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Review article

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Interventional therapies for pulmonary embolism

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Abstract

Pulmonary embolism (PE) is the leading cause of in-hospital death and the third most frequent cause of cardiovascular death. The clinical presentation of PE is variable, and choosing the appropriate treatment for individual patients can be challenging. Traditionally, treatment of PE has involved a choice of anticoagulation, thrombolysis or surgery; however, a range of percutaneous interventional technologies have been developed that are under investigation in patients with intermediate–high-risk or high-risk PE. These interventional technologies include catheter-directed thrombolysis (with or without ultrasound assistance), aspiration thrombectomy and combinations of the aforementioned principles. These interventional treatment options might lead to a more rapid improvement in right ventricular function and pulmonary and/or systemic haemodynamics in particular patients. However, evidence from randomized controlled trials on the safety and efficacy of these interventions compared with conservative therapies is lacking. In this Review, we discuss the underlying pathophysiology of PE, provide assistance with decision-making on patient selection and critically appraise the available clinical evidence on interventional, catheter-based approaches for PE treatment. Finally, we discuss future perspectives and unmet needs.

Sections

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Key points

- Pulmonary embolism (PE) remains the leading cause of preventable death in hospitalized patients; risk stratification of PE is advised on the basis of clinical presentation, haemodynamics and comorbidities.
- Patients with low-risk or intermediate–low-risk PE benefit from anticoagulation alone, whereas treatment of patients with intermediate–high-risk or high-risk PE poses difficulties; systemic thrombolysis is the first-line recommendation for patients with high-risk PE but is associated with severe adverse events, especially bleeding.
- In patients with intermediate–high-risk PE and those with high-risk PE and contraindications to thrombolysis, interventional therapies, such as catheter-directed thrombolysis (CDT), ultrasound-assisted CDT (USCDT), pharmacomechanical CDT and aspiration thrombectomy, are possible options.
- Despite showing promising results in reducing right ventricular dysfunction and relief of haemodynamic compromise in small studies and registries, these interventional therapies have not been rigorously investigated in adequately powered randomized controlled trials.
- CDT, USCDT and pharmacomechanical CDT reduce the dose of thrombolytics used, whereas aspiration thrombectomy eliminates the use of thrombolytics.
- Large, adequately powered, randomized controlled trials investigating low-dose thrombolysis, CDT, USCDT and large-bore thrombectomy are ongoing and more are planned.

Introduction

After myocardial infarction and stroke, venous thromboembolism (including pulmonary embolism (PE) and deep-vein thrombosis) is the third most frequent cause of cardiovascular death, leading to high socioeconomic burden and close to 1 million estimated deaths worldwide each year[1–5]. As the population ages and cancer becomes more prevalent, the incidence of PE is rising, making it a pressing clinical problem for modern health care[6]. PE also remains the most common preventable cause of death in hospitalized patients[7–10].

The pathophysiology of PE is complex and includes pulmonary vascular obstruction, acute inflammation and vasospasm; in chronic PE, changes in the pulmonary vasculature can also occur. In the acute phase, pulmonary arterial obstruction increases right-sided cardiac afterload and strain, which can lead to acute right ventricular (RV) dysfunction (RVD) and failure, causing impaired gas exchange and systemic hypoxia[11–13]. Anatomical obstruction and hypoxia elicit cascades of inflammation, injury and vasoconstriction through the release of powerful vasoconstrictors such as thromboxane A_2 and serotonin[14–16]. These factors have a greater effect on the vasculature with age, obesity, immobility, surgical procedures (especially orthopaedic surgery), states of thrombophilia, smoking, female sex, cancer and use of oral contraceptives[17–29].

In acute PE, stratification according to the risk of death guides optimal therapy[30] (Table 1). Approximately 40–60% of patients are classified as having low-risk PE, 35–55% as having intermediate-risk PE and 5% as having high-risk PE[6,8,10,30–35]. However, numbers vary widely between different studies (low risk 9–61%, intermediate risk 32–91% and high risk 4–33%), and low-risk PE in particular can be clinically inapparent and therefore prone to underdiagnosis[36–40].

Subsequent treatment of patients with PE is based on four principles: re-establishing perfusion, ensuring haemodynamic stability, enabling tissue oxygenation and avoiding disease recurrence. Haemodynamic stability and tissue oxygenation can be provided by volume optimization and the use of vasopressors, inotropes and/or extracorporeal membrane oxygenation as well as ventilatory support, if needed[30]. Conversely, reperfusion can be provided by various approaches. Patients with low-risk PE are usually treated by anticoagulation, either parenterally or orally. This treatment might also suffice for patients with intermediate–low-risk PE. By contrast, patients with intermediate–high-risk or high-risk PE might qualify for systemic thrombolysis (recommended in patients with high-risk PE and haemodynamic instability without contraindications for lysis) or interventional treatments in special circumstances. Ongoing clinical trials (PEITHO-3 (ref. 41) and HI-PEITHO[42]) will guide practice in this area. Indeed, current guidelines recommend thrombolysis as the first-line treatment in high-risk PE[30,43,44], but these drugs are associated with an increased risk of clinically significant bleeding and are used only in a minority (23–30%) of patients with high-risk PE[10,45]. Therefore, the rate of complications from intervention and the mortality from the underlying disease are both high. Only 50% of patients with high-risk PE survive[46], highlighting the need to improve therapies.

Several novel interventional treatment strategies have been introduced and are currently under scientific and clinical investigation. These strategies aim to reduce the rate of haemodynamic collapse, without significantly increasing the incidence of bleeding, which occurs with systemic doses of thrombolysis. In this Review, we provide an overview of the pathophysiology of PE and discuss interventional, device-based treatment strategies in PE, namely catheter-directed thrombolysis (CDT), ultrasound-assisted CDT (USCDT) and aspiration thrombectomy. We also discuss strategies for patient selection and describe ongoing and future studies (Fig. 1).

Pathophysiology

Blood clots that occlude the pulmonary arteries are most commonly of embolic origin (Fig. 2). The majority of emboli arise in the proximal deep veins of the lower extremities (the iliac, femoral and popliteal veins)[47,48] and more than half of patients with proximal deep-vein thrombosis develop PE[47–49]. The dominant effects of obstruction to blood flow are an increase in pressures proximal to the occlusion and reduced flow distal to the occlusion. Increased pulmonary arterial pressure (PAP), caused by blood flow obstruction, is accompanied by local vasoconstriction, which itself is mediated by hypoxia and the release of tissue mediators such as thromboxane A_2 (refs. 50–53) and serotonin[54–56]. Right-sided cardiac afterload increases, leading to higher myocardial oxygen consumption and increased cardiac filling pressures and, in some cases, to acute right-sided heart failure (acute cor pulmonale)[57]. Hypoxia and ischaemia in the downstream pulmonary vasculature and parenchyma ensue. Systemic hypoxaemia is mediated by a mismatch between lung perfusion and ventilation and the build-up of atelectatic lung zones as alveoli collapse in ischaemic areas due to a reduction in surfactant production[58]. With the progression of right-sided heart failure, cardiac output decreases, impairing oxygen saturation even further[58]. In addition to impaired oxygenation, gas exchange and RV function, peripheral lung infarctions occur in approximately 10% of patients with PE because of obstruction of segmental or subsegmental arteries[59]. All the above

Table 1 | Classification of PE severity and risk of early death

Risk of early death		Indicators of risk			
		Haemodynamic instability	Clinical parameters of PE severity and/or comorbidity[a]	Right ventricular dysfunction[b]	Elevated plasma levels of cardiac troponins
High		+	+	+	+
Intermediate	Intermediate–high	–	+	+	+
	Intermediate–low	–	+	One (or none) positive	
Low		–	–	–	– (if assessed[c])

Classification according to the 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism (PE)[30]. [a]PE Severity Index (PESI) class III–V or simplified PESI ≥1. [b]Measured using transthoracic echocardiography or computed tomography pulmonary angiography. [c]Assessment optional.

can lead to a downward spiral, with progressive RVD and left ventricular (LV) dysfunction, followed by circulatory collapse.

As the PAP rises, RVD occurs as a result of RV dilatation and increased RV wall tension, causing impaired coronary perfusion and, consequently, cardiac ischaemia with mixed disarray in cardiac distensibility and filling as well as contraction and ejection[60]. High plasma troponin levels, which are an indicator of myocardial injury, and high plasma levels of natriuretic peptides[61–63], suggestive of increased filling pressures and myocardial stretch, are indicators of sustained RVD and are associated with increased mortality (OR 5.90, 95% CI 2.68–12.95 for the risk of death with elevated plasma troponin levels)[64]. These changes are discernible; for example, echocardiography can be used to document RV dilatation. Among other observations, a pulmonary ejection acceleration time in the RV outflow tract of <60 ms and a decreased tricuspid annular plane systolic excursion can help to identify patients at higher risk of death[65–67]. Indeed, the presence of RVD is associated with an increased risk of early death in patients with PE (OR 2.53, 95% CI 1.17–5.50)[61]. PE can also have other adverse consequences, such as the development of chronic thromboembolic pulmonary disease (CTEPD), a post-PE sequela with or without pulmonary hypertension[68]; recurrence of PE and other venous thromboembolism; or post-PE syndrome, a clinically defined syndrome comprising impaired cardiac function, sustained dyspnoea and functional limitations[69,70]. Therefore, an ideal therapy would reduce both the acutely increased risk of death and the long-term sequelae of PE.

Risk evaluation and patient selection

Objective risk assessment is important for directing treatment decisions and selecting potential patients for advanced treatments[71–75] (Table 1). Clinical scores, such as the PE Severity Index (PESI) and simplified PESI (sPESI) (which are particularly useful for identifying lower-risk PE), the FAST score (heart-type fatty acid binding protein, syncope, tachycardia), and the Bova score (elevated cardiac troponin level, RVD, tachycardia >110 bpm, systolic blood pressure (SBP) 90–100 mmHg) (both the FAST score and the Bova score are particularly useful for identifying higher-risk PE), predict adverse outcomes in patients with acute PE, independent of imaging or biomarkers[76–85]. In addition to clinical scores, high-risk PE can be defined by haemodynamic characteristics[30]: cardiac arrest, obstructive shock (SBP <90 mmHg or vasopressor administration to achieve SBP >90 mmHg despite adequate filling status, in combination with end-organ hypoperfusion) and persistent hypotension (SBP <90 mmHg or an SBP drop by >40 mmHg for >15 min, if not caused by new-onset arrhythmia, hypovolaemia or sepsis). In addition, signs of systemic hypoxaemia, such as elevated blood lactate levels, are associated with worse outcomes[71].

Most patients with low-risk or intermediate–low-risk PE benefit from anticoagulation alone[86]. In patients with high-risk PE, systemic thrombolysis is considered first-line therapy. The 2019 ESC guidelines for the diagnosis and management of acute PE[30] recommend that patients with high-risk PE and contraindications to, or failure of, systemic thrombolysis should be considered for interventional reperfusion therapy (Box 1), whereas in patients with intermediate–high-risk PE, the ESC guidelines reserve interventional, surgical and thrombolytic therapies for those showing signs of deterioration despite anticoagulation. For patients with intermediate–high-risk PE with deteriorating clinical features, the ESC guidelines support the consideration of advanced therapies. Whether these interventions should be via systemic lysis, catheter lysis, or catheter or surgical thrombectomy remains the subject of ongoing studies, with strengths and weaknesses for each approach.

In a subset of patients with high-risk PE, systemic thrombolysis might not improve RV function or haemodynamics in the first 36–48 h after treatment initiation, and this is one scenario in which interventional reperfusion should be considered[30,43,44,87]. Of note, 'treatment failure' has not been clearly defined. Box 2 provides clinical, laboratory, echocardiographic and other measures to evaluate the condition of patients with PE. Given the complex mix of pathology, physiology and comorbidity present in many patients with PE and markers of adverse risk, treatment decisions are increasingly being processed by a multidisciplinary team — the PE response team (known as PERT) — which typically involves cardiologists, interventionalists, radiologists, pulmonologists, intensivists, angiologists and haematologists as well as clinical nurse specialists[88] (Fig. 3).

Established medical therapies

Anticoagulation

Anticoagulation can be delivered parenterally or orally, with direct oral anticoagulation being the first choice in patients with low-risk or intermediate–low-risk PE, if renal function allows[86,89]. Apixaban, edoxaban and rivaroxaban (direct inhibitors of factor Xa) and dabigatran (a direct inhibitor of thrombin) are recommended for the treatment and prevention of venous thromboembolism in otherwise healthy patients[30,90] (Table 2). However, in patients with severely impaired renal function (estimated glomerular filtration rate <15 ml/min/1.73 m^2), anticoagulant therapy with a vitamin K antagonist is recommended (in combination with low-molecular-weight heparin (LMWH) until the target international normalized ratio is reached)[91–93].

In patients with intermediate–high-risk PE, LMWH is the current standard of care. Intravenous unfractionated heparin (UFH) can be considered as an alternative, but it is often difficult to maintain the target

range of activated partial thromboplastin time. However, in patients receiving systemic thrombolysis, owing to the high risk of bleeding and the potential need to reverse anticoagulation in the setting of acute haemorrhage, UFH might be preferable to LMWH.

Systemic thrombolysis

Pharmacological thrombolysis in PE has been considered for years, partly because of the recapitulation of natural thrombolysis. Recombinant tissue plasminogen activator (rt-PA), urokinase and streptokinase have all been studied as agents for the delivery of systemic thrombolysis in PE[10,94]. Possible treatment regimens include either a loading dose followed by continuous infusion or accelerated regimens with infusion times ranging from 15 min (alteplase) to 2 h (alteplase, streptokinase and urokinase)[30].

Of note, the main randomized controlled trial (RCT) data supporting the use of systemic thrombolysis in PE associated with cardiogenic and obstructive shock (high-risk PE) consist of one trial that enrolled eight patients before it was prematurely terminated. The remaining clinical trials in this area included patients who were not in shock.

A meta-analysis of 15 RCTs involving 2,057 patients showed that, compared with heparin therapy, thrombolysis reduces all-cause mortality (OR 0.59, 95% CI 0.36–0.96, $P = 0.03$) and PE-related mortality (OR 0.29, 95% CI 0.14–0.60, $P < 0.001$) and prevents recurrent PE (OR 0.50, 95% CI 0.27–0.94, $P = 0.03$)[95]. However, systemic thrombolysis is associated with an increased risk of major bleeding (OR 2.91, 95% CI 1.95–4.36, $P < 0.001$ for all thrombolytics), including fatal and intracranial haemorrhage (OR 3.18, 95% CI 1.25–8.11, $P = 0.008$)[95]. In another meta-analysis of 16 RCTs with a heterogeneous population of 2,115 patients with PE (10% low risk, 71% intermediate risk, 1% high risk and 18% not classified)[96], the use of thrombolytics was associated with lower all-cause mortality (OR 0.53, 95% CI 0.32–0.88, $P = 0.01$) but still a greater risk of major bleeding (OR 2.73, 95% CI 1.91–3.91, $P < 0.01$)[96]. The number needed to treat for all-cause mortality was 59, and the number needed to harm (major bleeding) was 18 (ref. 96).

Given the increased risk of bleeding with systemic thrombolysis, studies have been conducted investigating half-dose regimens of thrombolytics[97,98]. A meta-analysis of five studies with a total of 440 patients compared systemic thrombolysis with low-dose rt-PA (0.6 mg/kg, maximum 50 mg) with standard-dose rt-PA (100 mg infusion in 2 h)[99]. However, no significant difference in bleeding rates was observed between the groups (OR 0.33, 95% CI 0.12–0.91, $P = 0.94$)[99]. Additionally, low-dose thrombolysis was not associated with a significant difference in the risk of major bleeding events (OR 0.73, 95% CI 0.14–3.98, $P = 0.72$), recurrent PE or all-cause death compared with the use of heparin[99]. Another meta-analysis comprising 780 patients from four observational studies and nine RCTs found that full-dose systemic thrombolysis was associated with a higher risk of bleeding across the pooled population compared with reduced-dose thrombolysis (OR 1.48, 95% CI 1.00–2.19)[100]. However, patients treated with low-dose systemic thrombolysis still had a fivefold increased risk of bleeding compared with those treated with anticoagulation (relative risk 5.08, 95% CI 1.39–18.6)[100]. In summary, these trials of reduced-dose thrombolysis did not reliably demonstrate functional improvements equivalent to those achieved with full-dose thrombolysis and were inadequately powered and heterogeneous in their design; therefore, reduced-dose thrombolysis is not recommended, and future investigation is still needed and currently ongoing[101–104].

The PEITHO-3 trial[41] will randomize 650 patients with intermediate–high-risk PE to receive either reduced-dose alteplase or standard-dose heparin anticoagulation. Eligible patients are required to meet criteria of elevated risk, such as SBP ≤110 mmHg, a history of heart failure or presenting to hospital with a respiratory rate of >20 breaths per min (ref. 41). The primary composite end point is all-cause death, haemodynamic decompensation and PE recurrence within 30 days. Secondary outcomes include, among others, bleeding complications (fatal or GUSTO (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) classification

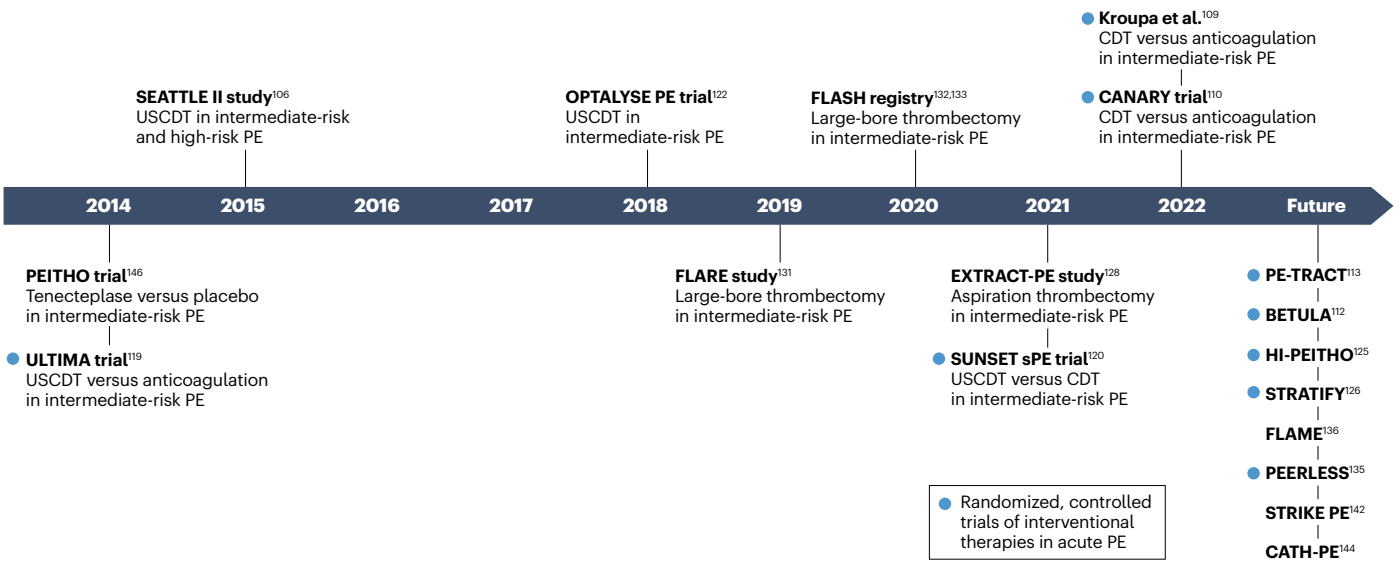

Fig. 1 | Timeline of studies of interventional therapies in PE. To date, four randomized controlled trials investigating interventional therapies in acute pulmonary embolism (PE) have been published. Five more randomized controlled trials are ongoing. Trials comparing different interventional strategies against standard-of-care and in a head-to-head comparison are particularly needed. CDT, catheter-directed thrombolysis; USCDT, ultrasound-assisted catheter-directed thrombolysis.

of severe or life-threatening bleeding), all-cause mortality and PE-related death[41].

In summary, systemic thrombolysis is a first-line treatment in high-risk PE and can also be considered in patients with preserved blood pressure but additional markers of risk such as SBP <110 mmHg, respiratory rate of >20 breaths per min or a history of chronic heart failure[30,44,87]. Although systemic thrombolysis does reduce the risk of haemodynamic collapse in these patients, it is also associated with an increased risk of major bleeding, which requires an individualized risk–benefit evaluation before administration is considered. Low-dose thrombolytic schemes are currently under investigation[41]. Whether systemic thrombolysis improves long-term outcomes, including the incidence of CTEPD or post-PE syndrome, remains uncertain[69,70].

Interventional therapies

Current recommendations

According to the 2019 ESC guidelines for the diagnosis and management of acute PE, the use of interventional, catheter-directed therapies should be considered only in patients with intermediate–high-risk PE who have haemodynamic and respiratory deterioration despite anticoagulation and in patients with high-risk PE in whom thrombolysis either has failed or is deemed not possible due to a contraindication (recommendation class IIa, level of evidence C)[30]. In a scientific statement from the AHA, the possibility of using interventional therapies in patients with high-risk PE and contraindications for lysis as an alternative reperfusion strategy is mentioned. However, they emphasize the scarcity of data, particularly regarding short-term and long-term outcomes[44]. In a 2021 CHEST guideline and expert panel report on the management of PE and deep-vein thrombosis, consideration of the use of interventional therapies is recommended in patients with high-risk PE presenting with shock, a high risk of bleeding and/or failed thrombolysis. However, this consideration is classified as weak with a low level of evidence[87]. In 2022, the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions published a consensus paper in which the authors emphasize that, although no robust data exist, there is a potential role for interventional therapies as an alternative reperfusion strategy at specialized centres[105]. Against this background and given the growing scientific and clinical interest in interventional therapies for PE, we summarize the available devices (Table 3) and discuss the published evidence and ongoing studies.

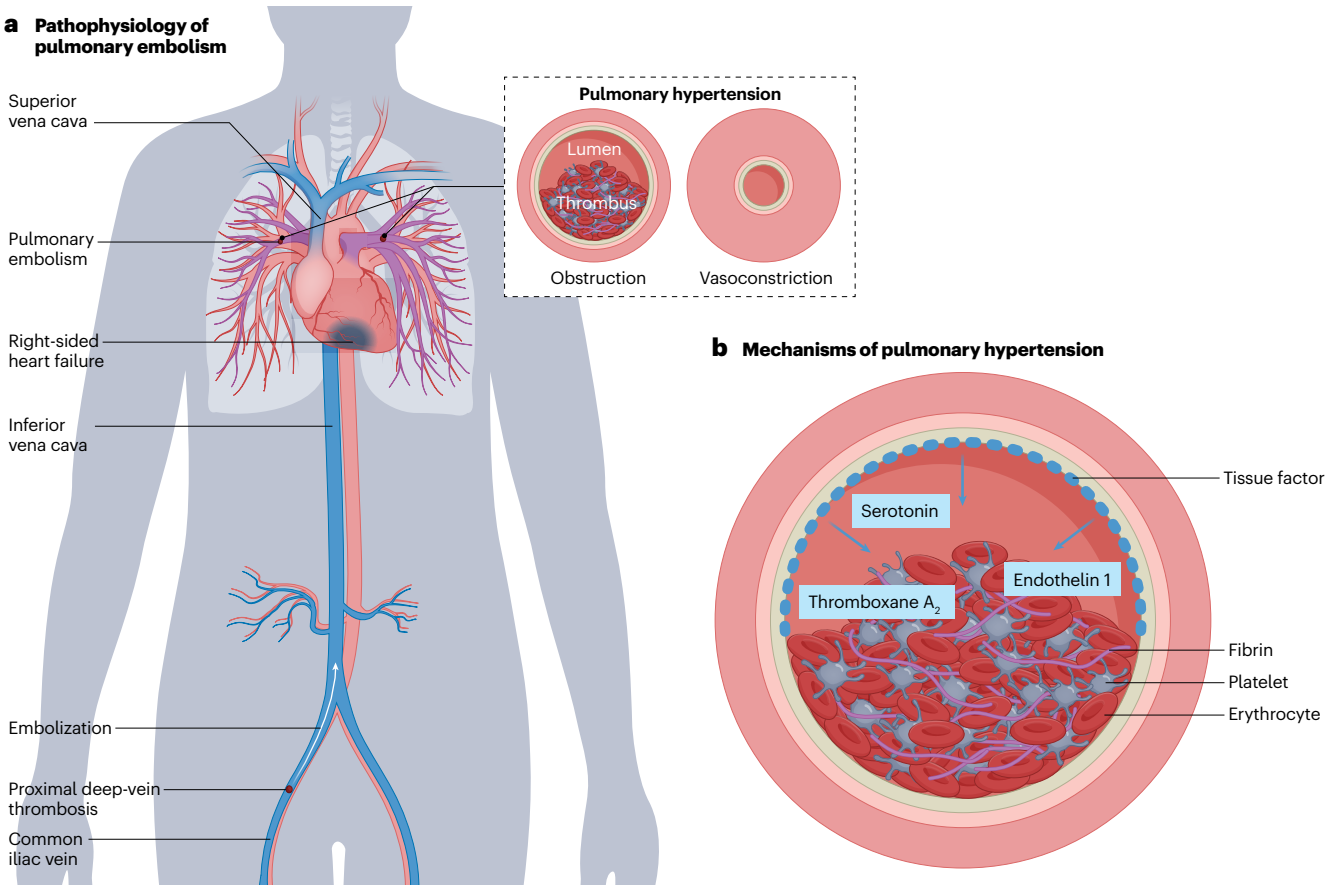

Fig. 2 | Pathophysiology of PE and concomitant pulmonary hypertension after pulmonary artery obstruction and vasoconstriction. a, Most commonly, pulmonary embolism (PE) results from proximal deep-vein thrombosis, with the majority of thrombi originating in the lower extremities. Promoted by risk factors, such as active cancer, smoking or obesity, prothrombotic influences outweigh antithrombotic mechanisms. **b**, Thrombi can obstruct the pulmonary arteries, thereby reducing blood flow and causing the production of vasoactive mediators, such as endothelin 1, serotonin and thromboxane A_2, which themselves further amplify vasoconstriction. The resulting high pulmonary artery pressures can cause cardiac dysfunction and even shock. Downstream effects include hypotension, anaerobic metabolism, respiratory failure and, finally, death.

Box 1

Contraindications to systemic thrombolysis

Major contraindications

- Allergy to compounds
- Ischaemic stroke in past 3 months
- Bleeding diathesis (haemophilia)
- Brain or spinal surgery in past 3 months
- Head trauma in past 3 months
- History of intracranial bleeding
- Current active bleeding
- Structural intracranial disease

Relative contraindications

- History of major bleeding (non-intracranial)
- Recent surgical or otherwise invasive procedure
- Pregnancy
- Older age (especially >75 years)

Catheter-directed thrombolysis

In CDT, pharmacological thrombolysis is delivered by catheters directly into the pulmonary arteries, thereby reducing the total dose of the thrombolytic agent and possibly reducing bleeding complications[106].

Uni-Fuse and Cragg–McNamara. Initially developed as a supportive treatment strategy for acute arterial limb ischaemia, the Uni-Fuse Infusion Catheter (AngioDynamics) and Cragg–McNamara Micro Therapeutics Infusion Catheter (Medtronic) have been repurposed to treat PE[107,108].

In 2022, the use of CDT was compared with anticoagulation alone in an RCT of 23 patients with intermediate-risk PE[109] (Table 4). The investigators used the Cragg–McNamara catheter to infuse 20 mg of alteplase directly into the pulmonary vasculature. The primary efficacy end point, measured at 48 h after randomization, was defined as a ≥25% reduction in the RV-to-LV ratio, a reduction in systolic PAP determined by echocardiography or a ≥30% reduction in the Qanadli score (a computed tomography pulmonary angiography (CTPA)-based score to evaluate pulmonary artery obstruction). Safety was assessed by the absence of intracranial or life-threatening bleeding. A reduction in the RV-to-LV ratio was more frequently achieved in the CDT group (7 out of 12 patients) than in the anticoagulation group (2 out of 11 patients; $P = 0.03$), as was a decrease in systolic PAP by ≥30% (11 out of 12 patients in the CDT group versus 2 out of 11 patients in the anticoagulation group; $P = 0.001$). Reduction in the Qanadli score did not significantly differ between the groups. Safety end points were similar in both groups, with no intracranial or life-threatening bleeding reported. When interpreting the results, one should keep in mind the small sample size and the short observation period, a factor that prevented statistically powered clinical end point evaluation.

In the open-label, randomized CANARY trial[110], CDT using the Cragg–McNamara catheter was compared with anticoagulation alone in patients with intermediate–high-risk PE (Table 4). Patients in the CDT group received either 12 mg alteplase (unilateral PE) or 24 mg alteplase (bilateral PE) over 24 h. Patients in the anticoagulation group received enoxaparin (1 mg/kg twice daily). The primary outcome was an RV-to-LV ratio of >0.9 at 3 months, assessed by echocardiography. A secondary composite end point described the proportion of patients with an RV-to-LV ratio of >0.9 at 72 h after randomization, the proportion of patients with unrecovered RV function at 3 months and the 3-month rate of all-cause death. The study was prematurely stopped due to the COVID-19 pandemic after randomization of 94 out of the 288 planned patients, 85 of whom completed the 3-month follow-up. At 3 months, the primary efficacy end point did not significantly differ between the groups. However, the mean RV-to-LV ratio was significantly lower in the CDT group than in the anticoagulation group (0.7, interquartile range (IQR) 0.6–0.7 versus 0.8, IQR 0.7–0.9; $P = 0.01$). Moreover, RV recovery was seen more frequently at 3 months after CDT (43 out of 46 patients versus 28 out of 39 patients; $P = 0.009$). Eight bleeding events were reported in the CDT group compared with none in the anticoagulation group. In total, three patients died, all of whom were in the anticoagulation group. In summary, the CANARY trial[110] is the largest RCT to date comparing CDT against anticoagulation, but

Box 2

Signs of clinical deterioration in pulmonary embolism

Clinical

- ↑ Heart rate
- ↑ Respiratory rate
- ↓ Blood pressure
- ↓ Diuresis
- ↓ Consciousness
- ↓ Blood oxygen saturation

Laboratory

- ↑ Serum lactate level
- ↑ Serum creatinine level
- ↑ Serum troponin T or troponin I levels
- ↑ Serum N-terminal pro-B-type natriuretic peptide level
- ↑ Serum liver enzyme levels
- ↑ International normalized ratio

Echocardiographic

- ↑ Pulmonary arterial pressure
- ↓ Tricuspid annular plane systolic excursion
- Peak systolic tricuspid valve gradient >60 mmHg
- Pulmonary ejection acceleration time in the right ventricular outflow tract <60 ms

Others

- Need for mechanical ventilation
- Need for extracorporeal membrane oxygenation
- Need for vasopressors and inotropes

Refs. 30,57,61–67,71,155–161

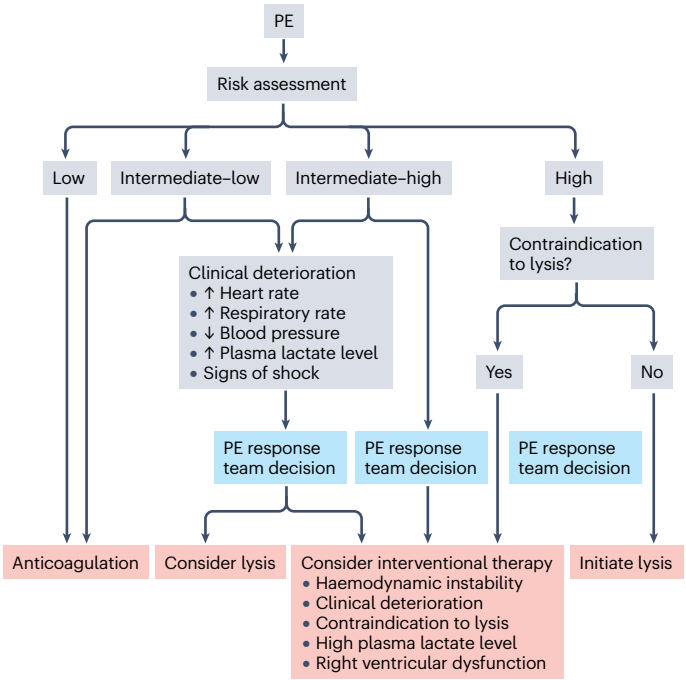

Fig. 3 | Treatment algorithm for PE. Interventional therapies can be considered in patients with high-risk pulmonary embolism (PE) and contraindications to systemic thrombolysis and in patients with intermediate-risk or low-risk PE if their condition deteriorates despite anticoagulation.

the trial was underpowered and prematurely stopped, so the findings should be regarded as hypothesis-generating only.

In addition to these RCTs, a meta-analysis of eight observational studies comprising a total of 11,932 patients with high-risk or intermediate–high-risk PE compared the safety and efficacy of systemic thrombolysis with that of CDT[111]. Compared with systemic thrombolysis, CDT was associated with significantly lower in-hospital mortality (risk ratio 0.52, 95% CI 0.40–0.68, $P < 0.001$). Major bleeding events occurred in 8.2% of patients in the CDT group and 7.9% of patients in the systemic thrombolysis group and were not significantly different between the two treatment modalities (pooled risk ratio 0.80, 95% CI 0.37–1.76, $P = 0.58$), except for intracranial haemorrhage, which occurred less frequently in patients treated with CDT (RR 0.66, 95% CI 0.47–0.94, $P = 0.02$)[111]. These data indicate that CDT can reduce the amount of thrombolytics administered but does not eliminate bleeding complications. However, most of the available evidence to date is of an observational nature and lacks hard end points.

In the ongoing, parallel-design BETULA RCT[112], low-dose CDT (4 mg or 8 mg alteplase per catheter administered over 2 h) using the Uni-Fuse system is being compared with anticoagulation with heparin alone in 60 patients with intermediate-risk PE and signs of RVD (Table 5). The primary end point is the change in RV-to-LV ratio at 24 h after the procedure. Reduction in thrombus burden after 24 h, 30-day mortality, length of hospital stay, recurrent PE and lung perfusion will be assessed as secondary outcomes.

PE-TRACT[113] is an open-label, assessor-blinded RCT, comparing either CDT or mechanical thrombectomy plus anticoagulation versus anticoagulation alone in 500 patients with intermediate–high-risk PE, proximal pulmonary artery thrombus and RVD (Table 5). Primary outcomes include cardiopulmonary exercise tolerance at 3 months (assessed by the maximum rate of oxygen consumption) and NYHA functional class at 12 months. Secondary end points include 6-min walking distance and the 36-item short form survey (both at 12 months) and clinical deterioration at 7 days. With this design, PE-TRACT seems to be one of the most promising ongoing studies because the current standard of care (anticoagulation) is being compared with CDT (or USCDT or mechanical thrombectomy, depending on operator choice). The study is funded by the National Heart, Lung, and Blood Institute, which distinguishes it from some other, industry-sponsored studies in the field. In the PE-TRACT trial, symptomatology will be assessed as well as bleeding events (incidence of International Society on Thrombosis and Haemostasis major bleeding at 7 days) and events of clinical deterioration.

In general, CDT seems to improve the RV-to-LV ratio and potentially lower in-hospital mortality but bleeding risks remain. To date, no adequately powered, large-scale RCT has been conducted to evaluate the potential effect of CDT on clinical end points. An urgent need exists for RCTs comparing CDT with anticoagulation and with other interventional modalities to assess effects on mortality and symptomatology. Many such studies are either ongoing or being planned.

Ultrasound-assisted CDT

In USCDT, high-frequency ultrasound energy is combined with pharmacological thrombolysis, with the aim to separate fibrin strands, thereby maximizing the surface area of the thrombus and optimizing the dose–effect relationship of the thrombolytic agents[114–118].

EKOS Endovascular System. In the open-label ULTIMA RCT[119], 59 patients with intermediate–high-risk PE and an RV-to-LV ratio of ≥1.0 were randomly assigned to receive UFH plus USCDT with 10–20 mg rt-PA over 15 h or UFH alone (Table 4). The mean RV-to-LV ratio (the primary outcome) was reduced through to 24 h by 0.30 ± 0.20 in the USCDT group compared with 0.03 ± 0.16 in the control group ($P < 0.001$). Mean PAP was reduced by 5.7 ± 7.6 mmHg within 12 h of USCDT ($n = 26$; $P < 0.001$). A total of three minor bleeding events were reported in the USCDT group compared with one minor bleeding event in the control group ($P = 0.61$). One patient in the anticoagulation group died from pancreatic cancer. Being the first trial of its kind, ULTIMA demonstrated the usefulness of USCDT in reducing the RV-to-LV ratio and PAP, while being associated with a lower risk of bleeding than that seen in previous trials of systemic thrombolysis. However, the sample size was small and the trial was not powered for hard clinical end points.

In the SUNSET sPE RCT[120], the effectiveness of USCDT (using the EKOS Endovascular System) was compared with that of CDT (using the Uni-Fuse or Cragg–McNamara systems) in reducing the thrombus burden in 82 patients with acute intermediate–high-risk PE (Table 4). Included patients were diagnosed by CTPA with an RV-to-LV ratio of >1.0 but did not have signs of haemodynamic instability. Catheters were placed either unilaterally or bilaterally, and thrombolytic agents were infused in a controlled setting at the intensive care unit. The primary outcome was thrombus load reduction using the refined modified Miller scoring system, and the secondary end point was change in RV-to-LV ratio, both measured by CTPA. However, the thrombolytic drugs applied were not standardized between the groups (but did not differ significantly); the mean dose of alteplase was 19 ± 7 mg for USCDT and 18 ± 7 mg for CDT ($P = 0.53$), which was infused over 14 ± 6 h and 14 ± 5 h, respectively ($P = 0.99$). Both treatment modalities reduced thrombus burden: obstruction index decreased from 71 ± 8% to 50 ± 17% ($P < 0.001$) in the USCDT group compared with

73 ± 7% to 51 ± 15% ($P < 0.001$) in the CDT group, with no significant difference between the two groups ($P = 0.77$). Mean RV-to-LV ratio was more markedly decreased in the CDT group than in the USCDT group (0.59 ± 0.42 versus 0.37 ± 0.34; $P = 0.01$). Additionally, two major bleeding events (one haemorrhagic stroke and one severe vaginal bleed) and three minor bleeding events (two cases of haematemesis and one case of flank haematoma) occurred after USCDT, whereas no bleeding complications occurred in the CDT group. When analysing these results, the lack of standardization of the thrombolytic regimens has to be emphasized[121]. Second, the power calculation assumed an ambitious degree of difference in effectiveness between the two modalities, which probably resulted in the trial being underpowered. These two aspects influence the findings and show the need for adequately powered and well-controlled, head-to-head studies comparing different interventional treatment approaches for PE[121].

In the multicentre, parallel-group OPTALYSE trial[122], 101 haemodynamically stable patients with intermediate-risk PE were randomly assigned to various dosing and timing strategies of USCDT using the EKOS Endovascular System (rt-PA dose: 4 mg, 6 mg or 12 mg per pulmonary artery; infusion duration: 2 h, 4 h or 6 h). Treatment using a shorter delivery duration and lower-dose rt-PA was associated with improved RV-to-LV ratio and reduced thrombotic burden. In the treatment groups, five major bleeding events were documented, which were not significantly different between groups (however, one intracranial bleed occurred in the highest-dose group). Additionally, two recurrent PEs and two deaths were reported in the whole study population. However, the trial lacked a comparator group and, therefore, the efficacy and safety of USCDT cannot easily be compared with other potential PE treatment modalities from this trial.

The prospective, single-group, multicentre SEATTLE II trial[106] included patients with high-risk ($n = 31$) or intermediate–high-risk ($n = 119$) PE with RVD. The trial assessed USCDT with a cumulative dose of rt-PA of 24 mg injected using the EKOS Endovascular System. For unilateral PE, rt-PA was injected with one cathether at a rate of 1 ml/h for 24 h; for bilateral PE, two catheters were inserted (one in each pulmonary artery) and delivered rt-PA at a rate of 1 ml/h for 12 h. Within 48 h of the procedure, systolic PAP was reduced by 14.4 mmHg ($P < 0.001$) and the RV-to-LV ratio was reduced by 0.42 ($P < 0.001$). Within 30 days of the procedure, 15 major bleeding events were documented. This single-group study reported improvements in short-term haemodynamic function after USCDT but lacks the control group needed to draw firm conclusions.

Preliminary results from the KNOCOUT PE trial[123] were presented in 2021. A total of 489 patients with intermediate–high-risk or high-risk PE (RV-to-LV ratio of >1.0 and elevated plasma troponin levels) who underwent USCDT with the EKOS system were prospectively analysed. The investigators reported an International Society on Thrombosis and Haemostasis major bleeding rate of 2.5% (12 out of 489 patients) and no intracerebral haemorrhages at 30 days. Procedural characteristics show a mean rt-PA dose of 17.9 mg (± 7.3 mg) and a mean infusion time of 10.4 h (± 5.2 h). The RV-to-LV ratio was reduced by 38.0% at 3-month follow-up[124].

USCDT has been associated with haemodynamic improvement in patients with intermediate-risk or high-risk PE. However, because thrombolysis is not avoided, bleeding risks remain, with wide variation in the reported frequency of bleeding events between studies. The optimal thrombolytic dose for use with USCDT remains uncertain, with OPTALYSE suggesting equivalence between regimens for RV unloading but a dose-dependent response in PAP and clot burden. No adequately powered RCT has investigated the safety and efficacy of CDT or USCDT in comparison with the standard of care, which is required to assess the incremental value of these therapies. Preliminary results from the large, prospective KNOCOUT PE registry suggest lower total bleeding rates (approximately 2.5%) with USDCT than previously reported.

Against this background, investigators in the HI-PEITHO trial[125] are currently randomly assigning ≥406 patients with intermediate-risk PE

Table 2 | Anticoagulation in patients with PE according to risk factors and comorbidities

Patient group	Direct oral anticoagulant				Vitamin K antagonist	Low-molecular-weight heparin
	Apixaban	Dabigatran	Edoxaban	Rivaroxaban		
3 months of treatment						
With transient risk factors[a]	5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily	INR adjusted	Weight adjusted
3–6 months of treatment						
With transient minor risk factors	5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily	INR adjusted	Weight adjusted
With cancer[b]	5 mg twice daily	Not recommended	60 mg once daily	20 mg once daily	INR adjusted	Weight adjusted
With cancer (no gastrointestinal bleeding)[b]	Not recommended	Not recommended	60 mg once daily	20 mg once daily	INR adjusted	Weight adjusted
Indefinite treatment						
Without identifiable risk factors	5 mg twice daily (2.5 mg twice daily after 6 months)	150 mg twice daily (dose reduction not recommended)	60 mg once daily (dose reduction not recommended)	20 mg once daily (10 mg twice daily after 6 months)	INR adjusted	Weight adjusted
With persistent risk factors	5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily	INR adjusted	Weight adjusted
With recurrent VTE or PE	5 mg twice daily	150 mg twice daily	60 mg once daily	20 mg once daily	INR adjusted	Weight adjusted

INR, international normalized ratio; PE, pulmonary embolism; VTE, venous thromboembolism. [a]Discontinuation recommended if PE or VTE are secondary to major transient risk factor. [b]Continuation beyond 6 months is recommended until the cancer is cured. Information from refs. 90,92,93,149–153.

to either USCDT (with the EKOS system) or anticoagulation alone in an adaptive trial design (Table 5). PE-related mortality, PE recurrence and haemodynamic decompensation (all after 7 days) will be assessed as primary end points[42]. Secondary outcomes include changes in the RV-to-LV ratio, necessity for cardiorespiratory support, GUSTO bleeding and other adverse events, and functional parameters. Patients with intermediate–high-risk PE, signs of elevated risk (two of the following: heart rate >100 bpm, SBP <110 mmHg or respiratory rate >20 breaths per min) and signs of RVD (RV-to-LV ratio >1.0) are included.

In addition, investigators in the STRATIFY RCT[126] aim to randomly assign 210 patients to either USCDT (20 mg of alteplase over 6 h plus UFH or LMWH within 12 h of randomization), low-dose systemic thrombolysis (20 mg of alteplase over 6 h plus UFH or LMWH) or anticoagulation (UFH or LMWH) only (Table 5). Eligible patients are those presenting with intermediate–high-risk PE, as defined by the current ESC guidelines[30], and visible thrombus in the main, lobar or segmental pulmonary artery on CTPA. The primary outcome is reduction in the Miller obstruction index. Secondary outcomes include bleeding complications, functional parameters and length of hospital stay, among others.

Pharmacomechanical CDT

In pharmacomechanical CDT, thrombi are both mechanically macerated and pharmacologically dissolved by thrombolytic agents. The catheters have baskets with meshes and side holes for infusion of thrombolytic drugs. As the thrombus in the pulmonary artery dissolves, the basket expands to maintain contact with the remaining thrombus.

BASHIR Endovascular Catheter. The BASHIR Endovascular Catheter (Thrombolex) is a 7 F-compatible infusion catheter consisting of a self-expanding basket of six nitinol infusion micro-catheters. In the RESCUE trial[127], the BASHIR catheter was evaluated in a prospective, single-group study of 109 patients with intermediate-risk acute PE. The RV-to-LV ratio decreased from 1.66 ± 0.04 to 1.10 ± 0.02 ($P < 0.001$)[127].

Table 3 | Interventional devices for pulmonary embolism

Device (manufacturer)	Size (F)	FDA approval?	RCT data?
Uni-Fuse Infusion Catheter (AngioDynamics)	4–5	Yes	Yes versus anticoagulation and USCDT
Cragg–McNamara Micro Therapeutics Infusion Catheter (Medtronic)	4–5	Yes	Yes versus anticoagulation and USCDT
EKOS Endovascular System (Boston Scientific)	5.4	Yes	Yes versus anticoagulation and CDT
Indigo Aspiration System (Penumbra)	3–12	Yes	No
FlowTriever Retrieval/Aspiration System (Inari Medical)	16–24	Yes	No
BASHIR Endovascular Catheter (Thrombolex)	7	No	No
AngioJet Ultra Thrombectomy System (Boston Scientific)	3–6	Black box warning[a]	No

CDT, catheter-directed thrombolysis; RCT, randomized controlled trial; USCDT, ultrasound-assisted catheter-directed thrombolysis. [a]Might lead to bradycardia, pulmonary vasospasm and worsening hypoxia as well as increased mortality[154].

No device-related major complications were reported and one PE-related death occurred within 1 month. The pulmonary artery obstruction, as measured by the refined modified Miller index, was reduced by 36% on a repeat CT scan at 48 h. Of note, the BASHIR catheter has not been directly compared with a control group. Further studies and RCTs are therefore necessary to assess its utility in patients with intermediate–high-risk PE.

Aspiration thrombectomy

In aspiration thrombectomy, thrombi in the pulmonary artery are aspirated by suction-generating catheters attached to a negative pressure pump (such as with the Indigo Aspiration System, Penumbra) or by using a syringe and creating a vacuum (such as with the FlowTriever Retrieval/Aspiration System, Inari Medical). The pulmonary artery is accessed percutaneously by either femoral or jugular venous access. When proximal to the occlusive thrombus, aspiration is performed[128]. In large-bore aspiration thrombectomy, 16–24 F catheters are advanced via femoral or jugular venous access and contain a catheter attached to a syringe. With these devices, if necessary, special discs can be advanced through the large-bore catheter to break and entrap thrombi, allowing subsequent extraction through the aspiration catheter[129,130] (Fig. 4).

FlowTriever. The FlowTriever Retrieval/Aspiration System is a mechanical, percutaneous, large-bore aspiration thrombectomy device indicated for use in the peripheral vasculature and pulmonary artery. The prospective, multicentre, single-arm FLARE study[131] assessed the safety and effectiveness of the first-generation FlowTriever device in 104 patients with intermediate–high-risk PE with RVD (RV-to-LV ratio >0.9). After a mean follow-up of 48 h, the RV-to-LV ratio was reduced by an average of 0.38 (from 1.56 before the intervention to 1.18 afterwards; $P < 0.0001$) and mean PAP was reduced by 2.0 mmHg ($P = 0.001$)[131]. Of note, 43 patients (41.3%) did not require a stay in the intensive care unit after the procedure, and the mean duration of the intensive care unit stay was 1.5 days. A total of six major adverse events were reported in four patients[131] (one major bleed, one pulmonary vascular injury, one pulmonary infarction with associated haemorrhage, two ventilatory deteriorations and one ventricular fibrillation caused by ST-segment elevation myocardial infarction with consequent coronary intervention)[131]. One patient died within 30 days of the procedure from respiratory failure as a consequence of undiagnosed metastatic breast cancer. No device-related deaths were reported. The rate of major bleeding was low (0.9%).

The ongoing, multicentre, prospective FLASH registry is designed to investigate the safety and effectiveness of the second-generation FlowTriever device[132,133]. The results from the first 800 patients included in the USA have been reported. Of these, approximately 8% had high-risk PE and 92% had intermediate-risk PE (of which 83% were intermediate–high-risk PE)[133]. Approximately one-third of the included patients had thrombolytic contraindications, representing a common PE cohort. At baseline, patients presented with a mean composite RV-to-LV ratio of 1.50 ± 0.46 (as assessed by CTPA) and a mean sPESI score of 1.6 ± 1.1, and 13% of patients presented with severe pulmonary hypertension with a systolic PAP of >70 mmHg (ref. 133). The total median procedure time was 66 min (IQR 51–92 min) and median blood loss due to aspiration was 225.0 ml (IQR 95–400 ml)[133]. A total of 734 patients completed the 30-day follow-up. After 30 days, six deaths were reported, none of which was deemed to be related to the device or the procedure; however, two deaths were due to PE or recurrent PE. Additionally, the 30-day rate of all-cause readmission to hospital was

Table 4 | Published RCTs on catheter-directed therapies in PE

Study	Device	Number of patients	Cohort	Comparison	Efficacy outcomes	Safety outcomes
Kroupa et al.[109]	Cragg–McNamara	23	Intermediate-risk PE	CDT versus anticoagulation	Reduction in RV-to-LV ratio in 7 of 12 patients versus 2 of 11 patients (P=0.03) Decrease in systolic PAP by >30% in 11 of 12 versus 2 of 11 patients (P=0.001) Reduction in Qanadli score: no significant difference	Safety end points achieved in both groups: no intracranial or life-threatening bleeding reported
CANARY[110]	Cragg–McNamara	85	Intermediate–high-risk PE	CDT versus anticoagulation	Mean RV-to-LV ratio: 0.7 versus 0.8 (P=0.01) RV recovery in 43 of 46 patients versus 28 of 39 patients (P=0.009)	Bleeding: 8 versus 0 Death: 0 versus 3
ULTIMA[119]	EKOS	59	Intermediate-risk PE	USCTD versus anticoagulation	Reduction in RV-to-LV ratio 0.30 versus 0.03 (P<0.001)	Minor bleeding: 4 versus 0
SUNSET sPE[120]	Cragg–McNamara, Uni-Fuse or EKOS	82	Intermediate-risk PE	CDT versus USCDT	Reduction in mean RV-to-LV ratio: 0.59 versus 0.37 (P=0.01) Reduction in mean difference in thrombus score: −10 versus −9 (P=0.76)	Major bleeding: 0 versus 2

CDT, catheter-directed thrombolysis; LV, left ventricular; PAP, pulmonary artery pressure; PE, pulmonary embolism; RCT, randomized controlled trial; RV, right ventricular; USCDT, ultrasound-assisted catheter-directed thrombolysis.

6.2% (1.4% related to PE). At 48 h after the procedure, 11 major bleeds (none of which was intracranial) and 3 intraprocedural major adverse events (2 clinical deterioration and 1 tricuspid valve injury) occurred, resulting in a major adverse event rate of 1.8% at 48 h. On-table mean PAP decreased from 32.6 ± 9.0 mmHg to 24.9 ± 8.9 mmHg (P < 0.0001) and RV-to-LV ratio as assessed by echocardiography at 48 h after the procedure decreased from 1.23 ± 0.36 to 0.98 ± 0.31 (P < 0.0001). Haemodynamic parameters, such as cardiac index and heart rate, improved, as did functional outcomes such as dyspnoea and the need for supplementary oxygen. In conclusion, these single-group, observational studies suggest that treatment with the FlowTriever system is associated with rapid haemodynamic recovery and a good safety profile, although future RCTs are needed to assess causality[132].

A retrospective analysis investigated 34 patients with high-risk PE (defined as cardiac arrest, persistent hypotension (SBP <90 mmHg), vasopressors required to achieve SBP >90 mmHg or an SBP drop of >40 mmHg for >15 min) or intermediate–high-risk PE with features of severe cardiorespiratory deterioration but a preserved SBP (defined as respiratory failure requiring intubation or haemodynamic evidence of cardiogenic shock — an indirect Fick cardiac index <1.8 l/min/m^2) who underwent large-bore thrombectomy[134]. At baseline, patients had a mean RV-to-LV ratio of 1.7 ± 0.1 and all presented with elevated plasma levels of cardiac natriuretic peptides, 18 patients had severe hypotension qualifying as high risk, 12 patients had intermediate–high-risk PE and had evidence of subclinical cardiogenic shock (Fick cardiac index <1.8 l/min/m^2), and 4 patients were in respiratory failure requiring intubation[134]. Mean PAP was reduced by 7.5 ± 1.1 mmHg (−23%; P = 0.0002) and RV performance improved by 20% (cardiac index increased by 0.4 ± 0.1 l/min/m^2; P = 0.0146) immediately after the procedure[134]. Procedural failure occurred in two patients (one death from severe PE and one extracorporeal membrane oxygenation after only minimal aspiration of thrombus and consecutive clinical deterioration with hypotension despite inotropes)[134]. Although retrospective, single-group and rather small, this analysis provides data on patients with high-risk PE and suggests that large-bore aspiration thrombectomy might be feasible in patients with higher-risk PE[134].

To summarize these findings, large-bore aspiration thrombectomy has been shown in single-group studies to reduce thrombus burden and PAP and to improve RVD in patients with high-risk or intermediate–high-risk PE. However, RCTs assessing the usefulness of these devices in comparison with medical treatment or other device-based approaches are lacking. Given that a substantial proportion of patients with PE have concomitant relative or absolute contraindications to thrombolysis, the use of large-bore aspiration thrombectomy has obvious potential advantages in these patients because no thrombolytic drugs are required. However, no firm conclusions can be drawn in the absence of data from RCTs.

RCTs are planned or ongoing in this area. The prospective, multicentre PEERLESS RCT[135] is designed to evaluate large-bore thrombectomy compared with CDT for patients with acute intermediate–high-risk PE (Table 5). A total of 550 patients in PESI class III–V, or with sPESI ≥1, haemodynamic stability, echocardiographic or CTPA-documented RVD, and elevated plasma levels of cardiac troponins will be included. The trial is designed to include a non-randomized cohort of up to 150 patients with an absolute contraindication to thrombolytics. The composite clinical end point is a win ratio of all-cause mortality, intracranial haemorrhage, major bleeding, clinical deterioration defined by haemodynamic or respiratory worsening, and/or escalation to bailout therapy, intensive care unit admission, and length of stay in the intensive care unit during the index hospitalization and after the index procedure (all within 7 days after the procedure).

The FLAME trial[136] will report outcomes of large-bore thrombectomy in up to 250 patients with high-risk PE. The composite end point is all-cause mortality, clinical deterioration, bailout and major bleeding. Furthermore, the VQPE trial[137] is designed to evaluate changes in ventilation and perfusion CTPA before and at 6 months after large-bore mechanical percutaneous thrombectomy compared with systemic anticoagulation alone in 50 patients with PE and signs of respiratory compromise.

Indigo Aspiration System. The single-group, multicentre EXTRACT-PE trial[128] included 119 patients with intermediate-risk PE (SBP >90 mmHg and RV-to-LV ratio >0.9) undergoing thrombus aspiration with the 8 F Indigo Aspiration System. The primary efficacy outcome was the difference in RV-to-LV ratio as assessed by CTPA, and the primary safety end point was a composite of device-related death, major bleeding

and device-related serious adverse events within 48 h. After the procedure, the RV-to-LV ratio decreased on average by 0.43 ± 0.26 (95% CI 0.38–0.47, $P < 0.0001$), corresponding to a 27 ± 13% reduction in RV-to-LV ratio (1.47 ± 0.30 before versus 1.04 ± 0.16 after)[128]. The mean reduction in systolic PAP was 4.3 mmHg (95% CI 2.6–5.9 mmHg, $P < 0.0001$). There were two major bleeding events (one leading to death) and one device-related serious adverse event (pulmonary vascular injury) in two patients, resulting in a major adverse event rate of 1.7% (95% CI 0.0–4.0%, $P < 0.0001$)[128], thereby meeting the predefined safety end point. Of note, mean procedural time was 37 min (95% CI 23.5–60.0 min) and the mean time in the intensive care unit was 1 day[128]. The trial lacked a control group, and follow-up was limited to 30 days. Therefore, although promising, these findings are considered hypothesis-generating.

Several small, prospective analyses have been conducted assessing the feasibility of the Indigo Aspiration System. However, all these studies are characterized by small sample sizes (n = 6–18) and single-group designs[138–141]. Given that most of the available evidence is observational, further studies evaluating the usefulness of the device are needed. Assessment of the next-generation Indigo device, the CAT12 (which has a 12 F catheter), is currently being carried out in the observational, single-arm STRIKE PE study[142]. The first RCT with the Indigo CAT12 device, the STORM-PE trial[143], has been announced and will begin recruitment shortly, involving 100 patients randomly assigned to aspiration thrombectomy with the CAT12 device or anticoagulation alone. The primary end point will be the RV-to-LV ratio at 48 h, with multiple secondary end points assessed at long-term follow-up. In addition, the CATH-PE case–control study[144] is designed to include 100 patients with high-risk or intermediate–high-risk PE who undergo aspiration thrombectomy with the Indigo device. Furthermore, aspiration thrombectomy with the Indigo device will be compared with hydromechanical defragmentation by pigtail catheters in 200 patients with intermediate–high-risk PE in an open-label, parallel-assignment, prospective RCT[145].

Indications for device-based management

PE remains the third leading cause of cardiovascular death, with unsatisfactorily high mortality[1,2]. Systemic thrombolysis, the first choice of treatment according to current guidelines, reduces mortality in patients with high-risk PE but is associated with an increased risk of bleeding, particularly in older patients (aged ≥75 years)[146]. In patients who are haemodynamically unstable, this trade-off seems acceptable. However, in patients with intermediate–high-risk PE and signs of RVD but without haemodynamic instability, the optimal management strategy remains uncertain. According to a meta-analysis, full-dose systemic thrombolytics do not significantly reduce mortality in these patients (OR 0.64, 95% CI 0.35–1.17) and are associated with bleeding events[95]. Given these circumstances, several interventional therapies are under clinical investigation with the aim of reducing bleeding complications by either lowering the total dose of thrombolytic agents administered (CDT and USCDT) or eliminating thrombolysis entirely (large-bore percutaneous mechanical thrombectomy or aspiration thrombectomy).

Moreover, a clinically relevant proportion of patients with high-risk PE present with concomitant contraindications for systemic thrombolysis[133]. In these patients, interventional treatment options seem to be a particularly attractive alternative reperfusion strategy[30]. Given that bleeding complications have not been eliminated by the use of CDT or USCDT, aspiration thrombectomy seems to be especially encouraging, although prospective registry enrolment in a real-world scenario and RCTs might report higher rates of bleeding complications from these devices than were reported in trials with retrospective consent.

Some of these interventional therapies have been shown to reduce RVD[110,120,128,131,132], an indicator of early mortality in patients with PE[61,75,147]. However, most of these data are derived from observational and retrospective studies that were not adequately powered to assess the effect on clinical end points and did not have an appropriate control group. Given that PE causes not only death but also sustained morbidity through diseases such as CTEPD and post-PE syndrome[69,70], the management of PE should also aim to improve long-term outcomes. Interventional therapies have been shown to reduce functional limitations as well as to improve haemodynamic measures in the short term in single-group studies. The question remains whether the removal of substantial amounts of thrombus from the pulmonary circulation could help to prevent physical impairment (post-PE syndrome) or

Table 5 | Ongoing RCTs on catheter-directed therapies in PE

Study	Device	Number of patients	Cohort	Comparison	Efficacy outcomes	Safety outcomes
BETULA[112]	Uni-Fuse	60	Intermediate-risk PE and signs of RVD	Low-dose CDT versus anticoagulation	RV-to-LV ratio, lung perfusion, length of hospital stay	In-hospital mortality, recurrent PE, major and minor bleeding
PE-TRACT[113]	CDT or USCDT device	500	Intermediate–high-risk PE	CDT or USCDT versus anticoagulation	Peak oxygen consumption, NYHA functional classification	ISTH major bleeding and clinical deterioration
HI-PEITHO[125]	EKOS	406 (adaptive design allowing further enrolment)	Intermediate–high-risk PE	USCDT versus anticoagulation	PE-related mortality, PE recurrence, cardiorespiratory decompensation or collapse	GUSTO and major bleeding per ISTH definition, SAE, all-cause mortality
STRATIFY[126]	EKOS	210	Intermediate-risk PE	USCDT versus low-dose systemic thrombolysis versus anticoagulation	Reduction in Miller score	TIMI bleeding, length of hospital stay, subjective dyspnoea, mortality
PEERLESS[135]	FlowTriever or CDT device	550	Intermediate–high-risk PE	Large-bore mechanical thrombectomy versus CDT	ICU admission, length of ICU stay during the index hospitalization and after the index procedure	All-cause mortality, ICH, major bleeding per ISTH definition, clinical deterioration

CDT, catheter-directed thrombolysis; GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; ICH, intracranial haemorrhage; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; LV, left ventricular; PE, pulmonary embolism; RV, right ventricular; RCT, randomized controlled trial; RVD, right ventricular dysfunction; SAE, serious adverse events; TIMI, thrombosis in myocardial infarction; USCDT, ultrasound-assisted catheter-directed thrombolysis.

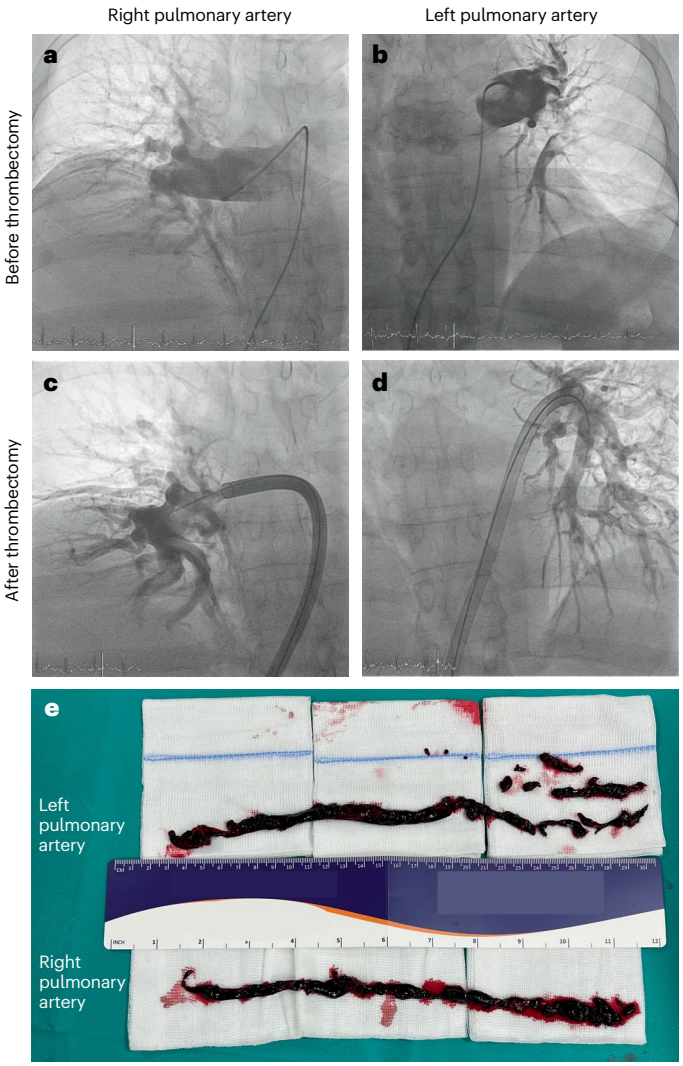

Fig. 4 | Large-bore thrombectomy. Pulmonary angiography of the right and left pulmonary arteries of a patient with acute bilateral intermediate–high-risk pulmonary embolism before (parts **a** and **b**) and after (parts **c** and **d**) large-bore thrombectomy using the FlowTriever Retrieval/Aspiration System (Inari Medical). Dye defects show intravascular thrombi. The aspirated thrombi from the right and left pulmonary arteries are shown (part **e**).

the development of CTEPD. Clinical trials evaluating the long-term effects of interventional treatments on functional outcomes are of utmost importance. The PE-TRACT[113] and HI-PEITHO[125] RCTs are of particular importance because these trials are designed to compare the present standard of care (anticoagulation) with novel interventional therapies (CDT or USCDT) in patients with intermediate–high-risk PE.

Conclusions

Interventional, device-based treatment of PE is rapidly evolving. However, most of the available clinical data are derived from studies without a control group receiving the current standard-of-care therapy. Therefore, interventional therapies cannot be routinely recommended in patients with intermediate–high-risk or high-risk PE until further evidence of their safety and efficacy is available. However, morbidity and mortality remain high when current management strategies are used to treat acute PE, suggesting that innovation is required, guided by appropriately conducted RCTs. Indeed, only four RCTs have so far been published (two evaluating CDT and two evaluating USCDT), none of which was adequately powered to detect differences in clinical outcomes.

In the real-world setting of acute PE, the decision-making processes should involve ad hoc interdisciplinary consultation by the PE response team of a hospital, based on local protocols and the available expertise and resources, for patients presenting with haemodynamically unstable, high-risk or intermediate–high-risk PE. Introduction of a PE response team is attractive for several reasons and is encouraged by current guidelines[30]. Implementing a PE response team is associated with increased use of advanced therapies in PE, seems to shorten the length of hospital stay and possibly even reduces mortality[31,39,148]. However, PE response teams have to be developed further to strengthen their positive effect on PE care. The PE response team should also make decisions concerning 'rescue' therapy for patients who develop haemodynamic decompensation despite therapeutic anticoagulation or even systemic thrombolysis as well as for those with contraindications to thrombolysis. Procedures should be performed by operators with adequate training and volume, and patients should preferably be included in ongoing prospective trials or at least in prospective registries to improve the operator volume and quality of evidence.

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F.G. and F.M. researched data for the article, discussed its content and wrote the manuscript. All the authors reviewed/edited the article before submission.

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