European Heart Journal Supplements (2019) **21** (Supplement I), I1–I13
The Heart of the Matter
doi:10.1093/eurheartj/suz222

ESC European Society of Cardiology

Immediate and late impact of reperfusion therapies in acute pulmonary embolism

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KEYWORDS
Pulmonary embolism;
Thrombolysis;
Risk stratification;
Bleeding;
Chronic thromboembolic pulmonary hypertension

Haemodynamic instability and right ventricular dysfunction are the key determinants of short-term prognosis in patients with acute pulmonary embolism (PE). Residual thrombi and persistent right ventricular dysfunction may contribute to post-PE functional impairment, and influence the risk of developing chronic thromboembolic pulmonary hypertension. Patients with haemodynamic instability at presentation (high-risk PE) require immediate primary reperfusion to relieve the obstruction in the pulmonary circulation and increase the chances of survival. Surgical removal of the thrombi or catheter-directed reperfusion strategies is alternatives in patients with contraindications to systemic thrombolysis. For haemodynamically stable patients with signs of right ventricular overload or dysfunction (intermediate-risk PE), systemic standard-dose thrombolysis is currently not recommended, because the risk of major bleeding associated with the treatment outweighs its benefits. In such cases, thrombolysis should be considered only as a rescue intervention if haemodynamic decompensation develops. Catheter-directed pharmaco-logical and pharmaco-mechanical techniques ensure swift recovery of echocardiographic and haemodynamic parameters and may be characterized by better safety profile than systemic thrombolysis. For survivors of acute PE, little is known on the effects of reperfusion therapies on the risk of chronic functional and haemodynamic impairment. In intermediate-risk PE patients, available data suggest that systemic thrombolysis may have little impact on long-term symptoms and functional limitation, echocardiographic parameters, and occurrence of chronic thromboembolic pulmonary hypertension. Ongoing and future interventional studies will clarify whether 'safer' reperfusion strategies may improve early clinical outcomes without increasing the risk of bleeding and contribute to reducing the burden of long-term complications after intermediate-risk PE.

Introduction

In the past decade, a favourable trend in the mortality and fatality of acute pulmonary embolism (PE) was observed worldwide.[1–3] It is unclear, however, whether this is related to the effective management of patients presenting with haemodynamic instability or to more frequent diagnosis of low-risk sub-segmental PE, which may be due to a wider use of high-resolution multi-detector computer tomography scans and to a lower threshold for suspicion.[4,5] On the other hand, reperfusion therapy can reverse the haemodynamic burden that acute PE imposes on the pulmonary circulation and the right heart, and improve survival in patients with haemodynamically unstable PE (high-risk PE).[5] The drug choice and appropriate dosage as well as the potential impact on late sequelae remain disputed.

The assessment of PE severity is essential to inform treatment choices in patients with acute PE and optimizes

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the risk-benefit ratio of interventions. Current guidelines recommend reperfusion therapies for patients presenting with haemodynamic decompensation (high-risk PE) due to their high risk of early death.[6,7] High-risk PE is defined by the presence of at least one of the following: '(i) cardiac arrest, (ii) obstructive shock (systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite an adequate filling status, end-organ hypoperfusion), or (iii) persistent hypotension (systolic BP <90 mmHg or a systolic BP drop ≥40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis)'.[7] In contrast, only if signs of haemodynamic instability develop should rescue systemic thrombolysis be considered for intermediate-risk acute PE patients, those without haemodynamic compromise but with comorbidities and aggravating conditions or clinical, imaging and laboratory indicators of PE severity that are associated with unfavourable short-term prognosis. In patients with intermediate-risk PE who do not deteriorate or fail to recover haemodynamically, routine systemic thrombolysis is not recommended, because the related risk of major bleeding largely outweighs its benefits.[7]

However, and partly due to the high risk of major bleeding complications, including fatal haemorrhage, only a minority of high-risk patients ultimately undergo reperfusion therapy according to recent registry studies.[8,9] Catheter-directed thrombolysis and thrombectomy, as well as reduced-dose systemic thrombolysis regimens, are emerging as promising and possibly safer options to improve short-term prognosis in intermediate-risk PE patients, although evidence from adequately designed randomized controlled trials focusing on clinical outcomes is still lacking.[7,10] In the present article, we review the current state of knowledge and outline future perspectives regarding the immediate and late impact of reperfusion therapies in patients with acute PE.

Table 1 Absolute and relative contraindications to thrombolytic therapy

Absolute contraindications
History of haemorrhagic stroke or stroke of unknown origin
Ischaemic stroke in the preceding 6 months
Central nervous system neoplasm
Major trauma, surgery, or head injury in the preceding 3 weeks
Active bleeding
Bleeding diathesis
Relative contraindications
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or first post-partum week
Non-compressible puncture site
Traumatic resuscitation
Refractory hypertension (systolic blood pressure >180 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer

Adapted from the current European Society of Cardiology guidelines for pulmonary embolism.[7]

Evolving reperfusion strategies to improve early outcomes

Full-dose systemic thrombolysis

High-risk pulmonary embolism

International guidelines unanimously recommend standard-dose systemic thrombolysis as the mainstay of therapy for acute PE associated with haemodynamic instability, because this condition can be fatal if the embolic obstruction to flow is not relieved. Surgical embolectomy or catheter-directed interventions represent reasonable alternatives if absolute contraindications to thrombolytic agents are present (*Table 1*), or as a rescue strategy.[6,7]

The indication to systemic thrombolysis is based on a number of small-sized trials on high-risk patients with acute PE which demonstrated significant haemodynamic improvement within minutes or hours of treatment. Surrogate parameters were primarily used to assess efficacy, and included total pulmonary resistance, the degree of angiographic resolution, and mean pulmonary artery pressure.[11] The high rate of major bleeding observed after the administration of systemic thrombolysis (~9%)[12] is considered acceptable given the particularly poor prognosis of high-risk PE, if left untreated. Three thrombolytic drugs, which can be delivered via a peripheral venous catheter, have been approved for high-risk acute PE: streptokinase, urokinase, and recombinant tissue plasminogen activator (rtPA). Possible treatment regimens include (i) a loading dose followed by continuous infusion or (ii) accelerated regimens with infusion times ranging from 15 min (alteplase) to 2 h (alteplase, streptokinase, and urokinase).[7] Other thrombolytic drugs, such as tenecteplase, reteplase, and desmoteplase, were evaluated in therapeutic trials in patients with acute PE but not formally approved for this indication.

Intermediate-risk pulmonary embolism

According to a recent meta-analysis focusing on intermediate-risk patients, systemic thrombolysis can, when compared with anticoagulation alone, improve survival [pooled odds ratio for death (OR) 0.59; 95%CI 0.36–0.96]; the benefits were confirmed if only PE-related deaths were taken into account (pooled OR 0.29; 95%CI 0.14–0.60).[11] However, the two- to three-fold higher risk of fatal (or intracranial) haemorrhage would preclude their use given the lack of any appreciable net clinical benefit.[11,13] The conclusions of this analysis were largely driven by data from the Pulmonary Embolism Thrombolysis (PEITHO) trial, in which thrombolysis with tenecteplase in intermediate-risk PE patients was associated with significantly higher risk of haemorrhagic stroke and major non-intracranial bleeding than anticoagulation alone.[14] More recently, a *post hoc* analysis of PEITHO investigated whether specific factors may interact with treatment (systemic full-dose thrombolysis vs. anticoagulation alone) to influence the combined outcome of all-cause death, non-fatal haemodynamic decompensation, and non-fatal

recurrent PE. This might help to identify intermediate-risk patients in whom the risk of death or early decompensation is so high that thrombolysis provides added value compared with anticoagulation. In that analysis, systemic blood pressure $\leq$110 mmHg, respiratory rate >20 breaths per minute and prior heart failure were found to be associated with an increased risk of adverse outcome in the placebo arm (anticoagulation alone) compared with the intervention arm (tenecteplase). The presence of at least one of these factors (vs. none) carried a relative risk of early adverse outcomes of 4.76 (95%CI 2.00–11.33; absolute 30-day outcome rate: 11.2% vs. 2.3%) in the placebo arm and 0.97 (95%CI 0.40–2.34; 3.7% vs. 3.8%) in the tenecteplase arm, suggesting a positive effect of systemic thrombolysis in this subgroup of patients.[15] These results may serve to facilitate the inclusion of 'higher risk' patients in future trials on reperfusion strategies for intermediate-risk PE.

Although general contraindications to systemic thrombolysis (*Table 1*) have been identified mostly based on expert consensus,[7] no risk assessment model has been introduced in clinical practice to guide the use of thrombolysis based on the risk of bleeding in specific patient subgroups.[14,16-19] *Post hoc* analyses of interventional trials indicated that some risk factors may increase the risk of thrombolysis-associated bleeding, e.g. femoral vein access for pulmonary angiography,[18] female sex,[14,20] older age,[14] peripheral vascular disease, and previous cerebrovascular accident.[17] Nevertheless, it is likely that significant improvement in the safety of thrombolytic therapy will be achieved mostly by reducing the dosage or administration route: initial evidence and the rationale for future trials designed to test this approach are summarized in the following paragraphs.

Low-dose systemic thrombolysis

With the development of new drug molecules still at a preliminary stage, a readily available strategy to improve the safety of systemic thrombolysis is the administration of a 'safer dose' (e.g. half dose or less) of thrombolytic agent. Three interventional studies investigated whether half-dose tPA (50 mg) reduces thrombus load enough to normalize angiographic imaging parameters;[21-23] half-dose thrombolysis appeared to be more effective than anticoagulation with heparin alone and as effective as full-dose thrombolysis (100 mg tPA). This effect was not confirmed in more recent studies focusing on surrogate echocardiographic parameters.[24,25]

The absolute rates of major bleeding in patients receiving low-dose systemic thrombolysis observed in all prior trials point to a lower risk of bleeding than full-dose thrombolysis (*Table 2*). However, the hypothesized safety advantage in intermediate-risk patients remains to be proven in the setting of adequately sized randomized controlled trials adopting standard anticoagulation as a comparator.

Catheter-directed techniques

Catheter-directed reperfusion techniques, including catheter-directed (ultrasound-assisted) local thrombolysis, catheter-directed mechanical embolectomy, and combined pharmaco-mechanical approaches are receiving increasing attention for use in patients with acute PE. All act primarily by relieving obstruction, which restores pulmonary blood flow and improves cardiac output. This effect is achieved with the administration of a low dose of thrombolytic agent or, in the case of catheter-directed mechanical embolectomy, without the administration of any thrombolytic drug. Numerous devices are available (*Table 3*), but evidence on their efficacy and safety is still mostly limited to observational studies or single-arm cohort studies with surrogate outcomes.

A conformity assessment and small clinical trials designed to support a 'reasonable assurance of safety and effectiveness' (and not large phase III trials necessary for the approval of novel drug compounds) are required by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to approve medical devices for specific indications, although the regulatory control varies according to the device classification.[26,27] Indeed, the FDA may require a premarket approval with additional evidence on safety (and effectiveness) for selected devices. However, such trials may not provide sufficient information for deciding about the best treatment strategy in specific patient subgroups because they often lack the power to study efficacy and safety compared with the standard of care. Of note, only the ultrasound-assisted device EkoSonic and the mechanical embolectomy device FlowTriever have been approved by the FDA for routine use in patients with PE.[28] Other devices had only been approved for the treatment of acute thrombosis in other vascular beds (*Table 3*).

Catheter-directed techniques may be preferred to surgical embolectomy due to the ease of use and lower risk of complications, although the results of a small cohort study and large admission databases are conflicting.[29-32] A 2018 meta-analysis of 20 (mostly observational) studies including 1168 patients assessed whether catheter-directed thrombolysis improved the haemodynamics of high-risk PE or prevented haemodynamic failure in intermediate-risk PE without major bleeding, in-hospital death, or stroke.[33] Success was reached in 81.3% (95%CI 72.5–89.1) of high-risk PE patients and 97.5% (95%CI 95.3–99.1) of intermediate-risk patients. In this latter group, the best evidence on catheter-directed techniques comes from studies evaluating ultrasound-assisted catheter-directed thrombolysis. The randomized ULTIMA trial compared the delivery of low dose (10 to 20 mg) rtPA by ultrasound-assisted catheter-directed thrombolysis over 15 h with a standard anticoagulant treatment in 59 intermediate-risk patients showing that catheter-directed thrombolysis was superior in improving 24 h right-to-left ventricular diameter ratio.[34] These results on surrogate echocardiographic outcomes were subsequently supported by interventional studies on the same device which tested different dosing strategies and duration of administration, namely the Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II) study, and the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism (OPTALYSE PE) randomized trial.[35,36] Finally, the recent Catheter-Directed Mechanical Thrombectomy for

Table 2 Major bleeding events after full-dose systemic thrombolysis, low-dose systemic thrombolysis, and catheter-directed thrombolysis in recent studies

Reference	*N* safety population (thrombolysis arm)	Population and type of study	Thrombolysis treatment arm	Percentage bleeding (time of assessment)	Classification criteria of bleeding events
Major bleeding events					
PEITHO[14]	502	Intermediate-high risk PE (RCT)	Systemic full-dose thrombolysis (single weight-adjusted bolus of 30–50 mg tenecteplase)	6.3% (7 days) 11.4% (7 days) 8.3% (7 days)	GUSTO severe bleeding (extracranial) ISTH major bleeding GUSTO severe bleeding
Wang *et al.*[25]	48	Haemodynamic instability or massive PE (RCT)	Systemic full-dose thrombolysis (rtPA 100 mg/2 h)	10% (14 days)	Fatal, intracranial, haemoglobin drop, >400 mL RBC transfusion
	55		Systemic half-dose thrombolysis (rtPA 50 mg/2 h)	3% (14 days)	Fatal, intracranial, haemoglobin drop, >400 mL RBC transfusion
TIPES[59]	28	Intermediate-high risk PE (RCT)	Systemic full-dose thrombolysis (single weight-adjusted bolus of 30–50 mg)	7.1% (7 days)	GUSTO severe bleeding
MOPETT[24]	61	Intermediate-risk PE (RCT)	Half-dose thrombolysis (single weight-adjusted bolus of maximally 50 mg)	0%	Not specified
ULTIMA[34]	30	Submassive risk PE (RCT)	Catheter-directed thrombolysis (rtPA 10 mg/lung/15 h)	0% (7 days)	ISTH major bleeding
SEATTLE II[35]	150	Submassive/massive PE (Interventional study)	Catheter-directed thrombolysis (t-PA at 24 mg/24 h for unilateral PE, 24 mg/12 h for bilateral PE)	10% (30 days)	GUSTO moderate to severe bleeding
OPTALYSE I[36]	27	Intermediate-risk PE (Interventional study)	Catheter-directed thrombolysis (4 mg/lung/2 h)	0% (3 days)	ISTH major bleeding
OPTALYSE II[36]	27		Catheter-directed thrombolysis (4 mg/lung/4 h)	3.7% (3 days)	ISTH major bleeding
OPTALYSE III[36]	28		Catheter-directed thrombolysis (6 mg/lung/6 h)	3.6% (3 days)	ISTH major bleeding
OPTALYSE IV[36]	18		Catheter-directed thrombolysis (12 mg/lung/6 h)	11.1% (3 days)	ISTH major bleeding
Fatal and intracranial bleeding events					
PEITHO[14]	502	Intermediate-high risk PE (RCT)	Systemic full-dose thrombolysis (single weight-adjusted bolus of 30–50 mg tenecteplase)	2.0% (7 days)	Intracranial bleeding

(continued)

Table 2 Continued

Reference	*N* safety population (thrombolysis arm)	Population and type of study	Thrombolysis treatment arm	Percentage bleeding (time of assessment)	Classification criteria of bleeding events
Wang *et al.*[25]	48	Haemodynamic instability or massive PE (RCT)	Systemic full-dose thrombolysis (rtPA 100 mg/2 h)	2% (14 days)	Fatal
	55		Systemic half-dose thrombolysis (rtPA 50 mg/2 h)	0% (14 days)	Fatal
TIPES[59]	28	Intermediate-high risk PE (RCT)	Systemic full-dose thrombolysis (single weight-adjusted bolus of 30 to 50 mg)	3.6% (7 days)	Fatal + intracranial bleeding
MOPETT[24]	61	Intermediate-risk PE (RCT)	Half-dose thrombolysis (single weight-adjusted bolus of maximally 50 mg)	0%	Not specified
ULTIMA[34]	30	Submassive risk PE (RCT)	Catheter-directed thrombolysis (rtPA 10 mg/lung/15 h)	0% (7 days)	Fatal + intracranial bleeding
SEATTLE II[35]	150	Submassive/massive PE (Interventional study)	Catheter-directed thrombolysis (t-PA at 24 mg/24 h for unilateral PE, 24 mg/12 h for bilateral PE)	0% (30 days)	Fatal + intracranial bleeding
OPTALYSE I	27	Intermediate-risk PE (Interventional study)	Catheter-directed thrombolysis (4 mg/lung/2 h)	0 (3 days)	Fatal + intracranial bleeding
OPTALYSE II	27		Catheter-directed thrombolysis (4 mg/lung/4 h)	1 (3.6%) (3 days)	Fatal + intracranial bleeding
OPTALYSE III	28		Catheter-directed thrombolysis (6 mg/lung/6 h)	0	Fatal + intracranial bleeding
OPTALYSE IV	18		Catheter-directed thrombolysis (12 mg/lung/6 h)	1 (3.6%) (11 days)	Fatal + intracranial bleeding

The safety population was used when this was specifically defined.
ISTH, International Society on Thrombosis and Haemostasis; PE, pulmonary embolism; RCT, randomized controlled trial.

Table 3 Overview of available devices for catheter-directed thrombolysis and embolectomy

Technique	Device (company)	Description	Evidence
Simple catheter-directed thrombolysis	Multi-sidehole pigtail catheter (Cook) UniFuse (AngioDynamics) Cragg-McNamara (Ev3 Endovascular)	The catheter is inserted directly into the thrombus and the thrombolytic agent is released.	Observational studies
Ultrasound-assisted catheter-directed thrombolysis	EkoSonic (BTG)	A second catheter lumen contains a filament with multiple low-energy ultrasound transducers; the waves open the clot ultrastructure in an attempt to facilitate thrombolytic binding.	ULTIMA; SEATTLE; OPTALYSE. Four prospective, single-group studies, $N = 404$. Two prospective randomized trials, $N = 30$ and $N = 80$ (one ongoing). All studies adopted surrogate outcomes
Catheter-directed embolectomy by fragmentation	Pigtail catheter	The pigtail is inserted in the distal part of the thrombus and rotated back and forth while retracting proximally. Distal embolization by the fragments and clinically relevant PAP increase have been reported[60]	Observational studies
Catheter-directed embolectomy by suction	AngioVac (AngioDynamics) Indigo (Penumbra)	The thrombus is aspirated via a pump, with AngioVac reintroducing excess aspirated blood via a veno-venous bypass but requiring large bores. The aspiration of excess blood may be haemodynamically relevant.	Observational studies
Catheter-directed embolectomy, rheolytic	AngioJet (Boston Scientifics)	High-pressure jet streams disrupt the thrombus, which is then trapped in a low-pressure zone generated by the Bernoulli principle behind the streams and aspirated in the catheter.	Observational studies FDA. Black-box warning for its use in patients with acute PE due to the high risk of haemoptysis, bradyarrhythmia, haemoglobinuria, renal failure, and death.
Catheter-directed embolectomy, rotational	Aspirex (Straub) Arrow-Trerotola (Teleflex) Cleaner (Argon Medical) Helix Clot Buster (Medtronic)	Rotating elements (spiral coils, baskets, sinusoidal wires) both disrupt the thrombus and trap it into low-pressure zones generated by the rotation itself. Catheter diameters >10 Fr may be required.	Observational studies
Catheter-directed embolectomy by entrapment	FlowTriever (Inari)	Self-expanding nitinol disks are placed into the thrombus, ensnare it by expanding, and are retracted into the catheter.	One single-arm phase II trial (FLARE; $N = 106$)

PE, pulmonary embolism.

Intermediate-Risk Acute Pulmonary Embolism (FLARE) study demonstrated that the use of the FlowTriever Catheter-directed embolectomy device significantly improved the RV/LV ratio of patients with intermediate-risk PE.[28] A recently published retrospective study on 46 patients from a single centre confirmed improvement in mean pulmonary artery pressure.[37] Therefore, this device may represent another suitable alternative to anticoagulation.

The safety profile of catheter-directed techniques, however, is complex and has not yet been systematically compared with the standards of care. Compared with the 7 day rates of major bleeding of systemic thrombolysis in PEITHO (8.3% according to GUSTO criteria and 11.5% by ISTH criteria), the major bleeding rates reported in the ULTIMA, SEATTLE-II, and OPTALYSE trials ranged from 0% to 10%, with the above-mentioned meta-analysis of retrospective studies estimating a rate of 6.7% for high-risk and 1.4% for intermediate-risk PE.[33] The advantage of catheter-directed thrombolysis may be more pronounced if only early fatal and intracerebral haemorrhages are considered: none occurred in the ULTIMA and SEATTLE II

studies, whereas in OPTALYSE only one event occurred (1.0%) (*Table 2*).[34–36] The safety of these techniques may be associated with specific external factors, including technical expertise. A *post hoc* analysis of the SEATTLE II trial suggested multiple venous access attempts were associated with a higher risk of major bleeding during or after the catheter-directed procedure.[16] Phase II and III studies only provide limited evidence on acute complications beyond (major) bleeding and death. In the FLARE study on FlowTriever, 4/106 (3.8%) patients experienced six major adverse events all adjudicated to be procedure related and not device related, including one major bleeding, two pulmonary vascular injuries, two respiratory deteriorations, and one ventricular fibrillation; an additional 14 patients experienced other not otherwise specified serious adverse events with a broad definition, none adjudicated to be device or procedure related, as well as two malfunctions.[28] A recent single-centre retrospective study reported 2/46 (4.3%) complications, including a self-limited haemoptysis and an acute anaemia.[37] Of the studies on EkoSonic, SEATTLE II reported no procedural complications,[35] ULTIMA reported no serious adverse events related to the study treatment,[34] and OPTALYSE PE did not report on non-death and non-bleeding safety outcomes.[36]

We searched the online Manufacturer and User Facility Device Experience (MAUDE) database, which contains medical device reports of suspected device-associated deaths, serious injuries, and malfunctions received by the FDA[38,39]. A total of 99 unique manufacturer-reviewed reports for the EkoSonic device and nine reports for the FlowTriever device from cases of PE or unspecified indication are contained in MAUDE (*Table 4*). Although these reports can by no means provide a reliable quantitative estimate of the absolute risks associated with each catheter-directed technique and should not be used to directly compare different devices, they provide us an overview of the characteristics of adverse events occurring in everyday practice. For EkoSonic, 61 malfunctions were reported: in almost half of these, the main problem was a break or other loss of material integrity. The ongoing KNOCOUT PE registry, that includes PE patient treated with the EkoSonic device, will provide more information[40]. Reports on cases treated with FlowTriever included two deaths by major bleeding and two fatal cardiac arrest with no further diagnosis were reported; most of the other non-fatal adverse events are major bleedings ($n = 2$). Future studies should assess whether the volume of patients at each centre may influence this risk. In *Table 4*, we have also reported adverse events related to the use of the Angiojet catheters, although they refer to the use of these devices for any possible indication, as they received a black-box warning by the FDA for its use in the pulmonary arteries due a possible high risk of procedure-related severe complications including haemoptysis, bradycardia, heart block, haemoglobinuria, renal failure, and death.[41]

Surgical embolectomy

Surgical embolectomy via pulmonary arteriotomy under normothermic cardiopulmonary bypass is indicated for patients with high-risk PE with contraindications to systemic thrombolysis or after failure of pharmaco-logical reperfusion. A 2017 meta-analysis of 56 studies found a post-operative in-hospital mortality rate of 26.3% (95%CI 22.5–30.5%) with a significant difference between studies conducted after vs. before 2000 in favour of the former (19.0%, 95%CI 14.6–24.3% and 32.1%, 95%CI 26.9–37.7%, respectively), suggesting improvement over time.[42] Only a minority of studies reported on other acute complications: the incidence was estimated at 7.0% (95%CI 4.9–9.8, reported in 17/56 studies) for surgical site complications, 3.0% (95%CI 1.7–5.2, 10/56 studies) for gastrointestinal bleeding, 4.0% (95%CI 2.1–7.3, 10/56 studies) for pulmonary bleeding, and 10.6% (95%CI 5.3–19.8%, 13/56 studies).[42] A reasonable approach to optimize the use of embolectomy may include the initial stabilization of the patient by venous-arterial extracorporeal membrane oxygenation (ECMO) prior to surgery, especially in patients with refractory circulatory collapse or cardiac arrest. In a recent retrospective study on 180 high-risk PE patients, 30-day mortality in patients treated with ECMO after surgical embolectomy was 29.4% (95%CI 51–89) compared with 76.5% (95%CI 57–97) for ECMO after failed fibrinolysis and 77.7% (95%CI 59–97) for ECMO alone.[43,44] The available evidence from observational cohort studies is limited by the use of surgical embolectomy as a last resort for patients with no other viable alternative: therefore, observational findings are likely to be confounded and difficult to interpret.

Long-term outcomes after reperfusion therapy

Post-PE syndrome (or post-PE impairment) is emerging as an important late complication of acute PE that affects the perceived burden of disease, risk of recurrence, quality of life, and healthcare expenditures.[45] It is defined as the combination of clinical, imaging, and haemodynamic signs of functional impairment that are highly prevalent in PE survivors. For instance, persistent dyspnoea or poor physical performance can persist for years after PE diagnosis, and approximately half of the survivors may exhibit some signs of persistent pulmonary hypertension or right ventricular dysfunction on echocardiography.[46] Although some symptoms may be related to deconditioning more than to the sequelae of acute PE, the patients' perception of their health status is often worse than before PE and, consistently, their quality of life and exercise capacity is diminished.[47] The recently published prospective Evaluation of Long-term Outcomes After Pulmonary Embolism (ELOPE) supports this concept by indicating that approximately 50% of 100 patients diagnosed with acute PE had exercise limitation 1 year after the index event, as defined by percent-predicted maximal oxygen consumption (VO_2) peak $<80\%$ on cardiopulmonary exercise testing.[48] Although several long-term outcomes are of clinical interest, none has been evaluated systematically in several interventional studies, and what little evidence exists is not comparable across studies because of small sample sizes and varying definitions of the outcomes.

Table 4 Deaths, non-fatal adverse events, and malfunctions reported by interventional studies and in the United States Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience database for three devices

	Interventional studies		MAUDE		
	EkoSonic	FlowTriever	EkoSonic	FlowTriever	Angiojet
Indication	PE[34–36]	PE[28]	PE or unspecified indication	PE or unspecified indication	Any indication
Reports	—	—	99	10	1007
Deaths					
Cardiac arrest with no diagnosis, *n*	1[36]	0	1	2	12
Distal embolization or PE	2[35]	0	0	0	9
Multi-organ failure	1[35]	0	1	0	8
Major bleeding	1[35]	0	5	2	2
Acute renal failure	0	0	0	0	7
Other or unclear	1[36]	1	0	0	8
Non-fatal adverse events					
Acute renal failure, *n*	0	1	1	0	32
Arrhythmias	0	1	13	0	16
Myocardial ischaemia	0	2	0	0	0
New procedure required	0	2	0	1	9
Distal embolization	0	2	1	1	9
Major bleeding	6[35,36]	1	0	2	5
Vascular damage	0	1	0	1	3
Respiratory tract infection or pneumonia	0	2	—	—	1
Sepsis	0	1	—	—	—
Pulmonary effusion	0	1	—	—	—
Other or unclear	3	15	3	1	38
Malfunctions or technical complications					
Obstruction, leak or deformation affecting aspiration or infusion, *n*	0	2	11	0	613
Break or other material integrity problem	0	0	28	1	78
Difficulty to advance or remove (entrapment), dislocation	0	0	3	0	92
Electric fault including power or connection loss, overheating, display or alarm problems	0	0	14	0	57
Incorrect use including damage by other device	0	0	4	0	5
Contamination	0	0	0	0	4
Packaging or labelling problem	0	0	0	0	6
Not identified	0	0	1	0	14

MAUDE reports are included up to and including August 2019 after removal of duplicates and of reports not evaluable by the manufacturer in order to account for the limitations of the surveillance data.[39,62]. For EkoSonic and FlowTriever, only reports in PE cases or cases with no indication are included, whereas the use of EkoSonic in patients with other indications (e.g. deep vein thrombosis) is not accounted for; for Angiojet devices, all reports for all indications were included, as their use in PE is limited by a black-box warning label. As each report of malfunction or technical complication may include more than one malfunction type, only the most severe one per report is shown. Reports for ULTIMA regarded complications at 90 days,[34] reports for the other studies or MAUDE complications at 30 days or in-hospital complications. In randomized controlled trials, only the complications occurring in the intervention arm were considered.

PE, pulmonary embolism.

Functional parameters

In the Tenecteplase or Placebo: Cardiopulmonary Out comes at 3 months (TOPCOAT) randomized trial ($n = 83$ patients with submassive PE), tenecteplase (vs. standard anticoagulation) improved the composite functional outcome, which comprised several items including poor functional capacity and death.[49] However, several clinical and functional parameters, such as the New York Heart Association (NYHA) functional class, 6 min of walk distance, and quality of life scores, had a similar distribution between treatment groups 90 days after PE.[49]

In PEITHO, the thrombolysis and the heparin-only group exhibited no difference with regards to persistent clinical symptoms or functional limitation (*Table 5*).[50,51]

Echocardiographic parameters

In PEITHO, no difference was found between the thrombolysis and the heparin-only group in echocardiographic

Table 5 Prospective studies on thrombolysis for acute pulmonary embolism reporting on long-term functional or haemodynamic outcomes

Reference	Population	Groups	Outcome	Follow-up	Thrombolysis	Control	Difference between groups
Kline *et al.*[49]	Intermediate-risk or submassive PE[a]	Tenecteplase ($n=37$) vs. placebo ($n=39$)	NYHA class III-IV	3 mo.	5.4%	20.5%	$P=0.051$
			RV dilation or hypokinesis		33.3%	37.8%	$P=0.64$
			6-min walking distance <330 m		16%	28%	$P=0.19$
			Composite positive functional outcome		85%	63%	$P=0.017$
Kline *et al.*[61]	Submassive PE	Alteplase ($n=18$) or heparin ($n=144$)	6 min of WD <330 m or NYHA score >2	6 mo.	28%	42%	—
MOPETT[24]	Moderate PE[a]	Half-dose tPA ($n=58$; for death, $n=61$) vs. anticoagulation alone ($n=56$; for death, $n=60$)	SPAP ≥40 mmHg	28 mo.	16%	57%	$P<0.001$
			Mean SPAP, mmHg	6 mo.	31±6	49±8	$P<0.001$
			Mean SPAP, mmHg	28 mo.	28±7	43±6	$P<0.001$
			Death		1.6%	5.0%	$P=0.30$
Kucher *et al.* (ULTIMA)[34]	Intermediate- or high-risk PE[a]	Catheter-directed thrombolysis ($n=30$) vs. anticoagulation alone ($n=29$)	Mean difference in RV/ LV ratio	24 h	0.30 ± 0.20	0.03±0.16	$P<0.001$
			Mean difference in RV/ LV ratio	90 dd	0.35 ± 0.22	0.24±0.19	$P=$ ns
			Mean difference in RV/RA pressure gradient, mmHg	24 h	9.8 ± 9.9	0.3±10.9	$P=0.03$
			Mean difference in RV/RA pressure gradient, mmHg	90 dd	12.3 ± 12.8	11.6±15.1	$P=$ ns
			Mean difference in TAPSE, mm	24 h	−3.1 ± 4.4	0.9±4.9	$P=0.02$
			Mean difference in TAPSE, mm	90 dd	−6.1 ± 4.6	−3.4 ± 5.4	$P=$ ns
Piazza *et al.* (SEATTLE II)[35]	Intermediate (79%) or high risk (21%) PE[a]	Low-dose Catheter-directed thrombolysis	Mean RV/LV ratio	Pre vs. post Catheter-directed thrombolysis (48 h)	1.55 ± 0.39 → 1.13 ± 0.2		$P<0.0001$
			Mean SPAP, mmHg		51.4 ± 16 → 36.9 ± 14.9		$P<0.0001$
			Modified Miller Index		22.5±5.7 → 15.8±5.9		$P<0.0001$

(continued)

Table 5 Continued

Reference	Population	Groups	Outcome	Follow-up	Thrombolysis	Control	Difference between groups
PEITHO[50,51]	Intermediate-risk PE[a]	Tenecteplase ($n = 359$) vs. placebo ($n = 350$)	ESC criteria for probability of CTEPH	38 months	60%	68%	$P =$ ns
			CTEPH		2.1%	3.2%	$P =$ ns
			NYHA III-IV		12%	10.9%	$P =$ ns
			Persistent clinical symptoms (all)		36.0%	30.1%	$P =$ ns
			Death from any cause between day 30 and long-term follow-up		20.3%	18.0%	$P =$ ns
			Right ventricular end-diastolic diameter >30 mm		23.6%	15.1%	$P =$ ns
			Hypokinesia of the right ventricular free wall (any view)		4.2%	3.4%	$P =$ ns
			Tricuspid annulus plane systolic excursion reduced, mean mmHg (SD)		23.6 (4.8)	23.9 (3.6)	$P =$ ns
			Systolic pulmonary artery pressure, mean mmHg (SD)		31.6 (12.3)	30.7 (10.2)	$P =$ ns
			Post-PE impairment (normalization of echo parameters + residual functional limitation)		14.3%	12.1%	$P =$ ns

[a]The studies marked with an asterisk are interventional studies.

AC, anticoagulant; Catheter-directed thrombolysis, catheter-directed thrombolysis; ns, not significant; NYHA, New York Heart Association; OR, odds ratio; PE, pulmonary embolism; RA, right atrium; RV/LV ratio, right-to-left ventricular ratio; RVED/LVED, right and left ventricular end-diastolic diameter ratio in the parasternal long-axis view; RVWM, right ventricular wall movements; SD, standard deviation; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; WD, walking distance.

parameters, or the combination of exertional dyspnoea with persistent or progressing right ventricular dysfunction echocardiographic parameters at 90 days (*Table 5*).[50,51] It must be emphasized that patients with long-term haemodynamic impairment presented with abnormal findings already at 6-month follow-up.[51]

Chronic thromboembolic pulmonary hypertension

The most severe form of post-PE complications is represented by chronic thromboembolic pulmonary hypertension (CTEPH). With an estimated incidence of 2–3% of all PE survivors,[52] this condition is characterized by pulmonary artery remodelling and subsequent perfusion defects and symptomatic pulmonary hypertension.[53] The effect of the initial PE treatment on the risk of subsequent pulmonary hypertension or CTEPH is a relatively recent field of study, although systemic thrombolysis has been previously suggested to reduce the risk of post-PE pulmonary hypertension and CTEPH compared with standard anticoagulation, possibly because of its lytic effect favouring the complete dissolution of the clots.[54] This concept was initially supported by the results of a small study on 121 patients with acute PE and a *post hoc* analysis of three European observational cohort studies of patients with acute PE followed for the occurrence of CTEPH.[24,55] However, the recently published long-term follow-up data from PEITHO suggested only a minimum (and, with the current sample size, not statistically significant) difference in the cumulative rate of confirmed CTEPH at 2 years: tenecteplase, 2.1% vs. anticoagulation alone, 3.2%.[50] Ongoing and future studies of low-dose systemic thrombolysis and catheter-directed reperfusion for acute intermediate-risk PE should confirm these findings.

Perspectives

Taken together, the above results underline the need to develop and prospectively evaluate dedicated follow-up protocols after acute PE in order to detect not only the most feared complication of PE, CTEPH, but also the highly prevalent post-PE syndrome, which may be associated with a diminished quality of life and worsening functional outcomes on the long term.[56–58] To ensure comparability across studies and provide reliable findings, this evaluation should be based on standardized, validated instruments. In the follow-up after acute pulmonary embolism (FOCUS) study, a total or almost 1100 consecutive patients with acute PE are being followed over a 2 years of standardized follow-up period and with predefined clinical, echocardiographic, functional, and laboratory assessments with the aim of identifying predictors of long-term complications, including functional and haemodynamic impairment and CTEPH.[58]

Beyond available tools designed to screen patients for the presence and severity of long-term complications, namely CTEPH,[7] a scale covering the entire spectrum of functional outcomes is currently being developed.[57] Such a scale, which is intended to be an analogous of the modified Rankin Scale for stroke, will be used on top of the assessment of 'classic' outcomes and will aid the demarcation of intervention effectiveness in the setting of clinical trials, accounting for limitations in usual activity, changes in lifestyle, physical disability, changes in social interactions, and the persistence of symptoms.[57]

Conclusions

Systemic thrombolysis reduces the thrombotic load and improves haemodynamic parameters in patients with acute PE. However, available evidence supports its use only in high-risk patients. In patients without haemodynamic instability, the risk of major haemorrhagic complications outweighs its possible clinical benefits. For this patient group, low-dose systemic thrombolysis and catheter-directed reperfusion techniques are being studied as an alternative in light of a possibly better safety profile. These hypotheses require confirmation by direct comparison to the standard of care in adequately designed trials with clinical outcomes.[62] Until such evidence is available, reperfusion therapy should be reserved for rescue in case of haemodynamic collapse during the initial days of standard anticoagulant treatment. Evidence on the impact of thrombolytic treatment on long-term outcomes, in particular on whether thrombolysis may improve the clinical, functional and echocardiographic parameters, is urgently needed.

Funding

This paper was published as part of a supplement financially supported by BTG Interventional Vascular Europe.

Conflicts of interest: F.A.K. reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion, the Dutch Heart foundation and the Dutch Thrombosis association. S.B. has received payment for travel accommodation and meeting expenses from Daiichi-Sankyo and Bayer HealthCare, and personal fees from Bayer HealthCare and BTG. Pharmaceuticals. L.V. has nothing to disclose.

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