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# Catheter-Based Reperfusion Therapies: A New Era in Management of Pulmonary Embolism?


*Pok-Tin Tang BA BM BCh MRCP (UK)*

Clinical Research Fellow

Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Headley Way, Headington, Oxford OX3 9DU


## Take Home Messages

- Pulmonary embolism (PE) is a major cause of cardiovascular mortality and morbidity.
- Traditional treatment algorithms restrict reperfusion therapy (systemic thrombolysis) to those with haemodynamic compromise due to associated bleeding risks.
- Catheter-based interventions for pulmonary embolism may provide an option for acute reperfusion therapy to patients with intermediate-risk PE.
- However, randomised controlled trials examining more robust and long-term endpoints are needed, alongside developments in clinical implementation.

## INTRODUCTION

Acute pulmonary embolism (PE) is a major cause of cardiovascular mortality. Traditionally, management predominantly involves supportive therapy, anticoagulation, and monitoring(1).

It is recognised that right ventricular (RV) overload, decompensation, and failure drive cardiovascular death in PE. However, the deleterious effects of RV failure beyond mortality (symptomatic limitation, chronic thromboembolic pulmonary hypertension) are overlooked by traditional treatment algorithms(1). Systemic thrombolysis is reserved for those with haemodynamic compromise due to risks of major bleeding (~10%)(2); one previous trial in intermediate-risk PE reported a lower risk of haemodynamic compromise for systemic thrombolysis compared with anticoagulation, but with a five-fold increased risk of major bleeding(3).

## INTERVENTIONAL MANAGEMENT OF PE: TECHNOLOGY AND TRIALS

In recent years, catheter-based therapies for PE management (catheter-directed thrombolysis [CDT], and mechanical thrombectomy [MT]) have emerged, potentially offering greater odds of successful reperfusion at lower risk, which may extend the benefits of acute reperfusion therapies

to patients with intermediate-risk PE. CDT involves infusion of thrombolytics at the main/lobar pulmonary arteries, allowing lower doses to be administered; some systems include ultrasound assistance (USAT) to disrupt thrombus and increase thrombolytic delivery. MT allows rapid clot debulking while minimising exposure to thrombolytics: existing technologies employ large-bore manual aspiration (LBMT), automatic syringe pump aspiration, and computer-assisted vacuum thrombectomy (CAVT)(4).

The ULTIMA trial was a landmark trial that first demonstrated a benefit for USAT over anticoagulation in early RV unloading (greater reduction in RV/LV ratio; **Table 1**)(5). Likewise, STORM-PE demonstrated this for CAVT(6), but both trials were small. The recently published PEERLESS and HI-PEITHO trials provide evidence at greater scale (~550 patients/trial) with data on clinical outcomes. PEERLESS compared CDT to LBMT (**Table 1**), favouring the latter in terms of clinical deterioration and 24-hour RV functional parameters and symptoms(7). HI-PEITHO compared USAT against anticoagulation: USAT was associated with a lower incidence of death, deterioration, or PE recurrence at 7 days (4.0% vs 10.3%) without significant increases in major bleeding(8). Two ongoing trials will compare MT against anticoagulation alone(9,10).

## ONGOING CHALLENGES

Despite promise and enthusiasm, several areas remain unaddressed by current evidence. Firstly, published trial endpoints deserve further scrutiny. Imaging evidence of early RV unloading (RV/LV ratio), the primary outcome of early trials, was used as a surrogate marker of medium- to long-term clinical benefit, but this cannot be assumed. In PEERLESS, LBMT was associated with slightly greater improvement in RV function (without difference in RV/LV ratio) at 24 hours, but no difference in symptoms at 30 days. In HI-PEITHO, USAT and anticoagulation were associated with similar reductions in RV/LV ratio at 48 hours (USAT -0.38, anticoagulation -0.27). Discordance between imaging and clinical outcomes highlights a need for the upcoming generation of PE trials to iterate on endpoint assessments. Ideally, the bar for interventions in intermediate-risk PE should be: i. reduced PE-related mortality (secondarily reduced deterioration and need for rescue support); or ii. improved long-term symptoms and functional status, with no significant increase in major bleeding beyond anticoagulation alone, and HI-PEITHO was a first step towards delivering this: improved clinical outcomes at lower bleeding risk (compared with systemic

thrombolysis(2)) approaching that of anticoagulation alone, is reassuring. However, it is important to note that the lower risk of acute clinical deterioration in the USAT group was predominantly driven by an endpoint defined by National Early Warning Score ≥9, rather than the other chosen endpoints (cardiac arrest, shock, or therapy escalation) or mortality. The current trials all report mortality data at 7 days, and are underpowered to detect differences (1-2%; but noting intermediate-risk PE is associated with 3-7% 30-day mortality risk(11)). Ongoing trials of MT will investigate medium-term mortality and functional outcomes; a 12-month analysis of HI-PEITHO is planned: these results will be key to the next phase of examining these technologies.

Secondly, the published trials are characterised by high screen failure rates. Randomisation rates as a proportion of screened patients (most common reason for exclusion), were as follows: ULTIMA 16% (no main pulmonary artery embolism); STORM-PE 13% (absence of one of echocardiographic and serum markers); HI-PEITHO 13% (not specified, though 125 for "unknown reason"). In PEERLESS, 8% of patients were excluded after randomisation for elevated systolic pulmonary arterial pressure (≥70mmHg, taken to indicate chronic PE). This limits generalisability and projected population benefits, and complicates real-world clinical workflows.

Finally, fundamental questions about these procedures, and infrastructure development, need addressing, summarised in **Figure 1**. One major question is over timing and location of interventions. In PEERLESS and STORM-PE, procedures were performed within 20-24 hours of presentation or randomisation, supporting in-hours intervention, though this would still require service coverage over weekends. It is not clear whether this should be delivered in a hub-and-spoke model (to overcome potentially low procedural volume at individual centres, and ensure rescue haemodynamic support available, at the cost of transfer-related delays) or per-centre. In contrast, HI-PEITHO delivered USAT within 2 hours of randomisation in 73% of cases: this seems infeasible without an established network of procedural expertise. There is no accepted definition of procedural success in MT: in STORM-PE, this was left to operator discretion, but potential endpoints might be angiographic, echocardiographic, or haemodynamic (reduction of systolic pulmonary pressure beyond a threshold).

## CONCLUSION

Catheter-based interventions for PE provide the exciting possibility of more proactive treatment for those with acute PE who are at risk of early deterioration or long-term sequelae. However, despite conceptual promise, many questions over these procedures remain to be answered.

## Disclosures

None.

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**Table 1. Summary of evidence for catheter-based interventions for management of acute pulmonary embolism.**

| Trial (Year) | Number of patients | Intervention vs comparator | Main inclusion criteria | Main exclusion criteria | Primary efficacy endpoint and result | Safety events |
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| ***Catheter-directed thrombolysis*** | | | | | | |
| ULTIMA (2013) | N=59 (30/29), 8 hospitals in Germany/ Switzerland | UFH and ultrasound-assisted catheter-directed thrombolysis (Ekosonic Endovascular System, Boston Scientific) 10mg rTPA over 15 hours) vs UFH alone | Intermediate-risk acute PE; 1 main or proximal lower lobe pulmonary artery involvement; RV/LV ratio ≥1 on TTE | PE symptom duration ≥14 days; High bleeding risk (history, recent thrombolytic therapy, international normalised ratio and platelet count) | Difference in RV/LV ratio from baseline to 24 hours; USAT: 1.28 ± 0.19 to 0.99 ± 0.17; UFH: 1.20 ± 0.14 to 1.17 ± 0.20; Mean difference 0.30±0.20 vs. 0.03±0.16 (P<0.001) | No haemodynamic decompensation or death at 90 days (one in control group related to cancer); no recurrence or major bleeding events |
| HI-PEITHO (2026) | N=544 (273/271), 63 international sites | Anticoagulation and ultrasound-assisted catheter-directed thrombolysis (Ekosonic Endovascular System, Boston Scientific) 2mg bolus followed by | Intermediate-high risk acute PE; 18-80 years old; Confirmed CTPA involving one main or proximal lobar pulmonary artery; ≥2 risk markers for early haemodynamic | Haemodynamic instability; Need for intensive care admission; PE symptom duration ≥14 days; High bleeding risk (history, concurrent anticoagulation, | Primary composite outcome of PE-related death, cardiorespiratory decompensation, or symptomatic recurrence by day 7; USAT: 4.0%; AC alone: 10.3%; | No between-group difference in major bleeding (30-day data presented); USAT: 4.1%; AC alone: 3.0%; Relative risk 1.4 (95% CI 0.6-3.4, p=0.64); |

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| | | 1mg/hr for 7 hours<br>vs<br>Anticoagulation alone | decompensation (heart rate, blood pressure, respiratory rate);<br>RV/LV ratio ≥1 on CTPA;<br>Elevated serum troponin. | recent thrombolysis, platelet count) | Relative risk 0.39 (95% CI 0.20-0.77, p=0.005) | No intracranial haemorrhage in either group |
| ***Mechanical Thrombectomy*** | | | | | | |
| STORM-PE (2026) | N=100 (50/50), 22 sites across the United States of America, Canada, New Zealand, and Poland | Anticoagulation and CAVT (Lightning Flash system, Penumbra)<br>vs<br>Anticoagulation alone (UFH or low molecular weight heparin) | Acute intermediate-high risk PE;<br>RV/LV ratio ≥1 on CTPA;<br>Elevated serum troponin | Haemodynamic instability;<br>PE symptom duration ≥14 days;<br>Contraindication to anticoagulation;<br>Significant elevation of systolic pulmonary artery pressure | Change in RV/LV ratio on CTPA between baseline and 48 hours;<br>CAVT 1.63 ± 0.36 to 1.11 ± 0.28 (mean reduction 0.52 ± 0.37);<br>AC 1.56 ± 0.35 to 1.32 ± 0.31 (mean reduction 0.24 ± 0.40);<br>Mean difference 0.27 | No differences in major adverse events;<br>One event of clinical deterioration requiring rescue therapy in CAVT arm;<br>One major bleeding event in each arm;<br>Two PE-related deaths in CAVT arm judged as non-procedure non-device related. |

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| PEERLESS II (Ongoing) | N=1200, 83 sites in the United States of America, Canada, Belgium, Denmark, France, Germany, Poland, Spain, Switzerland | Large-bore mechanical thrombectomy (FlowTriever system, Inari Medical) with anticoagulation vs Anticoagulation alone | Intermediate risk PE;<br>RV dilatation or dysfunction on CTPA or TTE;<br>Proximal filling defect in ≥1 main or lobar pulmonary artery;<br>≥1 other clinical risk factor (haemodynamic/ biomarker/ respiratory) | PE symptom duration ≥14 days;<br>Contraindication to anticoagulation;<br>Haemodynamic instability | Hierarchical win ratio (all-cause mortality at 30 days, clinical deterioration by 30 days [haemodynamic or respiratory], all-cause re-admission by 30 days, requirement for bailout therapy by 30 days], change in dyspnoea [modified Medical Research Council scale] at 48 hours);<br>***Ongoing*** | ***Ongoing*** |
| ***Within/Inter/Multi-technique comparisons*** | | | | | | |
| SEATTLE II (2015) | N=150, 22 sites in the United States of America | Ultrasound-facilitated catheter-directed thrombolysis (Ekosonic Endovascular System, EKOS), totalling 24mg tPA (either 1mg/h for 24h using 1 device, or 2mg/h | Massive or submassive PE;<br>RV/LV diameter >1 on CTPA | PE symptom duration ≥14 days;<br>Recent intracranial event;<br>High bleeding risk | RV/LV ratio 48 hours post-procedure;<br>Comparison as whole-group baseline 1.55 ± 0.39 to 48h 1.13 ± 0.2, p<0.0001 | Major bleeding within 72 hours;<br>9% |

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| | | for 12h using 2 devices) | | | | |
| SUNSET sPE (2021) | N=82 (41/41), 3 centres in the United States of America | USAT (Ekosonic Endovascular System, EKOS)<br>vs<br>Standard (Cragg-McNamara, Medtronic) or Uni-Fuse (Angiodynamics) side-hold catheter-directed thrombolysis | Acute intermediate risk PE;<br>RV/LV ratio >1 or elevated troponin/BNP | PE symptom duration ≥14 days;<br>Haemodynamic instability;<br>High bleeding risk | Thrombus load reduction on CT (modified Miller scoring system);<br>Statistically significant improvements in both groups (USAT 31 ± 4 to 22 ± 7; standard 33 ± 4 to 23 ± 7) without inter-group difference in benefit | Major bleeding in two cases (2%) |
| PEERLESS (2024) | N=550 (274/276), 57 sites in Germany, Switzerland, and the United States | Large-bore mechanical thrombectomy (FlowTriever system, Inari Medical)<br>vs<br>Catheter directed thrombolysis (either ultrasound-assisted [60%] or with standard catheter-directed thrombolysis | Intermediate risk PE;<br>RV dilatation or dysfunction on CTPA or TTE;<br>Proximal filling defect in ≥1 main or lobar pulmonary artery;<br>≥1 other clinical risk factor (history [heart failure or chronic lung disease] or clinical observation | PE symptom duration ≥14 days;<br>Clot-in-transit;<br>Unable to receive anticoagulation;<br>Systolic pulmonary artery pressure ≥70 mmHg on invasive on-table assessment | Hierarchical win ratio (all-cause mortality, intracranial haemorrhage, major bleeding, clinical deterioration requiring further bailout therapy, intensive care unit [ICU] length of stay);<br>Mechanical thrombectomy favoured over catheter-directed thrombolysis (win | No statistically significant differences in intracranial haemorrhage (0.7% vs 0.4%) or major bleeding (6.9% vs 6.9%) |

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| | | [four system options, no standardised regimen]) | derangement [heart rate ≥110 beats per minute or systolic blood pressure <100 mmHg or respiratory rate >30 or oxygen saturations <90%] or blood marker [elevated lactate or troponin]) | | ratio 5.01, 95% confidence intervals 3.68-6.97, P<0.001) | |
| PE-TRACT (Ongoing) | N=500, 40 sites in the United States of America | Catheter-directed therapy (mechanical thrombectomy or localised thrombolysis) with anticoagulation vs Anticoagulation alone | Acute intermediate-risk PE; Involvement of main or lobar pulmonary artery; RV/LV ratio >1 on CTPA | PE symptom duration ≥14 days; Haemodynamic instability; High bleeding risk | i. Peak $VO_2$ at 3 months; ii. New York Heart Association classification symptoms at 12 months (hierarchical – analysed if endpoint i positive); ***Ongoing*** | Composite of major bleeding, major cardiovascular or pulmonary injury, or major procedure-related events at 7 days; ***Ongoing*** |

*AC, anticoagulation; CAVT, computer-assisted vacuum thrombectomy; CTPA, computed tomographic pulmonary angiography; LV, left ventricular; PE, pulmonary embolism; RV, right ventricular; TTE, transthoracic echocardiography; UFH, unfractionated heparin, USAT, ultrasound-assisted catheter-directed thrombolysis.*

**Figure 1.** Potential pathway and developments required for delivery of catheter-based interventions for pulmonary embolism in clinical practice.