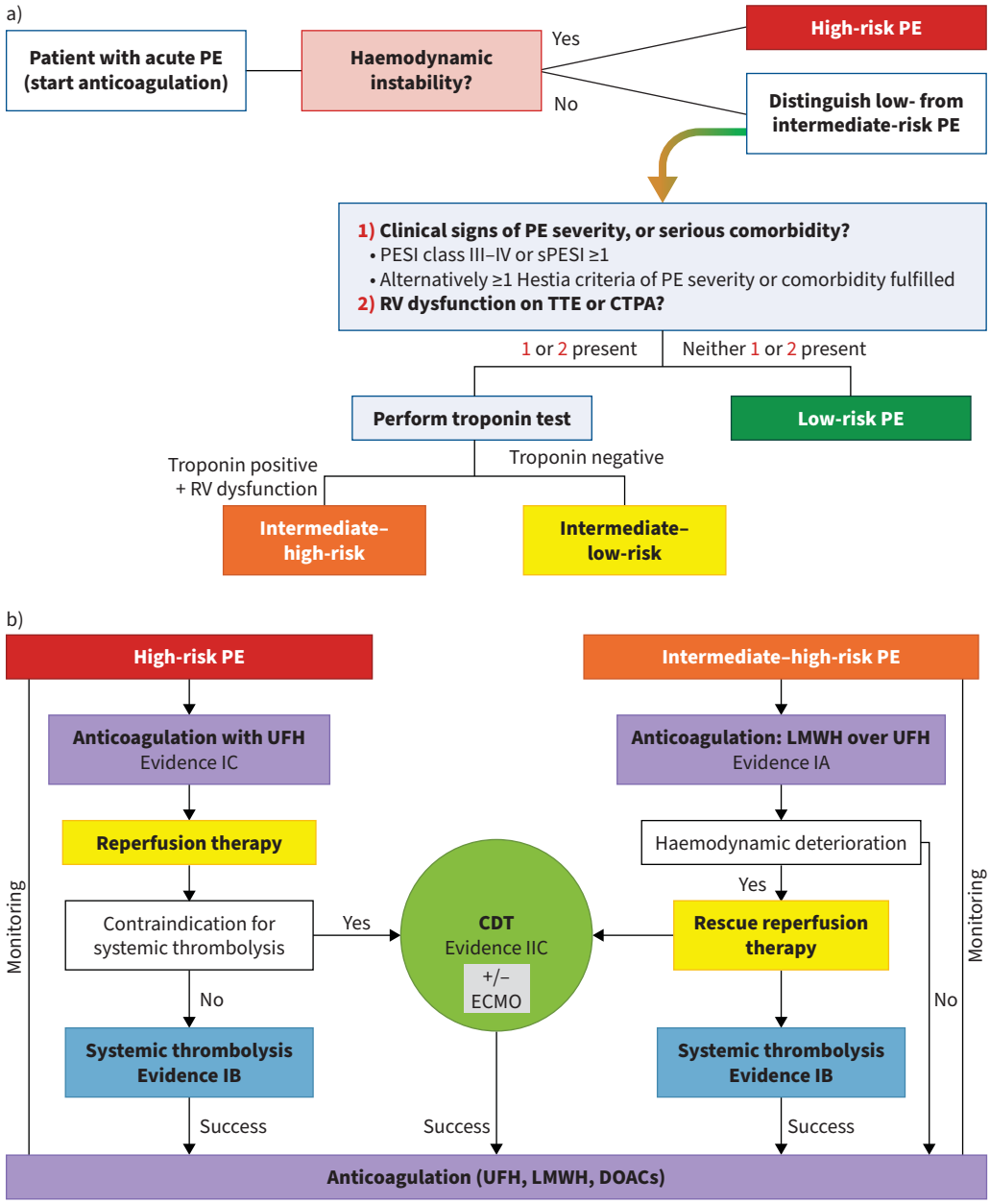

FIGURE 1 a) Prognostic stratification of acute pulmonary embolism (PE). Information from [4]. b) Proposed algorithm for catheter-directed therapies (CDT) in high-risk and intermediate-high risk PE. Reproduced and modified from [13] with permission. PESI: pulmonary embolism severity index; sPESI: simplified pulmonary embolism severity index; RV: right ventricular; TTE: transthoracic echocardiogram; CTPA: computed tomography pulmonary angiography; UFH: unfractionated heparin; LMWH: low-molecular weight heparin; ECMO: extracorporeal membrane oxygenation; DOAC: direct oral anticoagulant. GBP

PE therapy

Anticoagulant therapy is the basis of treatment for patients with PE, although in patients in high-risk PE or intermediate–high-risk PE with haemodynamic deterioration, rescue therapy with full-dose fibrinolysis or catheter-directed therapy (CDT) is required. Current guidelines on the management of PE recommend systemic thrombolysis therapy for high-risk PE (evidence IB) [4–6]. A meta-analysis that included 2057 patients with acute PE showed that thrombolytic therapy was associated with a significant reduction of overall mortality (OR 0.59, 95% CI 0.36–0.96) compared with anticoagulation alone [7]. Nevertheless, it has been estimated that more than half of high-risk PE patients do not receive systemic thrombolysis due to a perceived increased risk of bleeding or a contraindication to thrombolysis [8, 9]. The Pulmonary Embolism International THrOmbolysis (PEITHO) study confirmed the clinical efficacy of full-dose thrombolysis (using tenecteplase) in patients with intermediate–high risk [10]. However, stroke occurred in 12 patients (2.4%) in the thrombolysis arm (OR 12.10, 95% CI 1.57–93.39 *versus* heparin alone), being haemorrhagic in 10 cases [10]. Reduced-dose thrombolysis may be capable of improving safety while maintaining reperfusion efficacy. The PEITHO-3 study (ClinicalTrials.gov identifier: NCT04430569) is a randomised, placebo-controlled, trial with long-term follow-up that will assess the efficacy and safety of a reduced dosage of thrombolytic therapy (Alteplase 0.6 $mg \cdot kg^{-1}$) in patients with intermediate–high-risk acute PE. These results may lead to a change in the treatment of patients with intermediate-risk PE [11]. In these cases, percutaneous CDT or surgical embolectomy should be considered (evidence IIC) [5,6]. Kuo *et al*. [12] performed a systematic review and meta-analysis that evaluated the use of CDT for the treatment of massive PE in 594 patients. The pooled clinical success rate from CDT was 86.5% (95% CI 82.1–90.2%) and pooled risks of major procedural complications were 2.4% (95% CI 1.9–4.3%) [12]. In patients with intermediate–high-risk PE, parenteral or oral anticoagulation (without reperfusion techniques) is the appropriate treatment in most cases, but in those patients that develop haemodynamic deterioration it is suggested to use reperfusion therapy (thrombolytic therapy or CDT) (evidence IIC) [4–6, 10].

Although systemic fibrinolysis has been considered the treatment of choice in patients with high-risk or intermediate–high-risk PE who suffer haemodynamic deterioration during hospitalisation, there are conditions where thrombolysis cannot be used due to active bleeding, high risk of bleeding, or when systemic fibrinolysis failed. In this context, CDT has emerged, and appears to be an effective alternative in treating PE with a hypothetical lower risk of bleeding than systemic thrombolysis, acting directly in the thrombus with a much lower dose of thrombolytic drug or even without thrombolytic therapy [10, 12]. CDT techniques include catheter-directed clot aspiration or fragmentation, mechanical embolectomy, local thrombolysis, and combined pharmaco-mechanical approaches. Catheter-directed ultrasound-assisted thrombolysis (USAT) combines high-frequency, low-energy ultrasound waves to disintegrate the thrombus with local thrombolysis [13]. The most used technique is local thrombolysis using different catheter systems. However, evidence on the efficacy and safety of CDT has been limited to observational and small randomised trials. The ULTIMA trial randomised 59 patients with acute intermediate-risk PE to receive unfractionated heparin (UFH) or USAT. The mean±SD decrease in RV/left ventricle (LV) ratio from baseline to 24 h was significantly higher for the USAT group (0.30±0.20 *versus* 0.03±0.16; p<0.001) [14]. There were no differences in major and minor bleeding complications in both groups (10% in the USAT group and 3% in UFH group; p=0.61) [14]. In the SEATTLE II study (a prospective, single-arm, multicentre trial) that included 150 patients with high-risk and intermediate-risk PE, a significant decrease in RV/LV diameter ratio at 48 h post-procedure (1.55–1.13; mean difference: −0.42; p<0.0001) was observed, although there were 10% with major bleeding within 30 days of the procedure [15]. The most important limitation of this trial was the lack of a control group. Due to the high rate of bleeding, the OPTALYSE trial (randomised, prospective multicentre, parallel-group trial) evaluated if lowering the dose and procedure time would improve the safety of CDT without affecting the efficacy [16]. In this study, 101 patients with intermediate-risk PE were randomised to receive different regimens of tissue plasminogen activator (tPA) in which the dose ranged from 4 to 12 mg and the infusion duration from 2 to 6 h. ∼25% improvement in RV/LV diameter ratio was observed in all arms and the major bleeding rate was 4.0%, with two intracranial haemorrhage events (one attributed to tPA delivered by CDT) [16]. In the randomised SUNSET sPE (Standard *versus* Ultrasound-Assisted Catheter Thrombolysis for Submasssive Pulmonary Embolism) trial that included 81 patients, there was no significant difference in mean thrombus score reduction in patients undergoing USAT (EkoSonic System) compared with those undergoing combined catheter-directed treatment (fibrinolysis and thrombectomy) (cCDT) (UniFuse, angioDynamics or Cragg-McNamara, Medtronic) (p=0.76). Nevertheless, the small sample size prevents any conclusions [17].

Although the existing data appear favourable, it is necessary to have high-quality evidence from randomised controlled trials to define scenarios in which CDT may be considered. The FLowTriever for Acute Massive Pulmonary Embolism (FLAME) study that enrolled 115 patients with high-risk PE showed a lower mortality rate in patients undergoing mechanical thrombectomy with the FlowTriever system

compared with those treated with other therapies in the context arm (1.9% *versus* 29.5%, respectively) [18]. A recent analysis of the prospective FlowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH) study that evaluated 800 patients with high-risk (7.9%) and intermediate–high-risk (76.7%) PE reported 0.3% at 48-h mortality and 0.8% at 30-day mortality, no device-related deaths [19]. The CANARY trial compared the long-term effect of CDT plus anticoagulation (alteplase, 0.5 mg per catheter per h for 24 h) *versus* anticoagulation monotherapy in 94 patients with acute intermediate–high-risk acute PE [20]. The proportion of patients with an RV/LV ratio >0.9 at 3-month follow-up was numerically fewer in the CDT group compared with the anticoagulation monotherapy group (4.3% *versus* 12.8%; OR 0.31, 95% CI 0.06–1.69; p=0.24) [20]. One nonfatal gastrointestinal major bleeding occurred in the CDT group, and two patients assigned to the anticoagulation monotherapy group died due to PE during the follow-up.

Ongoing trials to evaluate CDT in PE

Currently, several trials are ongoing that evaluate CDT in acute PE. The Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) study compares CDT (EkoSonic Endovascular System) plus anticoagulation *versus* anticoagulation alone in 406 patients with intermediate–high-risk acute PE with elevated risk of early death and/or imminent haemodynamic collapse, defined by at least two of the following criteria: 1) heart rate ⩾100 beats per min; 2) systolic blood pressure ⩽110 mmHg; and 3) respiratory rate >20 breaths per min and/or oxygen saturation on pulse oximetry <90% (or partial arterial oxygen pressure <60 mmHg) at rest while breathing room air. The primary outcome is PE-related mortality, cardiorespiratory decompensation or collapse, or non-fatal symptomatic and objectively confirmed PE recurrence, within 7 days [21]. Likewise, the Pulmonary Embolism – Thrombus Removal With Catheter-Directed Therapy (PE-TRACT) trial evaluates CDT and anticoagulation *versus* anticoagulation alone in 500 patients with intermediate–high-risk acute PE [22]. It is estimated that 500 patients will be enrolled and the primary completion will be available in 2027. Recently, another clinical trial has been initiated: the Catheter-directed Thrombolysis in Intermediate-high Risk Acute Pulmonary Embolism (PRAGUE-26) study plans to include 558 patients with intermediate–high-risk acute PE [23]. The primary outcome of the study is a clinical composite of all-cause mortality, PE recurrence or cardiorespiratory decompensation, within 7 days of randomisation. This data will be available in 2026. If the results of these clinical trials confirm that the treatment arm is superior to the control arm, CDT will be established as treatment in patients with acute intermediate–high-risk PE. Table 1 shows the key studies (observational and randomised clinical trials) on CDT in patients with PE [14–22, 24–34].

Currently, the results with CDT are promising, but the evidence on the efficacy and safety remain low and require a dedicated randomised controlled trial assessing clinical useful end-points and not surrogate end-points (RV/LV). However, a retrospective review of 341 patients with massive or submassive PE treated with systemic heparin or CDT reported that the cost associated with the initial admission was significantly higher in the CDT group when compared with heparin (p=0.001) with a difference of USD 31 000 [35]. However, the cost analysis shows the heparin group had a higher long-term cost of treatment [35]. In addition, patients treated with CDT had fewer bleeding complications (4.2% *versus* 13.8%, p=0.005) and a lower mortality rate (3.9% *versus* 6.9%, p=0.309) compared with patients receiving systematic heparin [35].

Current role for CDT in PE

Nowadays, a role for CDT is considered in patients with high-risk or intermediate–high-risk PE who suffer haemodynamic deterioration during hospitalisation and that have active bleeding, high risk of bleeding, or when systemic fibrinolysis failed. Jara-Palomares *et al*. [36] developed and validated a score to stratify the risk of major bleeding after systemic thrombolysis. Predictors for major bleeding were recent major Bleeding (3 points), Age >75 years (1 point), active Cancer (1 point), and Syncope (1 point) (BACS) [36]. Among 1172 patients, the overall 30-day major bleeding rate in those classified as low-risk (none of the variables present, 0 points) was 2.9% (95% CI 1.6–4.9%), compared with 44% (95% CI 14–79%) in the high-risk group (>3 points). These data were validated in another cohort of patients (n=190) [36].

Of note, in patients with a contraindication for anticoagulation, the placement of an inferior vena cava (IVC) filter should be considered [4]. The Prevention of Recurrent Pulmonary Embolism by Cava Interruption 2 (PREPIC2) study randomised 399 hospitalised patients with severe acute PE associated deep vein thrombosis to receive a retrievable IVC filter plus anticoagulation *versus* anticoagulation alone. There were no significant differences in symptomatic recurrent PE at 3 months between the two groups (3.0% *versus* 1.5% respectively; relative risk with filter 2.00, 95% CI 0.51–7.89; p=0 .50 [37]. Importantly, extracorporeal membrane oxygenation (ECMO) may be considered, in combination with surgical embolectomy or catheter-directed treatment, in refractory circulatory collapse or cardiac arrest (evidence IIB) [4]. A meta-analysis that compared mechanical embolectomy and other strategies (systematic thrombolysis, CDT or

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TABLE 1 Summary of studies using catheter-directed therapies (CDT) in patients with acute pulmonary embolism (PE)

Trial name	Year	Sample Size	Population	Intervention	Control	Primary outcome	Efficacy	Safety
Randomised controlled trials testing the efficacy and safety of different modes of catheter-directed thrombolysis								
ULTIMA [14]	2014	59	Intermediate–high risk	USAT, EkoSonic Endovascular System (10 mg per 15 h)	Anticoagulation monotherapy	Change in 24-h TTE-based RV/LV ratio.	Mean RV/LV ratio was reduced 1.28 to 0.99 at 24 h (p<0.001) in USAT group *versus* 1.20 to 1.17 at 24 h (p=0.31) in heparin group	At 90 days, there was one death (control), no major bleeding, four minor bleeding episodes (three in the USAT group and one in the heparin group; p=0.61)
OPTALYSE PE [16]	2018	100	Intermediate risk	USAT, EkoSonic Endovascular System (4 mg per 2 h) (arm 1)	USAT, EkoSonic System (4 mg per 4 h) (arm 2) (6 mg per 6 h) (arm 3) (12 mg per 6 h) (arm 4)	Change in the 48-h CT-based RV/LV ratio	Mean RV/LV diameter ratio: Arm 1: 0.40 (24.0%) Arm 2: 0.35 (22.6%) Arm 3: 0.42 (26.3%) Arm 4: 0.48 (25.5%)	Major bleeding event rates: Arm 1: 0% Arm 2: 3.7% Arm 3: 3.6% Arm 4: 11.1%
SUNSET-sPE [17]	2021	81	Intermediate risk (submassive)	USAT, EkoSonic Endovascular System (8 mg per 8 h)	cCDT, UniFuse (AngioDynamics) or Cragg-McNamara (Medtronic) (8 mg per 8 h)	Change in the 48-h CT-based thrombus burden	No significant difference in mean thrombus burden. Mean reduction in RV/LV ratio (p=0.01): USAT: 0.37 cCDT: 0.59	Major bleeds: intervention four *versus* control zero
CANARY [20]	2022	94	Intermediate-high risk	cCDT, Cragg-McNamara (Medtronic) (12 mg per 24 h)	Anticoagulation monotherapy	Proportion of patients with a TTE-based RV/LV ratio >0.9 at a 3-month follow-up	4.3% in the cCDT group and 12.8% in the anticoagulation monotherapy group (p=0.24) Median RV/LV ratio at 3-month follow-up (p=0.01): cCDT: 0.7 Anticoagulation monotherapy: 0.8	One case of nonfatal major gastrointestinal bleeding occurred in the cCDT group
HI-PEITHO (NCT04790370) [21]		406	Intermediate–high risk with additional criteria of severity	USAT, EkoSonic Endovascular System (9 mg per 7 h)	Parenteral anticoagulation monotherapy	Composite of PE-related mortality, PE recurrence or cardiorespiratory decompensation or collapse, within 7 days of randomisation	Ongoing	Ongoing

Continued

TABLE 1 Continued

Trial name	Year	Sample Size	Population	Intervention	Control	Primary outcome	Efficacy	Safety
BETULA (NCT03854266) [24]		60	Intermediate–high risk	cCDT, Unifuse (AngioDynamics) (4 mg per 2 h)	Unfractionated heparin monotherapy	Improvement in RV/LV ratio at 24 h	Recruiting	Recruiting
PE-TRACT (NCT05591118) [22]		500	Intermediate risk	CDT consisting of mechanical thrombectomy or cCDT	Anticoagulation monotherapy	Peak oxygen consumption at a 3-month follow-up	Ongoing	Ongoing
PEERLESS (NCT05111613) [25]		550	Intermediate–high risk without absolute contraindication of thrombolysis	Mechanical thrombectomy, FlowTriever System	cCDT (any commercially available CDT system)	Composite clinical end-point of all-cause mortality, ICH, major bleeding, clinical deterioration, ICU admission, and ICU length of stay during hospitalisation	Recruiting	Recruiting
STORM-PE (NCT05684796) [26]		100	Intermediate–high risk	Mechanical aspiration, Indigo Aspiration System	Anticoagulation monotherapy	Change in the 48-h CT-based RV/LV ratio	Recruiting	Recruiting
STRATIFY (NCT04088292) [27]		210	Intermediate–high risk	USAT (20 mg per 6 h)	Anticoagulation monotherapy	Reduction in Miller score 48–96 h post-randomisation	Recruiting	Recruiting
Peripheral Systemic Thrombolysis *Versus* Catheter Directed Thrombolysis for Submassive PE (NCT03581877) [28]	2023	31	Intermediate risk	Peripheral low-dose thrombolysis (24 mg per 12 h)	USAT, EkoSonic Endovascular System (24 mg per 12 h)	Change in the 48-h TTE-based RV/LV ratio	Completed	Completed
Registry of prospective studies testing the efficacy and safety of different modes of catheter-directed thrombolysis								
SEATTLE II [15]	2015	150	Massive (n=31) Submassive (n=119)	USAT, EkoSonic Endovascular System (24 mg per 24 h)		Change in the 48-h CT-based RV/LV ratio	Mean RV/LV ratio decreased from 1.55 to 1.13 at 48 h ($p<0.0001$).	One GUSTO severe bleed; 16 GUSTO moderate bleed
KNOCKOUT PE Registry [29]	2018	1480	Intermediate–high risk or high risk	USAT, EkoSonic Endovascular System		Change in 24–48 h TTE-based RV/LV ratio Persistence of pulmonary hypertension	Ongoing	Ongoing
PERFECT [30]	2015	101	Massive (n=28) Submassive (n=73)	Massive PE: catheter-directed mechanical or pharmaco-mechanical thrombectomy Submassive PE: catheter-directed thrombolysis (UniFuse, EkoSonic or pig tail)		Clinical success was defined as: stabilisation of haemodynamic, improvement in pulmonary hypertension and/or right heart strain, and survival to hospital discharge	Clinical success: Massive PE: 85.7% (95% CI 67.3–96.0%) Submassive PE: 97.3% (95% CI 90.5–99.7%)	No major haemorrhages and no haemorrhagic strokes

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TABLE 1 Continued

Trial name	Year	Sample Size	Population	Intervention	Control	Primary outcome	Efficacy	Safety
FLARE [31]	2019	106	Intermediate–high risk	Mechanical thrombectomy, FlowTriever System (Inari)		Change in the 48-h CT-based RV/LV ratio	Mean RV/LV ratio 1.53 reduced to 1.15 at 48 h	Four patients (3.8%) experienced six major adverse events
EXTRACT-PE [32]	2021	119	Submassive PE	Mechanical aspiration, IndigoVac (Penumbra)		Change in the 48-h CT-based RV/LV ratio	Mean RV/LV ratio reduction was 0.43 (95% CI 0.38–0.47; p<0.0001) at 48 h	Two (1.7%) patients experienced three major adverse events
FLAME [18]	2023	115	High-risk PE	Mechanical thrombectomy, FlowTriever System (Inari)	Context arm	Composite incidence of all-cause mortality, clinical deterioration, bailout, and major bleeding at 45 days	FlowTriever: 17% Context arm: 63.9%	
FLASH interim results registry [33]	2022	250	Intermediate–risk (n=233) High risk (n= 17)	Mechanical thrombectomy, FlowTriever System (Inari)		Composite of MAEs: device-related death, major bleeding, and intraprocedural device- or procedure-related adverse events at 48 h	MAEs: three (1.2%), all of which were major bleeds that resolved without sequelae All-cause mortality was 0.4% at 30 days, with a single death that was unrelated to PE	
FLASH 6 months [34]	2023	799	High risk (n=64) Intermediate–high risk (n=616) Intermediate–low risk or unclassified (n=119)	Mechanical thrombectomy, FlowTriever System (Inari)		Evaluate RV function, MMRCD, 6MWT distances, and PE QoL scores at 6 months	Normal RV function increased from 15.1% to 95.1% (p<0.0001) MMRCD score improved from 3.0 to 0.0 (p<0.0001) 6MWT distances increased from 180 m to 398 m (p <0.001)	Prevalence of site-reported chronic thromboembolic pulmonary hypertension was 1.0% and chronic thromboembolic disease was 1.9%
FLASH full cohort [19]	2023	800	High risk (n=63) Intermediate–high risk (n=614)	Mechanical thrombectomy, FlowTriever System (Inari)		Composite of MAE: device-related death, major bleeding, device- or procedure-related adverse events	MAEs: 1.8% All-cause mortality was 0.3% at 48-h follow-up and 0.8% at 30-day follow-up, with no device-related deaths	

RV: right ventricular; LV: left ventricular; TTE: transthoracic echocardiogram; CT: computed tomography; cCDT: combined catheter-directed treatment (fibrinolysis and thrombectomy); GUSTO: Global Use of Streptokinase and t-PA for Occluded Coronary Arteries; ICH: intracerebral haemorrhage; ICU: intensive care unit; MAE: major adverse events; MMRCD: modified Medical Research Council dyspnoea scores; 6MWT: 6-min walk test; QoL: quality of life.

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ECMO) showed that mechanical embolectomy yields favourable results regardless of the timing of ECMO implantation in the reperfusion timeline, independent of thrombolysis administration or cardiac arrest presentation [38]. Figure 1 shows an algorithm for acute PE and timelines of CDT.

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