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REVIEW ARTICLE

Interventional therapies in acute pulmonary embolism

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ABSTRACT

Pulmonary embolism (PE) is the third most frequent cause of cardiovascular mortality and a frequent preventable complication in hospitalized patients. In recent years, several catheter-directed interventions (CDI) strategies and devices for treating acute PE have emerged, such as local thrombolysis, ultrasound-facilitated local thrombolysis, and medium- and large-bore aspiration catheters. Each device has different advantages and supporting literature, and thus, the choice should be individualized. Interventional treatment for PE is based on risk stratification, with current guidelines positioning CDI as a rescue treatment for high-risk PE patients in whom systemic thrombolysis has failed or is contraindicated and for intermediate-high-risk PE patients with clinical deterioration despite anticoagulation. However, clinical practice and several consensus documents favor a more invasive approach with CDI, anticipating clinical deterioration in patients at risk. This review outlines the available CDI options, the scientific evidence supporting these therapies, and the clinical scenarios in which they could be used.

Keywords: Embolectomy. Fibrinolytic therapy. Percutaneous aspiration thrombectomy. Pulmonary embolism. Therapeutic thrombolysis

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INTRODUCTION

In contemporary medicine, acute thrombotic occlusion of a coronary, cerebral, or peripheral artery triggers the need to restore distal flow through emergency intervention. This concept evolved in the last 30 years, largely due to the stunning evolution of percutaneous interventions, very well established in myocardial infarction and many stroke cases. However, the need to mechanically restore blood flow in acute pulmonary embolism (PE) is not so widely endorsed. Factors that limit PE intervention include lack of strong evidence, heterogeneity in PE intervention techniques and outcomes, limited accessibility to interventional therapy, and an underestimation of PE hemodynamic deterioration risk. Yet, acute PE is the first preventable cause of death in hospitalized patients, and venous thromboembolic disease (including PE and deep vein thrombosis) is the third cause of cardiovascular death after myocardial infarction and stroke[1,2].

According to the European Society of Cardiology (ESC) guidelines, the treatment of PE is based on patient risk assessment[1]. Reperfusion therapy with systemic thrombolysis (ST) is the first-line therapy for high-risk PE (hemodynamic instability: systolic blood pressure [SBP] < 90) and intermediate-high-risk PE who deteriorate on anticoagulant drugs. However, even in a clear indication for reperfusion, ST is used in roughly 30% of the cases in real life, not only because of formal contraindications but also because of a lack of guidelines compliance[3-5]. This noncompliance relates generally to fear of bleeding complications: the risk of major bleeding is ≈10–15%, especially in old comorbid patients[3]. Therefore, the need for a safer alternative to pharmacological reperfusion seems attractive. The intermediate-high-risk PE (i.e., positive cardiac biomarkers + right ventricular [RV] dysfunction) includes a wide spectrum of patients with varying mortality rates from 5 to 10%. The reason to avoid upfront reperfusion therapy with ST in this group of patients[1] is mainly due to the results of the Pulmonary embolism thrombolysis (PEITHO) trial, which demonstrated hemodynamic improvement in intermediate-high-risk PE patients but at the cost of a prohibitive increase in major bleeding[6]. Therefore, as a concept, reperfusion could have a role in intermediate-high-risk PE patients, provided the bleeding risk could be controlled.

Surgical embolectomy as a rescue therapy is rarely performed in highly selected centers, leaving catheter-directed interventions (CDIs) as the main alternative to pharmacological reperfusion. The therapy has evolved together with device iteration to a standardized, reproducible, safe, and effective intervention, lacking only strong randomized evidence. ESC guidelines suggest using CDI as a rescue treatment in patients with high-risk PE in whom ST has failed or is contraindicated and for intermediate-high-risk PE patients with clinical deterioration despite anticoagulation, with a IIa indication[1].

However, current clinical practice is going beyond the guidelines: CDIs are being used upfront in patients with intermediate-high-risk PE and additional risk parameters (e.g., lactate elevation) based on faster RV failure

improvement and hemodynamic parameters, with relatively low bleeding rates[2,7]. Additionally, they are currently used as an alternative to ST in those high-risk PE patients stable enough to be taken to the catheterization laboratory. To configure the next set of guidelines and settle the discrepancies between the current 2019 guidelines and clinical practice, several randomized studies with clinical outcomes are ongoing. Given the aforementioned discrepancies, in this review, we will outline the interventional alternatives and the different clinical scenarios in which they may be used.

INTERVENTIONAL STRATEGIES AND DEVICES

CDIs aim to actively remove the thrombus and accelerate pulmonary artery recanalization to normalize pulmonary perfusion. It is important to highlight that complete thrombus removal, as in cerebral or coronary interventions, is not usually required for clinical improvement, as the organ reserve is large, the consequences of lung infarction are not critical, and the life-threatening pathology is RV pressure overload. Broadly, these aims are similar to the ones sought by ST and might be expressed as "reperfusion," a word frequently used in the setting of myocardial infarction or stroke. CDIs have evolved significantly in the last decade, from the use of nonspecific devices and heterogeneous technical approaches to a more homogeneous set of specific devices and techniques now available. Fig. 1 summarizes the advantages of each CDI approach.

Nonspecific devices

Local thrombolysis

The rationale for local thrombolysis (LT) is essentially twofold: (i) to reduce the absolute thrombolytic dose by approximately 5- to 10-fold and (ii) to facilitate drug penetration into the clot. This therapy aims to have similar hemodynamic benefits to ST, with a lower incidence of major bleeding and almost zero intracranial bleeding. Pigtail and any multihole perfusion catheters (e.g., Uni-Fuse Infusion Catheter [AngioDynamics, New York, USA] and Cragg–McNamara Micro Therapeutics Infusion Catheter [Medtronic, Minneapolis, USA]) are normally used in these cases, by advancing them to the pulmonary arteries, where they can be used to measure pulmonary artery pressure, perform angiograms, and inject the thrombolytic drug (Fig. 2).

The dosing regimen is not standardized and usually involves the perfusion of 0.5–1.0 mg/h alteplase, with a total dose of 4–30 mg, compared with the standard ST alteplase dose of 100 mg. Sometimes an initial bolus is administered. Another significant advantage of this procedure is that the venous access might be downsized up to four French (Fr), thus allowing the operator to use an upper limb access, which is known to be associated with a lower incidence of peri-procedural major bleeding compared with femoral access[8,9].

Several studies, including randomized trials, have assessed the effectiveness of LT in acute PE. The open-label randomized

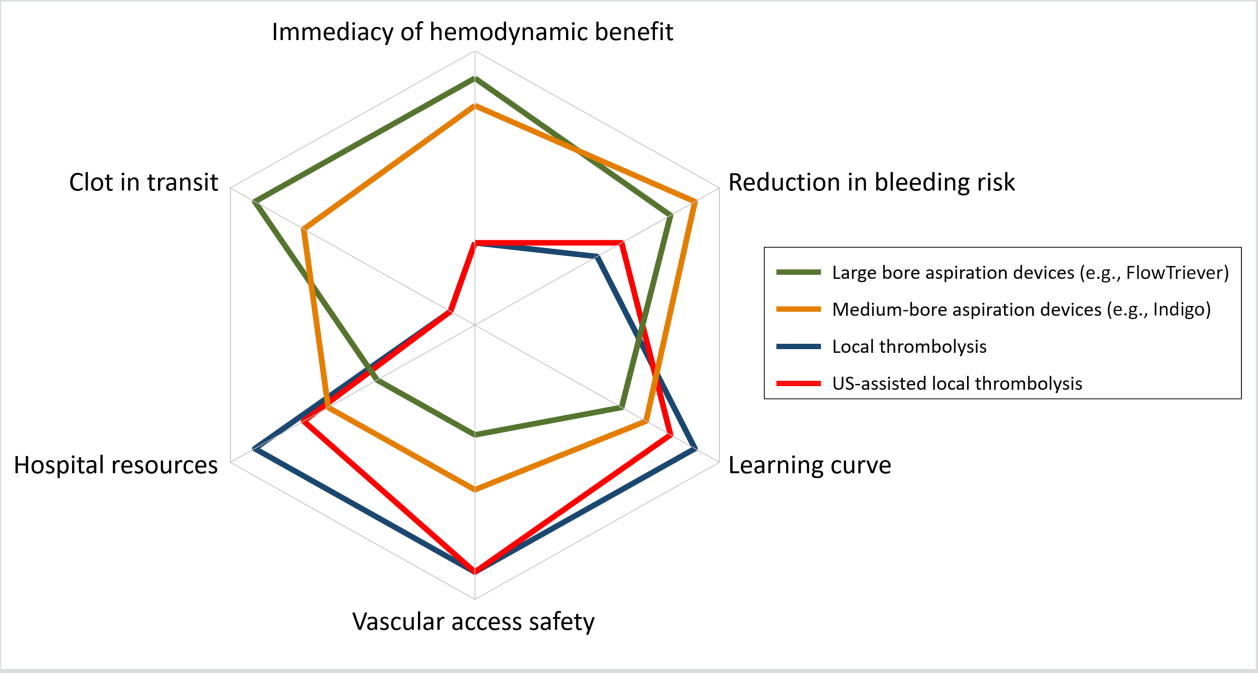

Figure 1. Radar plot representing the characteristics of the different CDI approaches.
CDI: catheter-directed interventions; US: ultrasound.

Catheter-directed thrombolysis versus anticoagulation monotherapy in patients with acute intermediate-high-risk pulmonary embolism (CANARY) trial compared LT with anticoagulation alone in 94 patients with intermediate-high-risk PE[10]. The study was prematurely stopped due to the COVID-19 pandemic, and the primary endpoint (i.e., RV-left ventricle [LV] ratio > 0.9 at 3 months) did not differ between groups. However, the mean RV-LV ratio was significantly lower in the LT group at 3 months, and the RV recovery was seen more frequently in this group. Eight bleeding events were reported, all of them being in the LT group. Another small randomized controlled trial compared LT with anticoagulation alone in 23 patients with intermediate-high-risk PE[11]. In this study, a reduction in the RV-LV ratio and a significant decrease in systolic pulmonary artery pressure were more frequent in the LT group. No major bleeding events were reported in this study. In a meta-analysis including 12 studies (11 observational, 1 trial) of patients with intermediate-high-risk PE, LT was associated with lower short- and long-term mortality as compared with anticoagulation alone, while the risk of bleeding did not differ between the two strategies[12]. Also, another meta-analysis, including observational studies, demonstrated a lower incidence of intracranial bleeding in patients treated with LT than ST, with no differences between the incidence of major bleeding in patients with intermediate-high and high-risk PE[13].

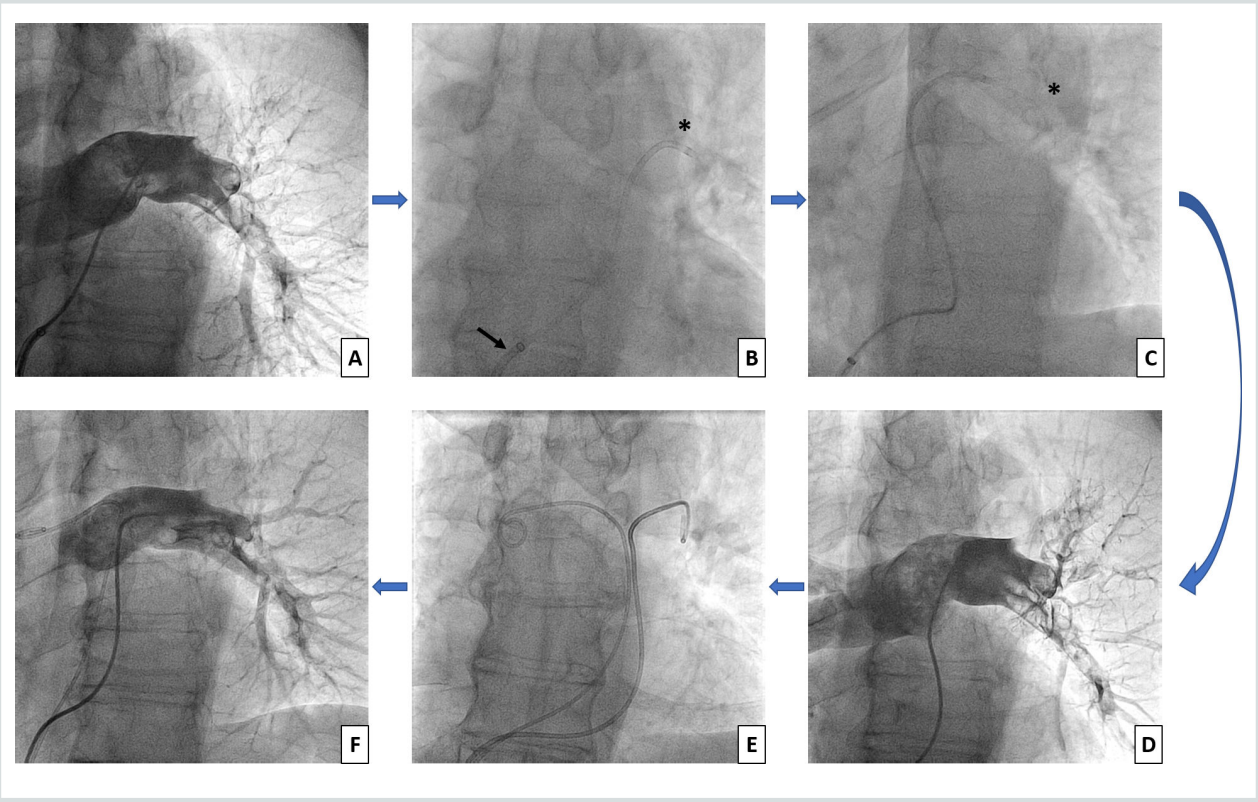

Figure 2. Representative case of interventional treatment for acute pulmonary embolism with nonspecific devices. **A:** left pulmonary artery angiogram at the procedure start. **B**: first, thrombus aspiration with a nondedicated catheter was performed using an 8-Fr Judkins right coronary guiding catheter (*) advanced through an 8.5-Fr deflectable sheath (arrow). **C:** afterward, thrombus fragmentation with a 6-Fr pigtail catheter was performed (*). **D:** the angiogram showed a modest improvement in pulmonary artery flow. **E:** two pigtail catheters were advanced, and a 24-hour perfusion of 8 mg alteplase was performed. **F:** the angiogram performed before catheter removal showed improved blood flow in the left pulmonary artery.

In summary, treatment with LT is inexpensive and technically easy, with the potential benefit of faster hemodynamic improvement as compared with anticoagulation alone. Although the risk of major bleeding may be lower than with ST, it is not negligible, and the safety of this therapy in patients with very high bleeding risk or contraindications to thrombolysis is uncertain. Moreover, the need for drug perfusion over several hours complicates the logistics of the procedure and limits its use in high-risk patients where there is a need for rapid reperfusion to reach hemodynamic stabilization.

Thrombus fragmentation

Nonspecific catheters such as pigtails can be used in a rotational fashion to disrupt the thrombus in an attempt to improve distal blood flow in the pulmonary arteries (Fig. 2). In fact, a survey conducted at the 2021 ESC Congress to 157 centers across Europe showed that mechanical fragmentation with

pigtail catheters was the most common CDI for acute PE at that moment[14]. However, clot fragmentation carries the risk of distal embolization, vascular wall injury, and a lack of consistent efficacy and safety data. It could, therefore, be considered only as an alternative in situations where no other CDI option is available.

Thrombus aspiration

The main goal of thrombectomy is to safely remove the thrombus from the vascular bed while avoiding distal embolization and sparing as much blood as feasible. If dedicated devices are lacking, large-diameter (≥8 Fr) guiding coronary catheters or long sheaths could be used (Fig. 2), aspiration by using a syringe connected to the catheter end. The mother-and-child technique, which involves advancing the coronary catheter inside a catheter with a larger diameter, improves efficiency, allowing catheter externalization in case of complete occlusion. The main advantages of this technique are similar to other nonspecific interventions, such as very low cost, wide availability, and (depending on size) lower risk vascular access. However, these devices will soon be replaced by dedicated devices, since the amount of thrombus that can be removed may be significantly lower.

Another aspiration device that has been used off-label for PE[15] despite not being specifically designed to this end, is the AngioVac system (AngioDynamics), which consists of a large 24-Fr catheter connected to a continuous aspiration pump, originally designed to remove peripheral venous thrombi.

Specific devices

CDI therapy awareness is increasing, driving a need for developing safer, more effective, and innovative devices. Several medical device companies have developed devices for the percutaneous treatment of PE. We will describe those that are currently marketed in Europe with indications for PE intervention as follows.

Local thrombolysis

The EKOS Endovascular System (Boston Scientific, Marlborough, USA) consists of a 5.4-Fr dual-lumen catheter, with one lumen used for thrombolytic infusion and the other for delivering ultrasound system and saline infusion to cool the system. Usually, two catheters are needed in bilateral PE. The performance of this device is based on the premise that delivering ultrasound energy within the thrombus may disrupt fibrin, assisting in mechanical disaggregation of the clot and thus allowing for the thrombolytic agent to access its site of biological action on the fibrin protein (ultrasound assisted-LT [USAT]). USAT can reduce procedural time and drug dose to as little as 4 mg per artery for 2 h[16] and was the first specific CDI device to be cleared by the Food and Drug Administration (FDA) for treating acute PE, thanks to the results of the Ultrasound accelerated thrombolysis of pulmonary embolism (ULTIMA) trial. This trial included 59 intermediate-high-risk PE

patients who were randomized to receive USAT versus anticoagulation alone[17]. The mean RV-LV ratio (the primary outcome) at 24 h was further reduced in the USAT group as compared with the control group, as well as the mean pulmonary artery pressure, with no differences in bleeding events between the two groups. The Prospective, single-arm multicenter trial of EkoSonic® endovascular system and activase for treatment of acute massive and submassive pulmonary embolism (SEATTLE II) included intermediate-high and high-risk PE patients who were treated with the EKOS system (alteplase dose: 24 mg)[18]. Within 48 h of the procedure, the pulmonary artery pressure and the RV-LV ratio were significantly reduced in these patients. A concerning incidence of major bleeding of 10% was reported; however, in this study, a significant percentage (21%) of the patients included had high-risk PE, which is known to be associated with a higher risk of major bleeding[19]. The standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism (SUNSET sPE) trial compared the effectiveness and safety of USAT with LT in 82 patients with acute intermediate-high-risk PE[20]. The thrombus burden reduction did not differ between groups, and the RV-LV ratio was further decreased in the LT group. However, due to the lack of procedural standardization in this trial, the results should be interpreted with caution. In any case, and as long as no clinical trials demonstrate the superiority of one therapy over the other, an argument could be made in favor of applying the advantages, disadvantages, and indications of LT to USAT.

The Bashir Endovascular Catheter (Thrombolex, Philadelphia, USA) is a 7-Fr compatible device that consists of a pharmaco-mechanical infusion catheter with an expandable basket that contains six nitinol-reinforced infusion limbs[21]. The Bashir device acts mechanically and through thrombolytic drug infusion across the cross-section of the thrombus. In the single-group Reperfusion with the Bashir endovascular catheter for intermediate-risk pulmonary embolism (RESCUE) trial, the Bashir catheter was evaluated in 109 patients with acute intermediate-high-risk PE, using a total alteplase dose of 12–14 mg per procedure[22]. In this study, the RV–LV ratio improved significantly, and no device-related major complications were reported.

In summary, specific LT devices are promising, but further clinical trials with clinical outcomes comparing them with anticoagulation and other devices in terms of efficacy and safety are needed. The High-risk pulmonary embolism thrombolysis (HI-PEITHO) trial (NCT04790370), which is currently recruiting could be the pivotal trial for USAT (Table 1). This large clinical trial will randomize more than 500 intermediate-high-risk PE patients (with additional risk criteria for hemodynamic collapse) to USAT plus anticoagulation or anticoagulation alone. For the first time, PE-related hard clinical endpoints will be assessed (mortality, PE recurrence, and cardiorespiratory decompensation or collapse). Therefore, the results of this study will constitute a milestone in the interventional treatment of acute PE and potentially lead

to an update in specific guideline indications.

Thrombus aspiration

A substantial evolution has been observed in this field during the last few years, with the design and iteration of large-caliber devices and novel aspiration and blood loss-saving systems. These features have made contemporary aspiration thrombectomy one of the most promising CDI therapies in acute PE.

The FlowTriever system (Inari Medical, California, USA) is a large-bore aspiration catheter available in sizes from 16 to 24 Fr, advanced to the proximal main or lobar pulmonary arteries to perform thrombus removal through a large syringe that produces a vacuum (Fig. 3)[23]. The catheter catalog includes a smaller 16-Fr catheter and a curved 20-Fr catheter to reach most lobar or proximal segmental thrombus locations. Additionally, this device provides the option of performing mechanical thrombectomy with special nitinol devices to manage more organized and adherent clots. Another important novel feature of this device is the FlowSaver system, which is designed to reduce blood loss by filtering aspirated thrombi for blood reinfusion back into the patient. The multicenter, single-arm, prospective FlowTriever pulmonary embolectomy clinical study (FLARE)[24] and FlowTriever system clinical study for acute pulmonary embolism (FLASH)[25] registries have demonstrated promising results of this device in >1,000 patients with intermediate-high and high-risk PE, showing a significant improvement in the RV-LV ratio and pulmonary artery pressure and a low incidence of adverse events in the short term. Furthermore, the FlowTriever for acute massive pulmonary embolism trial (FLAME) was a prospective, multicenter, nonrandomized parallel group that included 115 patients with high-risk PE who were treated with FlowTriever or with other contemporary therapies (context arm)[7]. The primary endpoint of this study was an in-hospital composite of all-cause mortality, bailout to alternate reperfusion therapy, clinical deterioration, and major bleeding, which occurred in 17% of FlowTriever patients and 64% of context arm patients ($p < 0.01$). Although this study was not randomized, and some selection bias must be acknowledged, these results are promising for this therapy in the context of high-risk PE patients.

The potential advantages of large-bore aspiration devices are the high amount of retrieved thrombus and the fast resolution of the obstruction, avoiding thrombolytic drugs. However, the pitfalls of these devices are the large venous access required (mostly femoral venous access) and a more time and technically demanding procedure.

Importantly, pivotal trials for large-bore mechanical thrombectomy for acute PE are currently ongoing (Table 1). The pulmonary embolism thrombectomy versus anticoagulation in intermediate-risk pulmonary embolism study (PEERLESS, NCT05111613), which has recently finished the recruitment stage and will present results in late 2024, randomized 550 intermediate-high-risk PE patients to receive

Table 1. Pivotal ongoing clinical trials in interventional treatment for acute pulmonary embolism

Clinical trials	*n*	Key inclusion criteria	Treatment arms	Primary endpoint
HI-PEITHO (NCT04790370)	544	– RV dysfunction (RV-LV ratio ≥ 1). – Serum troponin elevation. – At least two of the following: *Tachycardia ≥ 100 bpm. *SBP 90–110 mmHg for 15 min. *Respiratory rate > 20 per min or O_2 saturation < 90% on room air.	a. Anticoagulation alone. b. Anticoagulation + USAT (Ekos device)	– Within 7 days of randomization: *PE-related mortality *PE recurrence *Cardiorespiratory decompensation or collapse – Key secondary outcomes: major bleeding, all-cause mortality.
PEERLESS (NCT05111613)	550	– RV dysfunction. – Any one or more of the following: *Serum troponin elevation *History of heart failure *Chronic lung disease *Tachycardia ≥ 110 bpm *SBP 90–100 mmHg *O_2 saturation < 90% on room air *Syncope *Serum lactate elevation	a. Anticoagulation + large bore thrombus aspiration (FlowTriever device) b. Anticoagulation + LT (any commercially available LT system)	– Composite endpoint constructed as a win ratio, a hierarchy of the following (discharge or 7 days): 1. All-cause mortality. 2. Intracranial hemorrhage. 3. Major bleeding (ISTH). 4. Clinical deterioration. 5. Intensive care unit admission and length of stay.
PEERLESS II (NCT06055920)	1200	– RV dysfunction. – At least two items from each of the following categories: *Hemodynamic: SBP 90–100 mmHg, tachycardia > 100 bpm. *Biomarker: serum troponin elevation, elevated BNP or NT-proBNP, lactate elevation. *Respiratory: O_2 saturation < 90% on room air, supplemental O_2 ≥ 4 l/min, respiratory rate ≥ 20 per min, mMRC score > 0.	a. Anticoagulation alone. b. Anticoagulation + large bore thrombus aspiration (FlowTriever device).	– Composite endpoint constructed as a win ratio, a hierarchy of the following (discharge or 30 days): 1. Clinical deterioration. 2. All-cause hospital re-admission. 3. Bailout therapy. 4. Dyspnea, measured by mMRC at 48 h. – Key secondary outcomes: major bleeding, all-cause, and PE-related mortality.
PE-TRACT (NCT05591118)	500	– RV dysfunction. – No other risk parameters required.	a. Anticoagulation alone. b. Catheter-directed intervention (any FDA-cleared device, either thrombus aspiration or LT)	– Peak O_2 consumption at month 3. – NYHA classification at month 12. – Major bleeding (ISTH) at day 7.

FDA: Food and Drug Administration; ISTH: International Society on Thrombosis and Haemostasis; LT: local thrombolysis; LV: left ventricle; mMRC: modified Medical Research Council; NYHA: New York Heart Association; PE: pulmonary embolism; RV: right ventricle; SBP: systolic blood pressure; USAT: ultrasound-assisted local thrombolysis.

thrombus aspiration with the FlowTriever device or LT with any commercially available LT system. The primary endpoint in this study is a clinical composite endpoint at 7 days of hospital discharge, including a hierarchy of all-cause mortality, intracranial hemorrhage, major bleeding, clinical deterioration, or intensive care unit

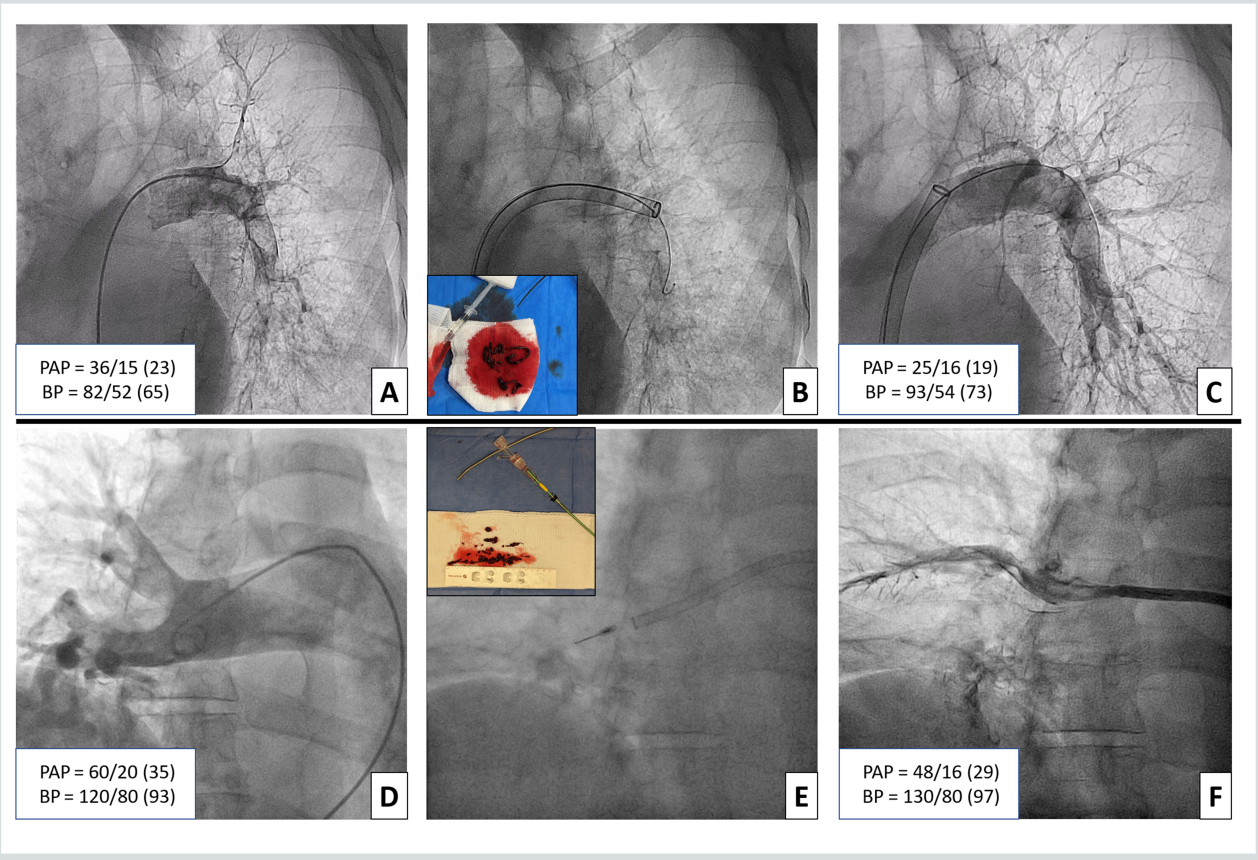

Figure 3. Thrombus aspiration in acute pulmonary embolism (PE). Representative cases of different dedicated devices for percutaneous thrombus aspiration in acute PE. **A–C:** representative case of a patient treated with FlowTriever. A high burden of proximal thrombus in the left pulmonary artery (**A**) was treated with a 24-Fr FlowTriever catheter (**B**), showing a good angiographic result with significant improvement of hemodynamic parameters (**C**). **D–F**: case of thrombus aspiration with Indigo Lightning 12 catheter. A large thrombus was detected in the right pulmonary artery (**D**), which was treated with the 12-Fr Indigo catheter with mechanical thrombus fragmentation and aspiration (**E**). Panel **F** shows a good selective angiographic result and significant hemodynamic improvement in the right pulmonary artery.

BP: blood pressure; PAP: pulmonary artery pressure.

admission and its length. The PEERLESS II (NCT06055920) is a multicenter clinical trial that is currently recruiting and will ultimately randomize 1,200 patients with intermediate-high-risk PE to receive thrombus aspiration with the FlowTriever system versus anticoagulation alone. The primary endpoint will also be a composite clinical endpoint, including a hierarchy of clinical deterioration, all-cause mortality, bailout therapy at 30-day follow-up, and dyspnea at 48 h. These two randomized clinical trials will address many unanswered questions about CDI in acute PE and will help clinicians make the best choice with their patients.

Another major player in the mechanical thrombectomy field is Penumbra (California, USA). The Indigo is an 8-Fr aspiration catheter connected to a continuous suction pump. This device includes a separator

wire with a soft tip that helps fragment the thrombus and feed the catheter. The single-group, multicenter prospective, multicenter study of the indigo aspiration system in acute pulmonary embolism (EXTRACT-PE) trial included 119 patients with intermediate-high risk[26]. The RV–LV ratio and the pulmonary artery pressure decreased significantly after the procedure, and the incidence of major adverse events was 1.7%. The potential advantages of these lower-size aspiration devices are that they may reach more distal thrombi in the pulmonary artery and thus encompass a wider spectrum of patients. The evolution is the ightning catheter, currently 12 Fr and soon evolving to 16 Fr, with the interesting feature that the pump has an electronic sensor that modulates aspiration to spare blood. This sensor feeds a computerized algorithm that provides pulsatile suction when the thrombus is engaged and stops suction when free-flowing blood is detected, therefore increasing the clot-to-blood ratio in the extraction process. The single-arm study STRIKE PE (a study of the lightning aspiration system for pulmonary embolism, NCT04798261) is currently evaluating long-term functional outcomes, safety, and performance with this technology.

In summary, thrombus aspiration with specific devices can have several advantages over other devices, such as a possible lower incidence of bleeding events by avoiding thrombolytic drugs and the possibility of removing a large amount of thrombus straightaway, which may be of special interest for more unstable patients. Therefore, the results of the large clinical trials being carried out are eagerly awaited.

CLINICAL SCENARIOS

After describing the portfolio of techniques and devices available, we should decide which patients will benefit from them. As stated before, the ESC Guidelines recommend CDI after failure of medical therapy[1]. Still, in clinical practice, CDI is a well-established strategy for electively treating intermediate-high-risk patients to prevent hemodynamic deterioration and facilitate faster RV strain relief. Some centers also consider electively performing CDI in high-risk cases without formal contraindications to ST.

Catheter-directed interventions in intermediate-high-risk PE

The majority of patients included in the trials of the different percutaneous devices, as well as the majority of patients that undergo CDI in clinical practice, are classified within the American classification of submassive PE, corresponding to hemodynamically stable PE patients with RV failure or positive biomarkers. However, in line with ESC guidelines, the European scenario is more restrictive, usually not considering CDI in intermediate-low risk but only in intermediate-high-risk PE.

The intermediate-high-risk group comprises patients with a wide spectrum of in-hospital mortality. Thirty-day PE-related mortality

ranges from 4.8% to 10.5% in different registries[27-29]. Moreover, the PEITHO trial showed that 5% of intermediate-high-risk patients who were treated with anticoagulation alone suffered hemodynamic decompensation or death, mostly within the first 3 days after their admission. Several clinical, imaging, and laboratory parameters are predictors of early PE-related death or hemodynamic decompensation[1,30-32] (Table 2). Bearing these factors in mind, several scores that predict the risk of decompensation in stable acute PE have emerged. The commonly used PE severity index (PESI), for instance, is particularly useful for identifying low-risk PE. In fact, the ESC guidelines recommend using the PESI to differentiate between intermediate-low risk (PESI class III–IV) and low-risk (PESI I-II) PE[1,33], being less helpful in the higher-end spectrum of mortality risk.

Other scores allow for the detection of patients at higher risk of decompensation in the intermediate-high-risk group, and thus, may help identify those patients who could benefit the most from reperfusion therapies within this group. Each of these scores includes several parameters from Table 2, as is the case of the Bova score (elevated cardiac troponin, RV dysfunction, tachycardia > 110 bpm, and systolic blood pressure [SBP] 90–100 mmHg) and the FAST score (elevated cardiac troponin, tachycardia > 100 bpm, and syncope). Shock index is the ratio between heart rate and systolic blood pressure, indicating hemodynamic compromise if ≥ 1. Importantly, serum lactate is probably the best isolated parameter that predicts deterioration in intermediate-high-risk patients[34]. Finally, the concept of normotensive shock (SBP > 90 mmHg with cardiac index ≤ 2.2 l/min/m^2) has been recently described in acute PE, and several parameters from Table 2 are predictors of this outcome[35]. This entity is associated with undesired outcomes, such as the need for vasopressors and in-hospital mortality.

Table 2. Major indicators of severity of pulmonary embolism in stable patients

Clinical
– Tachycardia > 100 bpm – SBP 90–100 mmHg – O_2 saturation > 90% on room air – Syncope at presentation – Comorbidities: chronic heart failure, active neoplasm
Imaging
– RV–LV ratio >1 (either by TTE or CTPA) – TAPSE ≤16 mm – Congested inferior vena cava
Laboratory
– Serum troponin elevation – BNP or NT-proBNP elevation – Serum lactate >2 mmol/L

Adapted from Ref. 14.

BNP, Brain natriuretic peptide; NT-proBNP, N-terminal pro b-type natriuretic peptide; NT CTPA: computed tomography pulmonary angiography; LV: left ventricle; RV: right ventricle; SBP: systolic blood pressure; TAPSE: tricuspid annular plane systolic excursion; TTE: transthoracic echocardiography.

As shown, several risk parameters are usually taken into account when making a decision for elective CDI by the PE response teams (PERT), although no single score or algorithm has been validated to date for this purpose. The ongoing trials will shape the picture of the patient with potential CDI indications, and the additional risk parameters used as inclusion criteria are summarized in Table 1.

Until these trials have produced results, and 5 years after the publication of guidelines, several scientific societies have produced consensus documents regarding the reperfusion treatment of acute PE (Fig. 4). More

interventional protocols recommend elective CDI in those intermediate-high-risk PE cases at risk of imminent decompensation[36]. The target of these more proactive treatment protocols is to prevent the onset of hemodynamic collapse rather than wait for it. A consensus statement by the ESC working group on pulmonary circulation and RV function and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) assessed the lack of a clear definition of "deterioration on anticoagulant drugs"[14]. They defined treatment failure in intermediate-high-risk PE patients under anticoagulation treatment as the development of cardiovascular instability necessitating cardiopulmonary resuscitation, mechanical ventilation, catecholamines, or mechanical circulatory support, which they consider a clear indication for reperfusion therapy. They also defined treatment failure as a lack of improvement when compromised vital signs are not alleviated after 24–48 h of therapeutic-dose anticoagulation in these patients. Therefore, they consider that reperfusion therapy, preferably after a discussion with the PERT, should be considered in this scenario, going beyond the ESC guidelines recommendations[14].

In summary, using CDI in intermediate-high-risk patients is a debatable decision, with different international protocol recommendations ranging from a more conservative attitude to a more invasive approach. Local resources, interventionalist expertise, and device availability are variables that should be considered for a specific protocol that each hospital and PERT should agree on to provide the best care to patients.

Catheter-directed interventions in high-risk PE

The definition of high-risk PE is based on hemodynamic instability with a binary cutoff (SBP < 90 mmHg). Considering the critical condition of these patients, and the usually rapid access to the standard treatment (ST), the use of CDI in clinical practice in this group is much more challenging than in stable patients. According to ESC guidelines[1], ST is the treatment of choice for these patients, although the mortality benefit is mainly based on a small clinical trial (n = 8) that was prematurely terminated[37]. Furthermore, as shown in multiple real-life studies, ST is used in less than half of patients with the indication[3-5] due to formal contraindications or fear of complications. Therefore, CDI could play an important role in this scenario.

According to ESC guidelines, the indication for CDI in high-risk PE patients is restricted to those patients with contraindications to ST or ST failure[1]. The consensus document from the ESC working group on pulmonary circulation and right ventricular function and the EAPCI defined this ST failure as a lack of improvement or hemodynamic deterioration in 2–4 h after the completion of full-dose thrombolysis, both being an indication for emergent treatment escalation[14].

However, it should be noted that not all high-risk PEs are created the same, as the ESC guidelines describe three categories at presentation: persistent hypotension (SBP < 90 mmHg), obstructive shock (hypotension + end-organ hypoperfusion), and cardiac arrest, with broad differences in adverse

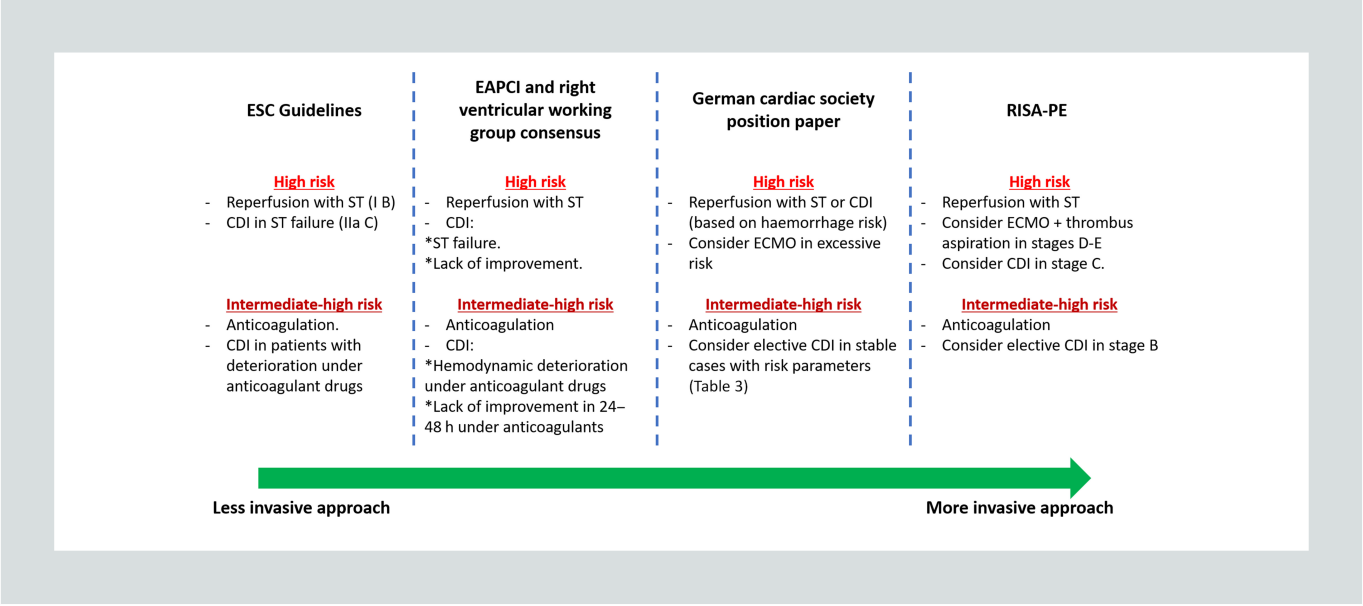

Figure 4. Different treatment strategies in patients with acute intermediate-high and high-risk pulmonary embolism.

CDI: catheter-directed interventions; EAPCI: European Association for Percutaneous Coronary Interventions; ECMO: extracorporeal membrane oxygenation; ESC: European Society of Cardiology; ST: systemic thrombolysis.

outcomes. According to a prospective single-center registry, in-hospital mortality for the three different presentations was 9.1, 18.4, and 59.5%, respectively[38]. Considering the prognostic disparities between the three presentations, different targeted treatment strategies may be used.

The group of patients with persistent hypotension without end-organ dysfunction represents a more stable situation, amenable for transfer to the catheterization laboratory, if prompt CDI is available, in the same way as primary percutaneous coronary intervention for myocardial infarction. Thus, in this subgroup of patients, where reperfusion therapy is needed, CDI could be a competitive option to avoid the feared bleeding complications of ST.

There are few large studies regarding mechanical circulatory support in the high-risk scenario. The largest meta-analysis included 635 high-risk PE patients from several observational studies, with cardiac arrest being the most frequent driver of extracorporeal membrane oxygenation (ECMO) implantation[39]. The incidence of all-cause mortality in this study was 41%[39], which was similar to other observational studies with similar populations, in which short-term all-cause mortality ranged from 40% to 60%[40,41]. However, another observational study included 20 patients in whom an aggressive ECMO protocol was performed, which consisted of an upfront implant of the device in all patients with high-risk PE and end-organ dysfunction (i.e., obstructive shock or cardiac arrest)[42]. The most frequent reperfusion therapy in this study was surgical embolectomy (55%), and the overall in-hospital survival rate was 95% (only one death). Although this is a small observational retrospective

study, and the results should be interpreted cautiously, these findings pave the way for a possible strategy with ECMO + large bore aspiration (less invasive than surgery and widely available) in this subgroup of very high-risk patients. However, further studies are needed to implement this invasive stance in routine clinical practice. Detailed technical information on the ECMO + large bore thrombus aspiration is beyond the scope of this review and is comprehensively addressed elsewhere[43].

The FLAME study, as stated before, is unique because it included only high-risk PE patients who were treated with FlowTriever, with promising results[7]. It is important to note that in the critical scenario of high-risk PE, thrombus aspiration may be a more appropriate CDI option than LT due to its immediate action. Despite all the information outlined above, the state of the art for high-risk PE patients is currently ST; therefore, randomized clinical trials in this complex setting are needed.

A non-binary approach

Considering all the emerging evidence and the upcoming results of randomized clinical trials, risk stratification at the higher end of the spectrum will likely be redefined in new categories with different therapeutic approaches available. Our research group recently suggested an updated risk classification adapting the widely accepted Society for Cardiovascular Angiography and Interventions (SCAI) approach to LV failure and cardiogenic shock. This new RISk classification Adapting SCAI shock stages to patients with PE (RISA-PE) includes five stages in a pyramidal shape representing the decreasing number of patients but the increasing mortality risk and support needed (Fig. 4)[44]. Patients were grouped as stage A (RV dysfunction and troponin elevation), B (A + serum lactate elevation > 2 mmol/l or shock index ≥ 1), C (persistent hypotension), D (obstructive shock), and E (cardiac arrest). This approach was associated with a nonbinary linear relation to all-cause in-hospital death and other adverse outcomes with increasing RISA-PE stage[44]. Moreover, it could be used for therapeutic considerations. Stages B and C, with higher mortality but enough stability to perform a procedure, are, in our opinion, the ideal target population for CDI if feasible. Finally, the critical patients included in stages D and E may be suitable for ST or the ECMO + thrombus aspiration strategy. Further studies validating this approach in different populations are warranted.

Clot in transit

A clot in transit refers to a mobile thrombus detected in the cava vein or right heart. Probably underdiagnosed, it is found in only 3–4% of all PE but in up to 18% of hemodynamically unstable PE patients, being associated with a greater risk of mortality[45]. Additionally, in the presence of patent foramen ovale or atrial septal defect, there is a risk for stroke or arterial embolism. There is no consensus regarding the optimal management in this scenario, and therapy options include anticoagulation, ST, and surgical embolectomy[46].

Importantly, this scenario may be suitable for CDI, especially for large-bore aspiration devices. There is a paucity of evidence regarding this strategy, but some case reports and case series have suggested good results using FlowTriever[47] and AngioVac systems[48]. In fact, a case series on the use of FlowTriever in a clot in transit[47] supported the FDA clearance of the device with this indication, especially if there is a concomitant indication for CDI due to an intermediate or high-risk PE.

CONCLUSION

Acute PE is a prevalent disease with nonnegligible mortality, especially in cases with intermediate-high and high risk. In the last decade, we have witnessed a breakthrough in interventional treatment strategies. CDIs have demonstrated safety and efficiency in providing hemodynamic improvement in these patients. Beyond the wide range of treatment strategies available, the most important remaining question is patient selection for this therapy. Hence, several risk factors, scores, and new risk classification scales have been developed recently. Ongoing randomized clinical trials will establish the indications for these therapies in patients with acute PE and will likely revolutionize therapeutic decision-making in the acute phase.

ETHICAL DISCLOSURES

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