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"Συγκριτικά αποτελέσματα των θεραπειών διάλυσης θρόμβων στην αντιμετώπιση ενδιάμεσου ή υψηλού κινδύνου πνευμονικής εμβολής: Συστηματική ανασκόπηση"

Υπό
Μαρία Αλατζά
Ειδικευόμενη Ακτινολογίας

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απαιτήσεων για την απόκτηση του
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Master of Science Thesis

"Comparative Outcomes of clot-dissolving therapies in the Management of Intermediate-Risk or Massive Pulmonary Embolism: Systematic Review"

by
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Resident in Radiology

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Περίληψη:

Ιστορικό:
Η πνευμονική εμβολή (ΠΕ) αποτελεί απειλητική για τη ζωή κατάσταση που απαιτεί επείγουσα και εξατομικευμένη διαχείριση βάσει κινδύνου. Αν και η συστηματική θρομβόλυση μειώνει την πρώιμη κλινική επιδείνωση σε ασθενείς υψηλού κινδύνου, ο σχετιζόμενος κίνδυνος αιμορραγίας —ιδίως η μεγάλη αιμορραγία (10–20%) και η ενδοκρανιακή αιμορραγία (2–3%)— περιορίζει τη χρήση της σε περιπτώσεις ενδιάμεσου κινδύνου (PEITHO: μεγάλη αιμορραγία 6.3% έναντι 1.2%; EKA 2.4% έναντι 0.2%; P < 0.001).
Οι θεραπείες με καθετηριασμό, όπως η θρομβόλυση με καθετήρα (CDT), η υπερηχοκαθοδηγούμενη θρομβόλυση (USAT) και η μηχανική θρομβεκτομή (PMT), έχουν αναδειχθεί ως εναλλακτικές, αλλά υπάρχουν περιορισμένα συγκριτικά δεδομένα για την ασφάλεια και την αποτελεσματικότητά τους.

Σκοπός:
Να γίνει συστηματική ανασκόπηση και σύγκριση των κλινικών αποτελεσμάτων — συμπεριλαμβανομένης της λειτουργίας της δεξιάς κοιλίας (RV), της λύσης του θρόμβου, του κινδύνου αιμορραγίας, της χρήσης ΜΕΘ και της μακροπρόθεσμης πρόγνωσης— μεταξύ συστηματικής θρομβόλυσης, CDT (κλασικής και υπερηχοκαθοδηγούμενης) και PMT σε ασθενείς με ΠΕ ενδιάμεσου και υψηλού κινδύνου.

Μέθοδοι:
Διενεργήθηκε συστηματική αναζήτηση σε PubMed και ScienceDirect (2001–2025) σύμφωνα με τις οδηγίες PRISMA. Περιλήφθηκαν τυχαιοποιημένες μελέτες, μητρώα και αναδρομικές αναλύσεις που αξιολόγησαν τις CDT, USAT, PMT (π.χ. FlowTriever) και συστηματική θρομβόλυση σε ΠΕ ενδιάμεσου και υψηλού κινδύνου. Ο κίνδυνος μεροληψίας αξιολογήθηκε με βάση το εργαλείο Cochrane και σχετικά κριτήρια για μη τυχαιοποιημένες μελέτες.

Αποτελέσματα:
Είκοσι μελέτες πληρούσαν τα κριτήρια εισαγωγής. Η συστηματική θρομβόλυση μείωσε σημαντικά την πρώιμη αιμοδυναμική απορρύθμιση (PEITHO: 2.6% έναντι 5.6%, P = 0.02), αλλά συνδέθηκε με τα υψηλότερα ποσοστά μεγάλης αιμορραγίας (6.3%; 95% CI: 4.5–8.7%) και EKA (2.4%; 95% CI: 1.3–4.2%).
Οι CDT και USAT επέφεραν παρόμοιες μειώσεις του δείκτη RV/LV (~25–30%) με κίνδυνο αιμορραγίας 2–10% (ULTIMA: μέση μείωση RV/LV 0.30; 95% CI: 0.22–0.39; P < 0.001). Δεν διαπιστώθηκε διαφορά αποτελεσματικότητας μεταξύ USAT και κλασικής CDT (SUNSET sPE: P = 0.76 για λύση θρόμβου· μεταβολή RV/LV: 0.59 ± 0.42 [SCDT] vs 0.37 ± 0.34 [USAT], P = 0.01).
Η PMT με το σύστημα FlowTriever παρουσίασε ευνοϊκό προφίλ ασφάλειας με χαμηλό ποσοστό μεγάλης αιμορραγίας (1–3%) (FLARE: 0.9%; 95% CI: 0.02–5.0%) και αντίστοιχη μείωση RV/LV (−0.38; 25.1%; P < 0.0001). Η RCT PEERLESS επιβεβαίωσε την υπεροχή του FlowTriever έναντι της CDT με win ratio 5.01 (95% CI: 3.68–6.97; P < 0.001). Η χρήση ΜΕΘ μειώθηκε ή αποφεύχθηκε σε έως και 41.3% των ασθενών με PMT. Περιορισμένα μακροπρόθεσμα δεδομένα δείχνουν βελτιωμένη αποκατάσταση της RV και μειωμένη επίπτωση χρόνιας πνευμονικής υπέρτασης (TriNetX: HR για PH με PMT vs CDT = 0.70; 95% CI: 0.55–0.90).

Συμπεράσματα:
Οι θεραπείες με καθετήρα, και κυρίως η PMT και η USAT, προσφέρουν αποτελεσματικές και ασφαλέστερες εναλλακτικές έναντι της συστηματικής θρομβόλυσης στην ΠΕ ενδιάμεσου κινδύνου. Η PMT εμφανίζει το καλύτερο προφίλ ασφάλειας, διατηρώντας την αποτελεσματικότητα. Οι διεπιστημονικές ομάδες αντιμετώπισης ΠΕ (PERT) είναι καίριας σημασίας για την εξατομίκευση της θεραπείας. Ωστόσο, απαιτούνται περαιτέρω τυχαιοποιημένες μελέτες —ειδικά PMT έναντι CDT— για την τελική καθοδήγηση της κλινικής πρακτικής και της μακροπρόθεσμης στρατηγικής.

Λέξεις-κλειδιά:
Πνευμονική εμβολή, θρομβόλυση με καθετήρα, μηχανική θρομβεκτομή, FlowTriever, συστηματική θρομβόλυση, δυσλειτουργία δεξιάς κοιλίας, PERT, αιμορραγικός κίνδυνος

Abstract

Background:
Pulmonary embolism (PE) is a life-threatening condition which requires urgent and risk-stratified management. While systemic thrombolysis reduces early clinical deterioration in high-risk PE, its associated bleeding risk—particularly major bleeding (10–20%) and intracranial haemorrhage (2–3%)—limits its use in intermediate-risk cases (PEITHO: major bleeding 6.3% vs 1.2%; ICH 2.4% vs 0.2%; P < 0.001). Catheter-directed thrombolysis (CDT), ultrasound-assisted thrombolysis (USAT), and mechanical thrombectomy (PMT) have emerged as alternatives, but comparative data on their safety and effectiveness remain limited.
Objectives:
To systematically review and compare clinical outcomes—including right ventricular (RV) function, thrombus resolution, bleeding risk, ICU utilization, and long-term prognosis—across systemic thrombolysis, catheter-directed thrombolysis (CDT: standard and ultrasound-assisted [USAT]), and percutaneous mechanical thrombectomy (PMT) in intermediate- and high-risk PE.
Methods:
We systematically searched PubMed and ScienceDirect (2001–2025) using PRISMA guidelines. Included studies were randomized controlled trials, registries, or retrospective analyses evaluating CDT, USAT, PMT (e.g., FlowTriever), and systemic thrombolysis in intermediate and high-risk PE. The risk of bias was assessed using the Cochrane tool and relevant non-randomized criteria.
Results:
Twenty studies met the inclusion criteria. Systemic thrombolysis significantly reduced early hemodynamic decompensation (PEITHO: 2.6% vs 5.6%, P = 0.02) but carried the highest major bleeding (6.3%; 95% CI: 4.5–8.7%) and ICH (2.4%; 95% CI: 1.3–4.2%) rates. CDT and USAT achieved similar RV/LV ratio reductions (~25–30%) with major bleeding risks ranging from 2–10% (ULTIMA: mean RV/LV ratio reduction 0.30; 95% CI: 0.22–0.39; P < 0.001). No significant efficacy difference was observed between USAT and standard CDT (SUNSET sPE: thrombus reduction P = 0.76; RV/LV change 0.59 ± 0.42 [SCDT] vs 0.37 ± 0.34 [USAT], P = 0.01).
PMT using the FlowTriever system demonstrated a favourable safety profile with major bleeding rates of 1–3% (FLARE: 0.9%; 95% CI: 0.02–5.0%) and similar RV/LV reduction (−0.38; 25.1%; P < 0.0001). The PEERLESS RCT confirmed the superiority of FlowTriever over CDT on a hierarchical composite outcome with a win ratio of 5.01 (95% CI: 3.68–6.97; P < 0.001). ICU utilization was reduced or avoided in up to 41.3% of patients undergoing PMT. Limited long-term data suggest improved RV recovery and reduced chronic pulmonary hypertension (TriNetX: HR for chronic PH with PMT vs CDT = 0.70; 95% CI: 0.55–0.90).
Conclusion:
Catheter-based therapies, particularly PMT and USAT, offer effective and safer alternatives to systemic thrombolysis for intermediate-risk PE. PMT shows the most favourable safety profile while maintaining efficacy. Multidisciplinary Pulmonary Embolism Response Teams (PERTs) are critical in individualized treatment selection. However, head-to-head randomized trials—especially comparing PMT and CDT—are urgently needed to define the optimal approach and inform long-term clinical decision-making.
Keywords:

Pulmonary embolism, catheter-directed thrombolysis, mechanical thrombectomy, FlowTriever, systemic thrombolysis, right ventricular dysfunction, PERT, bleeding risk

Abbreviations Table

Abbreviation	Definition
BARC	Bleeding Academic Research Consortium
CDL	Catheter-directed Thrombolysis
CDT	Catheter-directed Therapy
CTEPH	Chronic thromboembolic pulmonary hypertension
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
ECMO	Extracorporeal Membrane Oxygenation
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
ICH	Intracranial hemorrhage
ICU	Intensive care unit
ISTH	International Society on Thrombosis and Haemostasis
LBMT	Large-bore mechanical thrombectomy
LMWH	Low molecular weight heparin
NEWS	National Early Warning Score
NYHA	New York Heart Association
PE	Pulmonary Embolism
PERT	Pulmonary Embolism Response Team
PESI	Pulmonary Embolism Severity Index
PH	Pulmonary Hypertension
PMT	Percutaneous Mechanical Thrombectomy
QoL	Quality of life
RCTs	Randomized Controlled Trials
RV	Right Ventricle
RV/LV	Right Ventricle to Left Ventricle ratio
SCDT	Standard Catheter-Directed Thrombolysis
SPE	Surgical Pulmonary Embolectomy
UFH	Unfractionated Heparin
USAT	Ultrasound-Assisted Thrombolysis
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
mMRC	Modified Medical Research Council
rtPA	Recombinant tissue Plasminogen Activator
sPESI	Simplified Pulmonary Embolism Severity Index
tPA	tissue Plasminogen Activator

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1. Introduction

Pulmonary embolism (PE) is a critical global health concern with a significantly increased morbidity and mortality risk. It is defined as the sudden blockage of the pulmonary vasculature by a blood clot or embolus, most commonly originating from deep veins of the lower extremities.
PE is a disease that is often overlooked, making it one of the most underdiagnosed conditions. The exact incidence rate is difficult to determine. Most recent estimates report that it affects 1 in 1000 people annually across the globe, and about 20% of patients diagnosed with acute PE die within 90 days (1). Shockingly, sudden death is the first symptom in 25% of people with PE (2).
Its clinical significance lies in the profound potential complications which affect about 33% of venous thromboembolism patients who present with a reoccurrence within a decade (2). Chronic Thromboembolic pulmonary hypertension (CTEPH) can develop in patients following PE 3-6 months post-treatment and are associated with decreased quality of life and increased fatality(3).
Early diagnosis of PE cannot be overstated; it is crucial for improving prognostic outcomes.
The current cornerstone of intermediate-risk PE management is anticoagulation therapy, with Low Molecular Weight Heparin (LMWH), especially enoxaparin, or Unfractionated Heparin (UFH), used for initial treatment, and Direct Oral Anticoagulants (DOACs) such as rivaroxaban, apixaban and dabigatran for long-term or extended treatment. Since their introduction, DOACsbhave been favoured over Vitamin K Antagonists (VKAs) as they have significantly lower bleeding risk, allow shorter hospital duration, and, in certain low-risk cases, avoid hospitalization (4).
Systemic thrombolysis has been shown to improve outcomes in high-risk cases of massive PE. However, it carries substantial bleeding risks, such as major and fatal bleeding or intracranial haemorrhage (5).
Catheter-directed therapies (CDT), including standard catheter-directed thrombolysis (SCDT), ultrasound-assisted thrombolysis (USAT), and percutaneous mechanical thrombectomy (PMT), have emerged for intermediate- and high-risk PE and aim to rapidly reduce thrombus burden, improve right ventricular (RV) function, and prevent long-term complications such as CTEPH, with a more favourable safety profile, as bleeding remains a primary concern.
Despite increasing utilization, data comparing these modalities' effectiveness and safety profiles are limited. This systematic review synthesizes the recent evidence comparing catheter-based interventions, including SCDT, USAT, surgical pulmonary embolectomy (SPE), and PMT using devices such as the FlowTriever System, for intermediate- and high-risk PE, focusing on survival, thrombus resolution, RV function recovery, bleeding risk, and long-term clinical outcomes.

The following question is raised:
- In patients with intermediate-risk or massive pulmonary embolism (P), does treatment with standard catheter-directed thrombolysis (SCDT) (I), compared to standard anticoagulation, ultrasound-assisted thrombolysis (USAT), and mechanical thrombectomy (PMT) (C), improve clinical outcomes (O)

2. Literature Review

2.1: Pathophysiology of Pulmonary Embolism

PE occurs when thrombi, most commonly originating from deep veins of the lower extremities, embolize to the pulmonary arterial circulation. The obstruction of pulmonary arteries leads to an abrupt increase in pulmonary vascular resistance, resulting in impaired gas exchange, ventilation-perfusion mismatch, hypoxemia, and hemodynamic compromise. Reflex vasoconstriction and the release of inflammatory mediators exacerbate pulmonary hypertension and RV strain (6).

The pathogenesis of PE is based on Virchow's triad, which includes venous stasis, endothelial injury, and a hypercoagulable state. Most thrombi originate from Deep Venous Thrombosis (DVT) of the lower extremities, with common sites including the calf, femoropopliteal, and iliac veins. Less frequently, thrombi arise from veins of the mesenteries, renal veins, internal cerebral veins, or gastrocnemius veins (7).

Predisposing factors leading to thrombosis can be acquired or inherited, as the European Society of Cardiology (ESC) guidelines outline. These factors include advanced age, recent surgery, fractures or injuries to the lower extremities, prolonged immobilization, obesity, active malignancy, pregnancy, hormone replacement therapy, oral contraceptive use, a history of venous thromboembolism (VTE), chronic medical conditions, smoking, travelling lasting more than 4 hours, and genetic thrombophilias (8).

In this setting, a blood clot forms dislodges and travels from various body areas through the venous system to the right heart ventricle to completely or partially one or more pulmonary vessels.

The European Society of Cardiology/American Heart Association (2019) classifies pulmonary emboli based on their physiologic effects as follows:

High risk/massive PE: presenting as cardiac arrest and persistent hypotension <90 mmHg or a systolic BP drop > 40 mmHg for >15min due to impaired right ventricular function.

Intermediate risk/submassive PE: characterized by acute PE without systemic hypotension but with right ventricular dysfunction or increased cardiac troponin levels. It also included patients with a pulmonary embolism risk index of I or II or simplified Pulmonary Embolism Severity Index (sPESI) of 0 and signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels.

Low-risk PE: presenting with no RV dysfunction and elevated cardiac troponin levels with normal Pulmonary Embolism Severity Index (PESI) (8).

The consequences depend on various factors, including the size and number of the emboli, the right ventricular function, the underlying condition of the lung, and the body's intrinsic thrombolytic capability (7).

PE predominantly causes hypoxia through various mechanisms. These include ventilation/perfusion mismatch, tachypnea as a reflex increase in ventilation, atelectasis due to regional bronchoconstriction and abnormalities in surfactant, reduced central venous oxygen pressures due to decreased cardiac output, and right-left shut caused by the opening of patent foramen ovale due to increase in right atrial pressure (7).

The RV is particularly vulnerable to pressure overload. Acute PE causes RV dilation and dysfunction, which can progress to circulatory collapse. Unresolved cases may lead to CTEPH, which is associated with long-term morbidity (7).

Overall, the clinical impact of PE depends on thrombus burden, RV response, and the patient's underlying health.
Options such as systemic thrombolysis, CDT and PMT aim to rapidly restore pulmonary perfusion, relieve RV strain, and improve clinical outcomes.

2.2 Catheter directed therapies

Nowadays, CDT have evolved as key interventions for managing high-risk and some selected cases of intermediate-risk PE. They can be categorized into catheter-directed thrombolysis (CDL) and PMT.
CDL is a developing nuanced approach to managing PE. It offers minimally invasive targeted therapy that delivers thrombolytic agents, such as tissue plasminogen activator (tPA), directly to the thrombus or embolus via catheterization. This method allows for lower doses of thrombolytics compared to systemic administration, thereby reducing the risk of major hemorrhagic complications, particularly intracranial bleeding (9).
Advanced techniques, such as the EKOS Endovascular System used for USAT, use ultrasonic waves to facilitate deeper penetration of thrombolytic agents into the clot matrix, enhancing thrombus dissolution (10).
PMT involves the percutaneous removal of thrombotic material without the use of thrombolytic agents or in combination with low-dose thrombolytics. The development of Aspiration thrombectomy devices such as the Indigo system and the FlowTriever system, physically aspirate the clot from the pulmonary arteries. Rheolytic thrombectomy systems, such as the AngioJet, use high-velocity saline jets to fragment and evacuate the thrombus. Rotational thrombectomy and fragmentation devices mechanically disrupt thrombus to restore pulmonary perfusion (11).
Mechanical thrombectomy, a purely mechanical method of thrombus lysis, could be indicated as a treatment option in patients with contraindications to systemic thrombolysis (12).
According to the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines, CDT may be indicated in high-risk PE patients with contraindications to or failure of systemic thrombolysis and intermediate-high-risk PE patients demonstrating clinical deterioration, RV dysfunction, or elevated biomarkers when systemic thrombolysis arise potentially fatal bleeding risks (13).

Device	Mechanism of thrombus removal	Technical data#	Source of clinical evidence in pulmonary embolism	Vascular access	CE certificate for PE therapy
Pigtail catheters	Fragmentation and thrombolytic infusion	Diameter 6-8 Fr	Case series	F/J	Not applicable
Indigo system (Penumbra)	Aspiration with mechanical fragmentation	Diameter 8 Fr, 12 Fr Length 115 cm	EXTRACT-PE – single-arm trial[26].	F/J	YES
AngioVac (Angiodynamics)	Large lumen aspiration tube with the system of veno-venous bypass	Diameter 22 Fr	Case series (difficult for PE)	F	NO*
BASHIR endovascular catheter (Thrombolex)	Mechanical fragmentation, aspiration and thrombolytic infusion	Diameter 7 Fr Length 92.5 cm Treatment zone 12.5 cm	Case series	F	NO
FlowTriever System (Inari)	Aspiration with or without mechanical fragmentation	Diameter 16, 20 and 24 Fr Nitinol mesh diameter S 6-10 mm, M 11-14 mm, L 15-18 mm and XL 19-25 mm	FLARE – single-arm trial[25]. FLASH[53]	F	YES
ASPIREX (Straub medical)	Fragmentation and aspiration	Diameter 6 Fr, 8 Fr and 10 Fr Length 85, 110 and 135 cm	Case series	F	YES
AngioJet (Boston Scientific)	Rheolytic thrombectomy with aspiration and possibility for thrombolytic injections	Diameter 6-8 Fr Length 120 cm	Case series	F/J	YES
EkoSonic (Boston Scientific)	Thrombolytic infusion with ultrasound dispersion	Diameter 5 Fr Length 106 and 135 cm Treatment zone 6, 12, 18, 24, 30, 40 and 50 cm	ULTIMA – RCT SEATTLE II – single-arm trial OPTALYSE – investigation of different doses of tPA and time for infusion SUNSET sPE - Standard vs. ultrasound-assisted thrombolysis in submassive PE[36-38,51]	F/J	YES
UniFuse (Angiodynamics)	Thrombolytic infusion	Diameter 4 Fr and 5 Fr Length 45, 90 and 135 cm Treatment zone 2, 5, 10, 15, 20, 30, 40 and 50 cm	SUNSET sPE RCT Standard vs. ultrasound-assisted thrombolysis in submassive PE[51] Case series	F	NO
Cragg-McNamara (Medtronic)	Thrombolytic infusion	Diameter 4 Fr and 5 Fr Length 40, 65, 100, 135 cm Treatment zone 5, 10, 20, 40 and 50 cm	The SUNSET sPE RCT Standard vs. ultrasound-assisted thrombolysis in submassive PE[51] Case series	F	NO
Fountain infusion system (Merit Medical)	Thrombolytic infusion	Diameter 4 and 5 Fr Length 45, 90 and 135 cm Treatment zone 5, 10, 20, 30, 40 and 50 cm	Case series	F	NO

Colour-coded mechanism: blue: aspiration; red: fragmentation; green: thrombolytic; definition of treatment zone: treatment areas – this part of the catheter allows for local thrombolytic delivery through multiple ports along its length. #diameter of the device, length of catheter, treatment zone. *FDA cleared for removal of undesirable intravascular material. CE: (Conformité Européenne) – certificate of conformity; F: femoral; J: jugular; PE: pulmonary embolism; RCT: randomised controlled trial; tPA: tissue plasminogen activator

Table 1: The most relevant available CDT techniques (13).

Patient selection should be individualized based on a thorough assessment of thrombus burden, hemodynamic status, bleeding risk, and institutional expertise (8)(13).

Advantages of catheter-directed therapies include a targeted delivery that minimizes systemic exposure to thrombolytics. According to Sailen & Naidu et al., many CDT techniques employ thrombolytics; however, the dose utilized is generally about one-third the dose given for systemic thrombolytics. Furthermore, they exhibit a rapid restoration of pulmonary blood flow and right ventricular function and reduced rates of major bleeding compared to systemic thrombolysis. Also, they pose a potential for

treatment without thrombolytics with purely mechanical approaches in patients contraindicated for systemic thrombolysis (14).
Limitations and risks should not be overlooked. According to Avgerinos et al., catheter-directed interventions for acute PE are not risk-free, and their use should be individualized based on a risk-benefit ratio. Procedural complications risks include vascular injury, pulmonary artery perforation, and arrhythmias.
Therefore, careful patient selection and appropriate centre expertise employing a multidisciplinary team are important components for intervention success and minimizing complications. There is also a potential risk for incomplete thrombus removal or recurrent embolism (15).
The limited availability of randomized controlled trials should also be considered, as most current evidence is primarily based on registries and observational studies.

2.3: Major bleeding stratification

Bleeding risk remains a central concern in the use of thrombolytic therapies for intermediate-risk and massive PE. This review extracted and stratified major bleeding outcomes from key clinical trials to evaluate the comparative safety of clot-dissolving approaches.
Major bleeding was variably defined across the included studies; therefore, it is crucial to review definitions from widely accepted classification systems and assess how the bleeding is reported in clinical trials included in this review. The selected Randomized Control Trials (RCTs) encountered in this systematic review define major bleeding by established criteria such as GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), ISTH (International Society on Thrombosis and Haemostasis), or BARC (Bleeding Academic Research Consortium). Thrombolysis in Myocardial Infarction (TIMI) bleeding classification was not selected as a classification system of bleeding risk in the RCTs included in this review. Moreover, some trials, such as CANARY, did not specify the bleeding classification system used, limiting direct comparability.

Definitions of Major Bleeding:

- GUSTO: Defines major bleeding as severe or life-threatening haemorrhage requiring blood transfusion or surgical intervention or causing hemodynamic compromise.
- ISTH: Classifies major bleeding as fatal bleeding, symptomatic bleeding in critical areas or organs, or bleeding causing a ≥2 g/dL haemoglobin drop or leading to transfusion of ≥2 units of blood.
- BARC: It uses a graded scale (Type 1–5), where Type 3–5 is typically considered major. Type 3 includes overt bleeding plus haemoglobin drop, cardiac tamponade, or bleeding requiring intervention (16).
- The Thrombolysis in Myocardial Infarction (TIMI) bleeding classification includes major and minor bleeding and defines patients with intracranial haemorrhage, a ≥5 g/dl decrease in haemoglobin concentration, or a ≥15 % absolute decrease in hematocrit(16).

Variation in major bleeding definitions is an important criterion to consider as it affects comparability across studies. For example, a study using ISTH criteria may report higher bleeding incidence due to the inclusion of laboratory-based thresholds (e.g., haemoglobin drop), whereas GUSTO focuses more on clinical outcomes like hemodynamic instability.

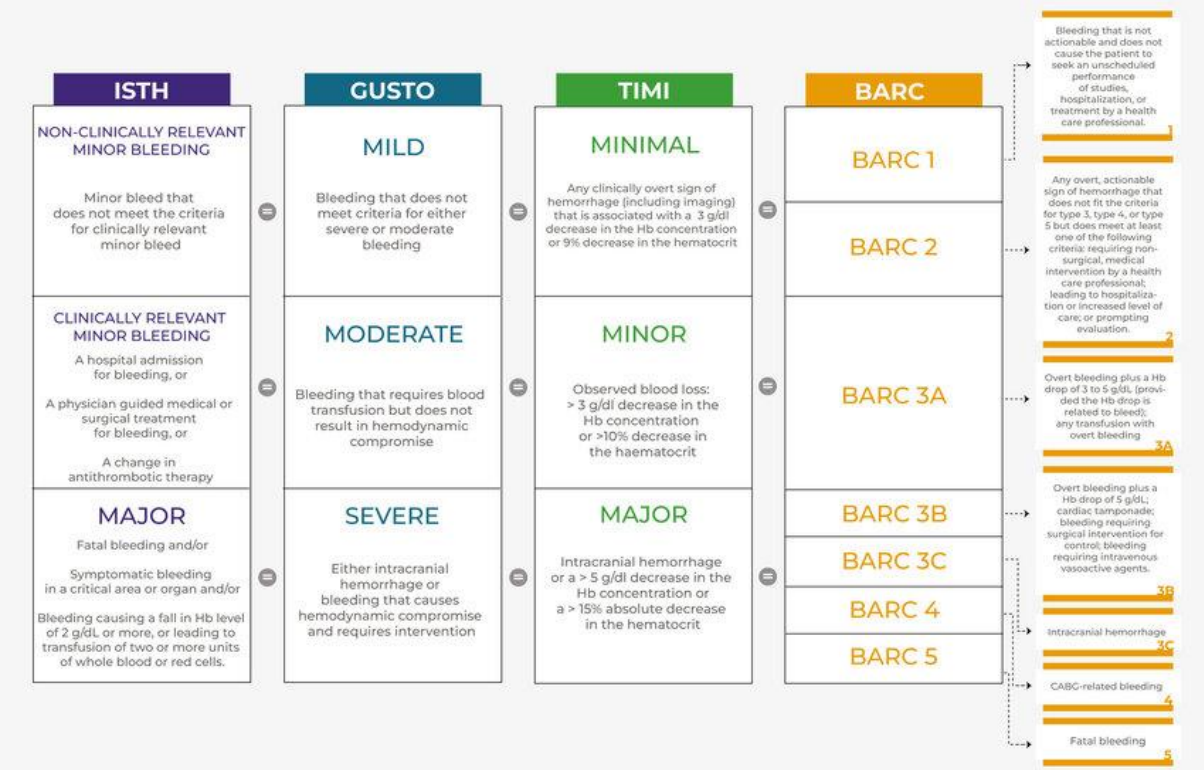

Figure 1: Comparison of the most used bleeding classifications (16).

3. Aims

This systematic review aims to critically evaluate and compare the safety and efficacy of systemic thrombolysis, CDT, USAT, and PMT in treating intermediate- and high-risk PE.
The objectives include evaluating the comparative effectiveness of improving clinical and hemodynamic outcomes by focusing on RV function recovery, thrombus resolution, and reduction in right-to-left ventricular ratio (RV/LV) ratio to evaluate bleeding risks associated with each therapeutic strategy, particularly major bleeding and intracranial haemorrhage. Also, investigate additional relevant outcomes such as ICU utilization, mortality, recurrent PE, long-term complications, CTEPH, and quality of life (QoL).
Ultimately, this review seeks to inform clinical decision-making in PE management by synthesizing findings across the RCTS retrospective studies and registry data by identifying the therapeutic approaches that provide optimal efficacy while minimizing harm, especially for patients in the intermediate-risk category, where treatment decisions are most nuanced.
Additionally, it aims to highlight current evidence gaps and the need for further head-to-head trials—particularly between PMT and CDT—to establish clear guidelines for personalized PE treatment.

4. Methods

4.1 Literature Selection

This systematic literature review has used the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) as a guideline to ensure quality and confidence in its results.
Thorough research was conducted using PubMed and ScienceDirect databases, covering publications from 2001-2025. Search terms included combinations of keywords such as “pulmonary embolism,” “catheter-directed thrombolysis,” “ultrasound-assisted thrombolysis,” “mechanical thrombectomy,” and “systemic thrombolysis”, “CDT outcomes.” The audit was limited to clinical trials and research articles only.
A total of 336 records were identified through database searches (198 from PubMed and 138 from Science Direct). An additional 21 records were identified through other methods, including manual reference screening of relevant systematic reviews and extraction from reputable clinical guideline sources such as the European Society of Cardiology (ESC), American Heart Association (AHA), and American College of Cardiology (ACC) and conference materials from the London Royal College of Physicians.
Inclusion criteria were RCTs, registry-based analyses, retrospective cohort studies, studies evaluating CDT, USAT, PMT or systemic thrombolysis, and adult patients with intermediate—or high-risk PE.
Exclusion criteria included studies focusing solely on deep vein thrombosis (DVT), peripheral arterial disease, post-thrombotic syndrome, atrial fibrillation, acute ischemic stroke, case reports and studies with sample size <60 patients and those published in languages other than English. Additionally, studies examining pediatric,

obese and oncologic patients were also excluded due to small pool and inability to produce comparative outcomes.
Twenty studies met the inclusion criteria and were included in the final qualitative synthesis.

The PRISMA flow diagram visually summarises the study selection process (Figure 2).

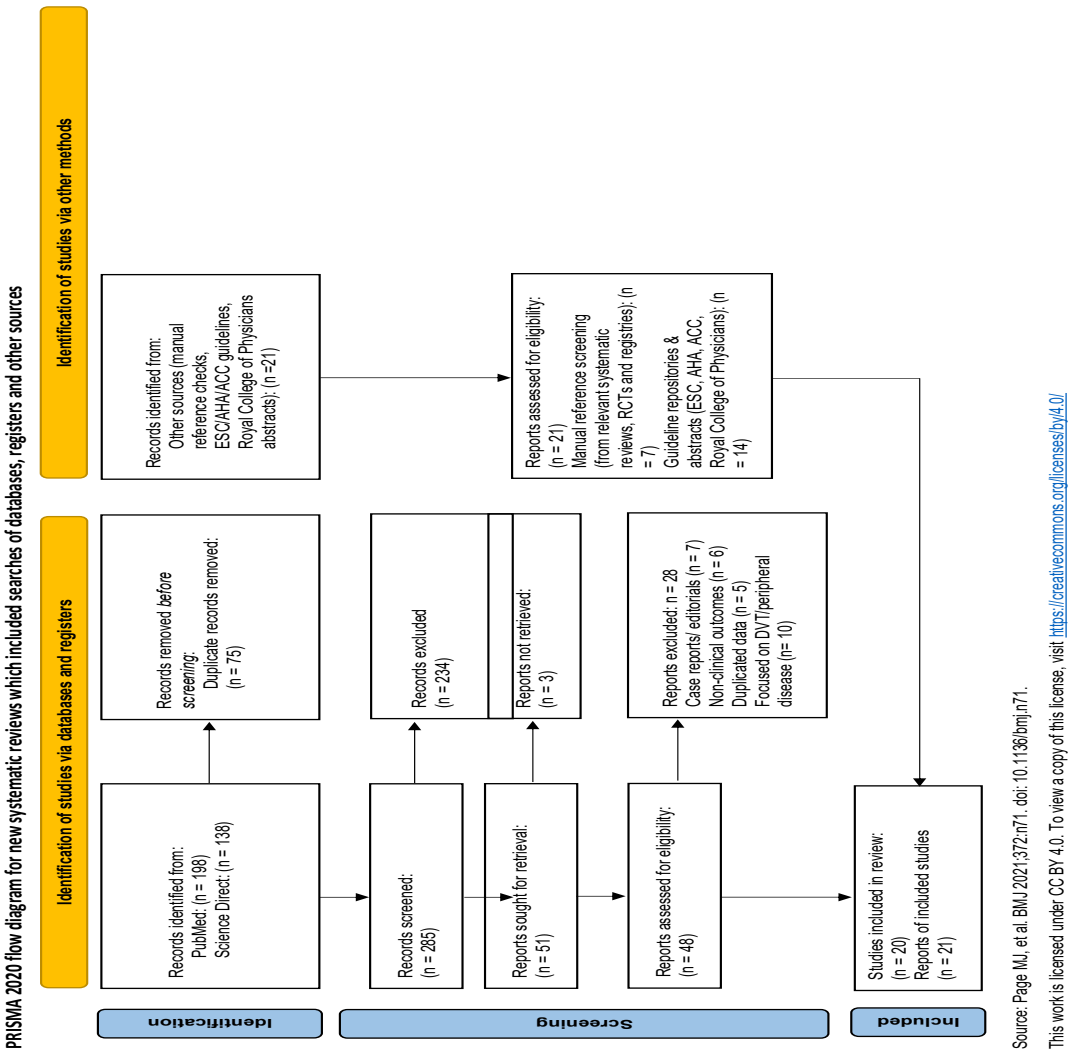

Figure 2: PRISMA flow chart

4.2 Study Characteristics

Data were extracted and summarized based on study design, patient population, interventions, comparator, and relevant clinical outcomes.
The selected studies ranged from different geographic regions and publication years, reflecting the growing interest in CDTs.
RCTs (e.g., PEITHO, ULTIMA, MOPETT, PEERLESS, OPTALYSE PE, CANARY, SUNSET sPE) provided high-quality data on early hemodynamic outcomes and safety metrics. At the same time, prospective registries and large-scale retrospective analyses (e.g., SEATTLE II, FLARE, Retrospective analysis using TriNetX, National

Inpatient Sample) offered complementary insights into real-world effectiveness and long-term prognosis.
Sample sizes varied significantly, ranging from under 60 patients (e.g., TIPES, Kroupa et al.) to over 1,000 patients (e.g., PEITHO, TriNetX). Intervention arms included full-dose and low-dose thrombolysis (tenecteplase, alteplase), CDT and USAT (e.g., EKOS Endovascular system), PMT using aspiration or large-bore devices (e.g., FlowTriever system), and standard anticoagulation regimens (e.g., UFH, LMWH, DOACs).
Clinical endpoints extracted included hemodynamic outcomes such as RV/LV ratio, pulmonary artery pressure, clinical deterioration, need for escalation of care, bleeding complications: major bleeding, intracranial haemorrhage (ICH), ICU utilization and duration, 30-day mortality, and long-term outcomes (e.g., CTEPH, RV function).
Most studies used validated criteria such as ISTH, BARC, or GUSTO to define major bleeding. The RV/LV ratio was consistently used as a marker for RV function.
Follow-up periods ranged from 24 hours to 5 years.
The Cochrane Risk of Bias tool for RCTs assessed the risk of bias. The risk of bias in non-randomized control trials was also assessed, as they do not apply to the Cochrane Risk of Bias.

Study	Design	Population	Intervention	Comparator	Outcomes
TOPCOAT	RCT	Submassive PE (RV strain)	Tenecteplase + LMWH	Placebo + LMWH	"Improved composite functional and clinical outcomes; 1 fatal ICH
MOPETT	RCT	Moderate PE	Low-dose tPA + Heparin	Heparin alone	Lower pulmonary hypertension and shorter hospitalization; no major bleeding
MAPPET-3	RCT	Submassive PE	Full-dose Alteplase + Heparin	Heparin alone	Reduced treatment escalation; mortality similar; no fatal/cerebral bleeding
PEITHO	RCT	Intermediate-risk PE (RV dysfunction + troponin)	Tenecteplase + Heparin	Placebo + Heparin	Lower decompensation; higher major bleeding and ICH
TIPES	RCT	Hemodynamically stable PE with RV dysfunction	Tenecteplase	Placebo	Improved RV/LV ratio at 24h; some major bleeds including ICH
HI-PEITHO	RCT (planned)	Intermediate-high risk PE	USAT + anticoagulation	Anticoagulation alone	Pending
National Inpatient Sample	Database analysis	PE patients 2016-2020	USAT	SCDT	No mortality or bleeding difference after adjustment

Single-center RCT	RCT	Intermediate high-high risk PE	USAT	Surgical embolectomy	SPE had greater RV/LV reduction
SEATTLE II	Single-arm trial	Massive and submassive PE	USAT	None	Improved RV/LV, reduced PA pressure, 10% moderate bleeding
PE-TRACT	RCT (ongoing)	Intermediate-risk PE	CDT + anticoagulation	Anticoagulation alone	Pending
ULTIMA	RCT	Intermediate-risk PE	USAT	Heparin	Superior RV/LV reduction with USAT
SUNSET sPE	RCT	Submassive PE	USAT	SCDT	Similar thrombus reduction, SCDT had better RV/LV improvement
TriNetX Retrospective	Database analysis	PE patients 2017-2023	PMT	CDT	Lower bleeding and better long-term outcomes with PMT
PEERLESS	RCT	Intermediate-risk PE	LBMT	CDT	Lower deterioration, ICU use with LBMT
PE Response Registry	Retrospective	Acute PE with follow-up imaging	Reperfusion therapies	Anticoagulation alone	Better clot resolution, RV function, lower mortality
Multicenter National Registry	Registry	Intermediate-high and high-risk PE	CDT (varied types)	None	90.9% success, lower mortality in IHR-PE
OPTALYSE PE	RCT	Intermediate-risk PE	USCDT (varied dose/duration)	None	Improved RV function, low bleeding

FLARE	Prospective single-arm	Intermediate-risk PE	PMT (FlowTriever)	None	Significant RV/LV improvement, low bleeding
Randomized Pilot Study	Pilot RCT	Intermediate-high risk PE	CDT	Anticoagulation alone	Greater RV function and pressure improvement
CANARY	RCT	Intermediate-high risk PE (RV dysfunction)	CDT	Heparin	Faster RV recovery, lower RV dysfunction

Table 2: Studies characteristics based on design, population, comparator, outcomes and conclusions.

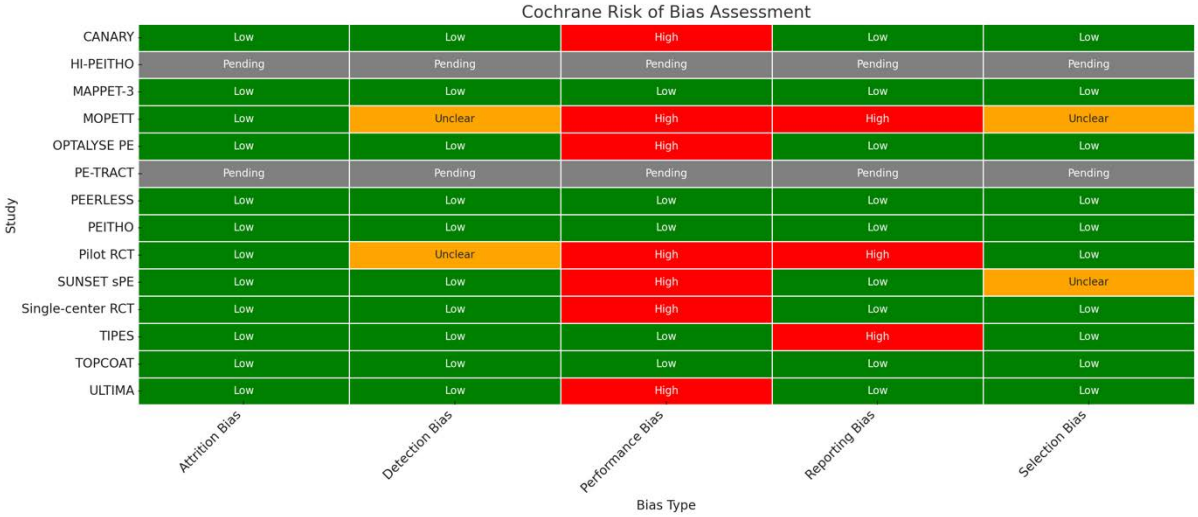

Table 3: Cochrane Risk of Bias Assessment for RCTs

Study	Design	Notes on Bias
National Inpatient Sample	Retrospective DB study	High risk of confounding and selection bias
TriNetX Retrospective	Retrospective cohort	Propensity-matched but still risk of unmeasured confounding
PE Response Registry	Retrospective registry	Selection bias, lack of randomization
Multicenter National Registry	Registry	Heterogeneous interventions; no control group

SEATTLE II	Single-arm	No control group; observational limitations
FLARE	Single-arm	No comparator; objective outcomes reduce bias but not risk of selection bias

Table 4: Bias assessment of the non-randomized studies

5. Results

5.1 Systemic Thrombolysis vs anticoagulation

Five randomized controlled trials evaluating systemic thrombolysis in patients with intermediate-risk or moderate PE were included. These studies examined the impact of fibrinolytic therapy — predominantly using tenecteplase or alteplase — on clinical outcomes, RV function, and long-term pulmonary hemodynamics, with varying results.

The PEITHO trial, the largest of its kind, enrolled 1005 normotensive patients with PE and both RV dysfunction and myocardial injury. Patients randomized to tenecteplase plus heparin experienced a significantly lower rate of early death or hemodynamic decompensation (2.6% vs 5.6%, P = 0.02). However, this benefit was offset by an increased risk of major extracranial bleeding (6.3% vs 1.2%) and hemorrhagic stroke (2.4% vs 0.2%) within 7 days. Mortality at 30 days was low and comparable between groups (2.4% vs 3.2%) (17).

The MAPPET-3 trial similarly investigated systemic thrombolysis using heparin plus alteplase and heparin plus placebo in 256 patients with submassive PE who were separated into respective groups after randomization. Thrombolysis significantly reduced the need for treatment escalation (10.2% vs 24.6%, P = 0.004), although in-hospital mortality did not differ (3.4% vs 2.2%). No fatal or ICHs occurred, suggesting a more favourable safety profile in this trial (18).

The TOPCOAT trial included 83 patients with RV strain and compared tenecteplase to placebo alongside low molecular weight heparin. Although the trial was stopped early due to slow enrollment, it showed a statistically significant reduction in composite outcomes, including death, intubation, shock, and poor physical functioning at 90 days (15% vs 37%; P = 0.017). However, a fatal ICH occurred in the thrombolysis group, reinforcing safety concerns (19).

The MOPETT trial explored using "safe-dose" thrombolysis, administering 50 mg of tPA in 121 patients with moderate PE. This low-dose strategy significantly reduced the incidence of pulmonary hypertension (PH) at 28 months (16% vs 57%; P < 0.001) and shortened hospital stay without any major bleeding events. Mortality and recurrent PE were also numerically lower, though not statistically significant. These results suggest that reduced-dose thrombolysis may offer a safer long-term benefit, though the study was single-center and open-label (20).

Finally, the TIPES trial enrolled 58 hemodynamically stable patients with echocardiographic RV dysfunction. Patients randomized to tenecteplase showed a significantly greater RV/LV ratio reduction at 24 hours (mean reduction 0.31 vs 0.10; P = 0.04). Three clinical events occurred in the placebo group compared to one

recurrent PE and two major bleeding events (including one intracranial) in the tenecteplase group. While demonstrating early RV benefit, the trial was underpowered as the bleeding risk remained a concern, and the clinical outcome impact required further validation (21).
These RCTs reinforce the complex risk-benefit profile of systemic thrombolysis in intermediate-risk pulmonary embolism in terms of efficacy, safety, and low-dose strategies. Across trials (e.g., PEITHO, MAPPET-3, TOPCOAT, TIPES), thrombolysis consistently reduces early surrogate outcomes such as RV dysfunction, escalation of care, and pulmonary artery pressures. Some trials (TOPCOAT, MOPETT) also indicate long-term QoL or hemodynamic benefits, though these are secondary outcomes.
Major bleeding, particularly ICH, remains a significant concern with full-dose tenecteplase or alteplase. In PEITHO, the ICH rate was 2.4%, a critical consideration when treating intermediate-risk patients who are otherwise hemodynamically stable. Low-dose strategies (MOPETT) and catheter-based interventions may offer a better safety margin, but further head-to-head trials are needed.
These RCTs support the conclusion that systemic thrombolysis offers clinical benefit in intermediate-risk PE, particularly in preventing early decompensation and reducing RV overload. However, non-negligible bleeding risks offset this benefit, particularly with full-dose regimens. Reduced-dose regimens and catheter-based delivery methods (e.g., CDL, USAT) may preserve efficacy while minimizing harm, highlighting the need for individualized, risk-adapted treatment approaches.

5.2 Ultrasound/ Catheter-directed thrombolysis vs. standard anticoagulation

Evaluating the risk-benefit ratio of USAT to heparin anticoagulation is of profound significance. Heparin has remained the mainstay of intermediate and high-risk PE management, as the high bleeding risk of full-dose systemic thrombolysis and the lack of trials researching the clinical significance of the newest clot-dissolving therapies underscores the urgent need for more research in this area (22).
In a multicenter randomized trial, Kucher et al. evaluated whether USAT is superior to anticoagulation alone in reversing RV dilation.
Fifty-nine patients with acute PE and an RV/LV ratio ≥1.0 were enrolled. Those in the anticoagulation group received an intravenous bolus of 80 IU/kg unfractionated heparin (UFH), followed by a continuous infusion adjusted to maintain therapeutic activated partial thromboplastin time for at least 24 hours. The post-procedural anticoagulation therapy duration was 3 months. In the USAT group, patients were treated with the Ekosonic MACH4e system, receiving rtPA (recombinant tissue Plasminogen Activator) at 1 mg/h with saline coolant, then reduced to 0.5 mg/h after 5 hours for 15 hours. The mean RV/LV ratio decreased significantly from 1.28 to 0.99 at 24 hours ($P < 0.001$), compared to a minimal change in the heparin group (0.30 vs. 0.03; $P < 0.001$). USAT also improved pulmonary artery pressures and cardiac index. Over 90 days, there was one death (heparin group), no major bleeding, and four minor bleeding events. Despite limitations like small sample size and lack of a thrombolysis-only comparator, the ULTIMA trial showed USAT was superior to anticoagulation alone in reversing RV dilation without increased bleeding (23).
The OPTALYSE PE trial further contributed to these findings by investigating whether lower doses of tPA and shorter delivery durations with USAT could maintain efficacy while reducing bleeding risk in intermediate-risk PE. Four dosing regimens were

tested in this multicenter randomized study of 101 patients, ranging from 4 mg/lung over 2 hours to 12 mg/lung over 6 hours. All arms demonstrated significant improvement in RV/LV ratio (~22% to 26%) and thrombus burden (refined modified Miller score), regardless of dose or duration. The major bleeding rate was low (4%), with only one intracranial hemorrhage attributed to the USAT protocol. The trial supported the feasibility of using reduced-dose and shorter-duration USAT to achieve meaningful clinical outcomes with an improved safety profile, particularly in patients at elevated bleeding risk (24).

Similarly, Kroupa et al. investigated the efficacy of SCDT over standard anticoagulation, with a primary endpoint of improving RV function, decreasing pulmonary pressure, and reducing thrombus burden (25).

Twenty-three patients with intermediate-high risk acute PE participated in the trial and were divided after randomization, 12 in the SCDT group and 11 in the standard care group(25). A continuous alteplase infusion was administered at 1 mg/hr/catheter and continued for 10 hours (total dose 20 mg) in the SCDT group(25). The standard anticoagulation group received LWMH at full therapeutic dose. Computed tomography angiography revealed a RV/LV reduction ≥25% in 7 of 12 patients in the SCDT group compared to 2 of 11 patients in the standard care group. Additionally, a systolic pulmonary artery pressure reduction of ≥30% or normotension at 24 hours after randomization was present in 10 of 12 patients in the SCDT group, again compared to 2 of 11 patients in the standard care group (p=0.001)(25). According to BARC, no intracranial or major bleeding occurred. The trial concluded that SCDT is effective and safe, improving key prognostic indicators (25).

In addition, the CANARY trial (2023), an open-label, multicenter randomized study, assessed the efficacy of SCDT versus anticoagulation monotherapy in patients with intermediate-high-risk PE. The trial included 94 patients before early termination due to the COVID-19 pandemic. At 3 months, patients in the SCDT group had significantly lower RV/LV ratios (median 0.7 vs 0.8; P = 0.01), and fewer patients had RV/LV >0.9 at 72 hours (27.0% vs 52.1%; P = 0.01). A composite outcome of death or persistent RV dilation at 3 months occurred less frequently with SCDT (4.3% vs 17.3%; P = 0.048), and only one major (nonfatal gastrointestinal) bleed occurred. These results suggest that the potential for SCDT to enhance early and sustained RV recovery while maintaining an acceptable safety profile (26).

In terms of efficacy, both trials prove that advanced thrombolysis with USAT or SCDT significantly improves RV function and hemodynamics compared to standard anticoagulation. Kucher et al. found a substantial RV/LV ratio reduction in the USAT group at 24 hours. Kroupa et al. demonstrated a significant reduction in RV/LV ratio and systolic pulmonary artery pressure with SCDT. Both interventions (USAT and SCDT) showed better outcomes than standard anticoagulation regarding RV/LV ratio and pulmonary pressures (23),(25).

In terms of efficacy, all three trials demonstrate that both advanced thrombolytic strategies (USAT, SCDT) significantly improve RV function and pulmonary hemodynamics compared to standard anticoagulation. Kucher et al. found a substantial RV/LV ratio reduction with USAT at 24 hours. Kroupa et al. showed marked reductions in both RV/LV ratio and pulmonary pressures. Similarly, the CANARY trial demonstrated sustained RV improvement and reduced composite adverse outcomes at three months in the SCDT group (23),(25).

Regarding safety, all three studies reported low to no major bleeding complications. Minor bleeding occurred in the USAT group (3 cases) in Kucher et al.'s study and was absent in the SCDT group in Kroupa et al.'s trial (23). The CANARY trial

reported only one major but nonfatal gastrointestinal bleeding event (26). These findings suggest catheter-based thrombolytic strategies offer a safer profile than systemic thrombolysis in selected patients.
However, all three trials had relatively small sample sizes, which may limit the generalizability of the findings.
Notably, the SEATTLE II trial included a prespecified sub-analysis of elderly patients (≥65 years), a group often underrepresented in thrombolysis studies due to bleeding concerns. In this cohort, 62 elderly and 88 younger patients with massive or submassive PE underwent USAT with low-dose fibrinolysis (24 mg tPA). Both groups experienced significant reductions in RV/LV diameter ratio (−0.47 in elderly vs −0.39 in younger patients, p = 0.31), pulmonary artery pressures, and modified Miller scores over 48 hours. While major bleeding occurred more often in the elderly group (15% vs 7%), the difference was not statistically significant (p = 0.17), and no intracranial haemorrhage was observed in either group. This finding suggests that low-dose, catheter-directed fibrinolysis is effective and reasonably safe in elderly PE patients, even those with higher baseline comorbidities (27).
Further studies with larger sample sizes and rigorous monitoring of anticoagulation therapy are needed to confirm these findings and establish the long-term safety and efficacy of these treatments. Additionally, future research should include control groups with standardized thrombolysis protocols to better isolate the contributions of ultrasound and catheter-directed interventions.
To this end, the PE-TRACT trial (Pulmonary Embolism: Thrombus Removal with Catheter-Directed Therapy) is a large, ongoing multicenter randomized trial designed to evaluate whether CDT plus anticoagulation improves long-term outcomes compared to anticoagulation alone in patients with intermediate-risk PE. Unlike prior trials focused on early RV recovery, PE-TRACT prioritizes patient-centered endpoints, such as peak oxygen uptake (VO_2) at 3 months and New York Heart Association (NYHA) Functional Classification at 12 months. These co-primary outcomes are assessed using a gatekeeping approach to preserve statistical rigour. The trial will also evaluate the safety, quality of life, and cost-effectiveness, providing a comprehensive assessment of CDT's role in improving long-term recovery (28).
The Higher-Risk Pulmonary Embolism Thrombolysis (HI-PEITHO) study is the first large-scale multinational, multicenter randomized controlled trial to fill the data gaps and provide evidence of USAT's impact on patients.
The primary endpoint of HI-PEITHO focuses not only on PE-related mortality but also on cardiorespiratory decompensation, collapse, non-fatal symptomatic and objectively confirmed reoccurrence within 7 days of initial USAT treatment (29).
Implementing the National Early Warning Score (NEWS) is vital to ensuring patient safety and the validity of the results. It sets clear rules and transparent criteria for early recognition and reaction to patients' vital status (22). The NEWS score assesses respiratory rate, oxygen saturation, additional oxygen supplementation requirement, body temperature, systolic blood pressure, heart rate, and level of consciousness to discriminate which patients are at highest risk for cardiac arrest, intensive care unit (ICU) admission, and/or death within 24 hours of assessment and provide better prognostic outcomes (30).

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Figure 3: The NEWS score system reproduced from the Royal College of Physicians (31).

Cardiorespiratory collapse or decompensation is defined as one or more of the following:
(a) cardiac arrest or need for cardiopulmonary resuscitation at any time between randomization and day 7,
(b) signs of shock, i.e., new-onset persistent arterial hypotension (SBP <90 mm Hg, or SBP drop by ≥40 mm Hg over ≥15 minutes, despite an adequate volume status; or need for vasopressors to maintain SBP ≥90 mm Hg), accompanied by end-organ hypoperfusion (altered mental status; oliguria/anuria; or increased serum lactate) at any time between randomization and day 7
(c) placement on extracorporeal membrane oxygenation (ECMO) at any time between randomization and day 7,
(d) intubation or initiation of non-invasive mechanical ventilation at any time between randomization and day 7 and
(e) a NEWS of 9 or higher, between 24 hours and 7 days after randomization, confirmed on two consecutive measurements 15 minutes apart (22),(29).
The study will examine secondary outcomes of the trial derived from individual components of the primary outcome, including bleeding complications, echocardiographic measures of RV recovery, and recurrent venous thromboembolism. It will also examine patient-reported outcomes, including serious adverse effects, QoL, and health economic analysis focusing on the length of hospital stay, resource utilization, and indirect costs (22).
HI-PEITHO results are highly anticipated. In either case, they will inform international guidelines on evaluating catheter-directed reperfusion treatment and establish it as a standard care option for managing intermediate and high-risk PE.

5.3 Comparative Effectiveness and Safety of Catheter-Based Therapies for Pulmonary Embolism

Catheter-based interventions, including SCDT, USAT, SPE, and PMT using devices like the FlowTriever System, are compared based on recent evidence.
Data from national registries, randomized controlled trials, and retrospective cohort studies from 2016 to 2023 were included. Outcomes assessed included in-hospital and long-term mortality, thrombus burden reduction, RV/LV ratio changes, bleeding complications, ICU stay, and readmission rates.
The findings from a large-scale retrospective analysis of the National Inpatient Sample (2016-2020) and the SUNSET sPE (Standard vs. Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism) trial were integrated (32)(33).
The retrospective study analyzed 39,430 patients who underwent CDL, comparing in-hospital mortality and bleeding complications between SCDT and USAT (33). The SUNSET sPE trial compared thrombus clearance and RV function improvement between the two techniques in eighty-one submassive PE patients.
In the retrospective study, in-hospital mortality was lower for USAT compared to SCDT (2.7% vs 3.8%, P = .04). However, after multivariable regression, no significant difference in mortality was observed (OR 0.75; 95% CI 0.52-1.08; P = .13)(32).
In the retrospective study, rates of ICH (0.6% vs 0.4%; P = .47) and major no intracranial bleeding (4.2% vs 4.1%; P = .72) were similar between USAT and SCDT (33). In the SUNSET sPE trial, major bleeding occurred in two patients, both in the USAT group (32).
The SUNSET sPE trial found no significant difference in pulmonary arterial thrombus clearance between USAT and SCDT (P = .76). Both modalities resulted in significant thrombus reduction.
The reduction in the RV/LV ratio was more significant in the SCDT group (0.59 ± 0.42) than in the USAT group (0.37 ± 0.34, P = .01). The conclusive findings indicate that USAT and SCDT have comparable efficacy in thrombus reduction and similar safety profiles regarding bleeding complications (32). Data from the retrospective analysis suggest lower in-hospital mortality with USAT, whereas the SUNSET sPE trial does not signify a difference (32)(33). SCDT may provide a more remarkable improvement in RV function. Further research is needed to evaluate long-term outcomes and optimal patient selection between these CDTs in PE management.
A single-centre phase II randomized non-inferiority trial compared USAT to SPE in 27 patients with intermediate-high or high-risk PE but was stopped early due to slow enrollment. Although the primary aim was to demonstrate non-inferiority of USAT, results suggested that SPE may provide greater improvement in RV/LV ratio (−0.53 vs −0.34; mean difference 0.152; 95% CI 0.032–0.271; Pnon-inferiority = 0.80; Psuperiority = 0.013) and greater thrombus burden reduction (Qanadli score change −11.36 vs −7.23; P = .032). Clinical and functional outcomes at 12 months were similar between groups, but the trial concluded that USAT was not inferior to SPE (34).
PMT has emerged as a compelling alternative, particularly with the FlowTriever system. A retrospective analysis using TriNetX data demonstrated that PMT has a better safety profile than CDL. This extensive multicenter study, which analyzed electronic health records from over 250 million patients, included 2978 patients who underwent PMT and 1137 who underwent CDL between January 2017 and August

2023. After 1:1 propensity score matching, 1102 patients in each group were compared (35).
Key 30-day outcomes showed no significant difference in all-cause mortality, acute respiratory failure, or blood transfusions. However, PMT was associated with significantly lower rates of gastrointestinal bleeding (OR 0.42; 95% CI, 0.28–0.63), ICH (OR 0.46; 95% CI, 0.24–0.89), myocardial infarction (OR 0.54; 95% CI, 0.41–0.76), and PH (OR 0.53; 95% CI, 0.41–0.68) (35).
Both treatment groups had comparable all-cause mortality and respiratory failure rates at five years. Notably, PMT patients had significantly reduced rates of chronic PH (HR 0.70; 95% CI, 0.55–0.90), right heart failure (HR 0.49; 95% CI, 0.37–0.65), and emergency department visits (348 vs 426; P < .01). The composite outcome for chronic PH, which included chronic thromboembolic PH, chronic cor pulmonale, and chronic PE, also favoured PMT. These findings suggest that PMT may offer sustained hemodynamic benefits and reduced long-term morbidity compared with CDL (35).
The PEERLESS randomized controlled trial compared large-bore mechanical thrombectomy (LBMT) using FlowTriever to CDT in 550 patients with intermediate-risk PE. LBMT significantly outperformed CDL in a hierarchical win ratio composite of clinical outcomes, including clinical deterioration, escalation to bailout therapy, and ICU utilization, with a win ratio of 5.01 (P<0.001). ICU admissions were less frequent and shorter with LBMT, and readmission rates were lower. Mortality and major bleeding were similar between the groups. Functional outcomes at 24 hours favoured LBMT, with better NYHA and modified Medical Research Council (mMRC) dyspnea scores, improved RV function, and lower respiratory rates. Overall, the study met its primary endpoint, with a significant win ratio of 5.01 (95% CI 3.68–6.97; P<0.001), indicating that LBMT outperformed CDT on a hierarchical composite of mortality, ICH, major bleeding, clinical deterioration, and ICU admission (36).
The FLARE trial is a prospective, single-arm, multicenter study that evaluated the safety and effectiveness of PMT using the FlowTriever system in patients with acute intermediate-risk PE. A total of 106 patients across 18 U.S. sites were enrolled. Patients were treated without thrombolytics. RV/LV ratio significantly decreased from 1.56 to 1.15 (mean reduction 0.38; 25.1%; p<0.0001). Major bleeding occurred in only one patient (0.9%), with no cases of ICH. Most patients had reduced ICU and hospital stays, and 41.3% required no ICU stay. These findings affirm FlowTriever's safety and efficacy in improving hemodynamics while minimizing bleeding risks. Despite the non-randomized design and short follow-up, FLARE supports the FlowTriever system as a valuable option for patients with contraindications to thrombolytics (37).
A multicenter European registry of 253 patients reported a 90.9% success rate for CDT. However, in-hospital mortality remained high among high-risk patients (37.6%) despite successful intervention, compared to intermediate-high-risk patients (2.5%). Both USAT and SCDT offer effective thrombus resolution and RV function improvement, though neither is superior. Especially using the FlowTriever system, PMT shows a favourable safety profile, reduced bleeding risk, and better long-term outcomes. The LBMT may provide more significant procedural advantages, including reduced ICU admissions and clinical deterioration risks (38).
These recent advancements in catheter-based interventions have broadened the therapeutic landscape for intermediate- and high-risk PE. While SCDT and USAT have demonstrated comparable efficacy in thrombus resolution and safety in multiple trials, such as the SUNSET sPE and large-scale retrospective analyses, neither

approach has shown clear superiority (32)(33). On the other hand, SPE, although invasive, may provide greater reductions in RV/LV ratio and thrombus burden in select patients, as seen in the Strotecky et al. trial (34).
PMT particularly with the FlowTriever system, provides a favourable safety profile, superior procedural efficiency, and better long-term outcomes establishing it as a promising alternative. The TriNetX retrospective study and the PEERLESS randomized controlled trial both support the use of LBMT over CDL, showing significantly reduced bleeding complications, lower ICU usage, improved hemodynamic recovery, and reduced chronic complications such as PH and right heart failure (35),(36). The FLARE trial further supports the FlowTriever system's value, especially in patients contraindicated for thrombolytics (37).
In conclusion, while CDL therapies remain effective and relatively safe, PMT with the FlowTriever system, offers significant procedural and long-term advantages. Additional randomized trials and long-term data are needed to define optimal patient selection further and establish the role of these evolving therapies in PE management praxis.

5.4 Outcomes

5.4.1 Major Bleeding

Major bleeding is a pivotal safety concern when assessing clot-dissolving therapies for PE, especially in intermediate- and high-risk cases.
Across the selected studies included in this systematic review, systemic thrombolysis (e.g., PEITHO, TOPCOAT) carries the highest major bleeding and ICH risk (17),(19). In the PEITHO trial, bleeding outcomes were classified using ISTH criteria, resulting in a higher incidence of major bleeding (6.3%), including 2.4% ICH (17). In contrast, trials like MOPETT used lower thrombolytic doses and reported no major bleeding but did not specify a formal bleeding classification, which may underreport less overt events (20).
USAT and SCDT demonstrate lower bleeding risks, particularly when using low-dose regimens. However, bleeding risk is not uniform across patient populations. Elderly patients, those with renal impairment, and those on concomitant antiplatelets are disproportionately affected. Notably, SEATTLE II included elderly subgroups, showing higher but acceptable bleeding rates with USAT (27).
PMT (e.g., FlowTriever in FLARE and PEERLESS) shows the lowest bleeding incidence, including negligible ICH rates (36),(37).
Some trials included in the review did not specify the bleeding classification system (e.g., CANARY), which complicates the direct comparison of safety outcomes (26).

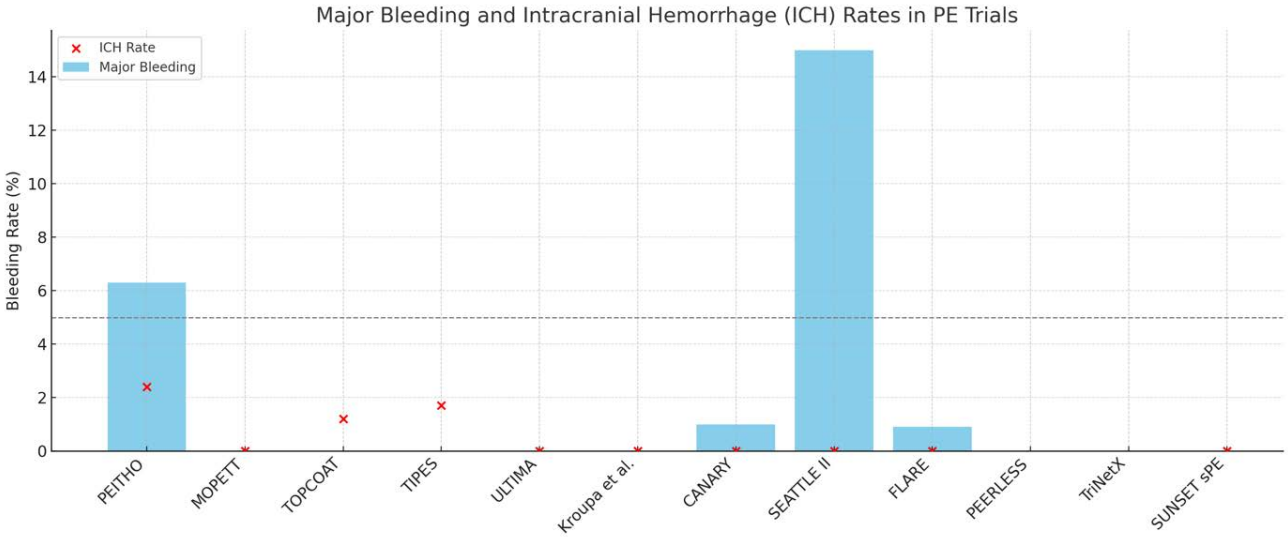

Figure 4: The major bleeding and ICH rates across the PE trials
Blue bars represent the major bleeding rate.
Red dots indicate ICH rates, when reported.
The dashed line at 5% marks a common safety threshold in clinical decision-making.

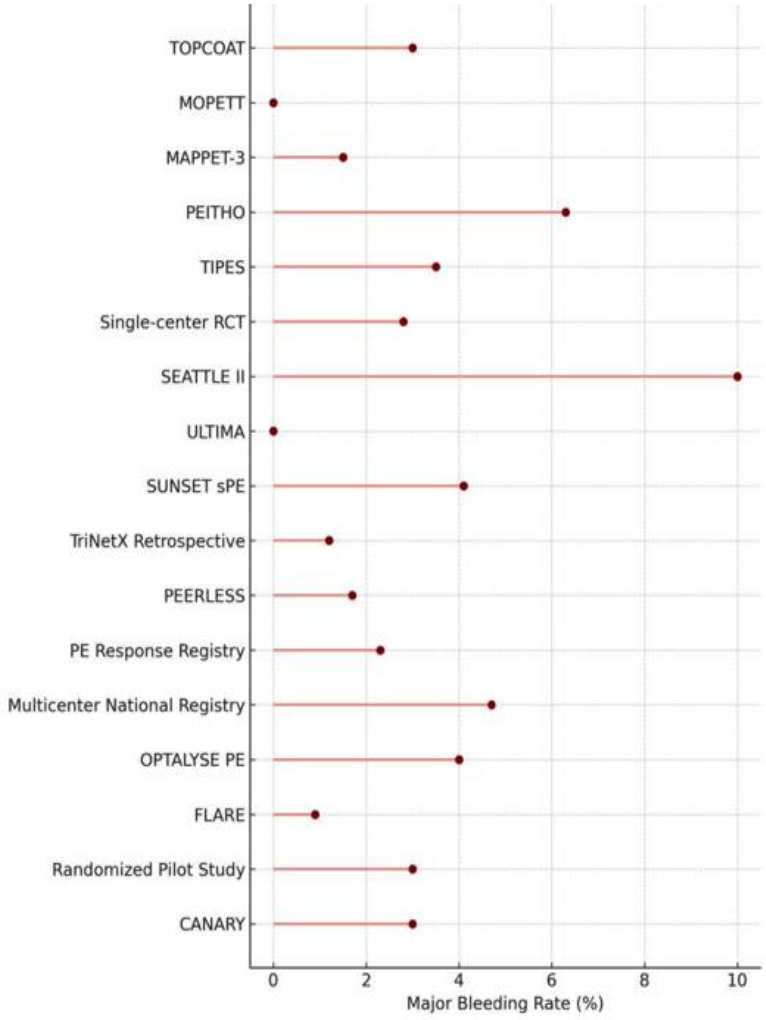

Figure 5: Major Bleeding Rate by Study

This plot further illustrates these data across a broader range of trials, including registry and retrospective analyses. Notably, intracranial hemorrhage (ICH), while rare, occurred almost exclusively in thrombolysis trials, emphasizing the safety advantage of catheter-based approaches

Understanding the bleeding risk enables us to properly select systemic thrombolysis, CDT, and PMT, providing optimal treatment. The risk-benefit ratio of thrombolysis is narrow in intermediate-risk PE patients who are hemodynamically stable. Therefore, precise bleeding classification is crucial in clinical decisions as broad definitions and lack of comparative data could cause overestimation of the actual bleeding risk preventing appropriate candidates from receiving thrombolysis, while underestimation it may lead to its use in patients whose risks outweigh the benefits. Adopting ISTH or BARC across future PE trials could enhance comparability, improve meta-analytic accuracy, and provide more precise clinical recommendations.

5.4.2 RV/LV ratio Reduction

To further stratify the clinical efficacy of clot-dissolving therapies, RV/LV ratio reduction was used as a surrogate marker of right ventricular (RV) function improvement. In this systematic review, we analyzed data from the key trials of the 20 studies that reported complete and comparable quantitative data on RV/LV ratio reduction evaluating systemic thrombolysis, CDL, USAT, and PMT.
The most substantial RV/LV reductions were reported in trials comparing USAT with surgical embolectomy (Strotecky et al., 53%) and in the SUNSET sPE trial (37.3%), which compared USAT and standard CDT (32)(34). Trials evaluating USAT alone (ULTIMA, OPTALYSE PE, SEATTLE II) consistently achieved ~25% reductions in RV/LV ratio, indicating robust hemodynamic improvement (23),(24),(27). The FLARE trial demonstrated similar results with PMT (25.1%), supporting the efficacy of mechanical thrombectomy without thrombolytics (37).
Systemic thrombolysis trials (PEITHO, TOPCOAT, TIPES) showed moderate reductions (~20–31%), though increased bleeding risk often offset these benefits (17)(19)(21). CDT trials (Kroupa et al., CANARY) also showed RV/LV reductions of 25–30%, emphasizing their role in intermediate-risk PE treatment strategies (25),(26).

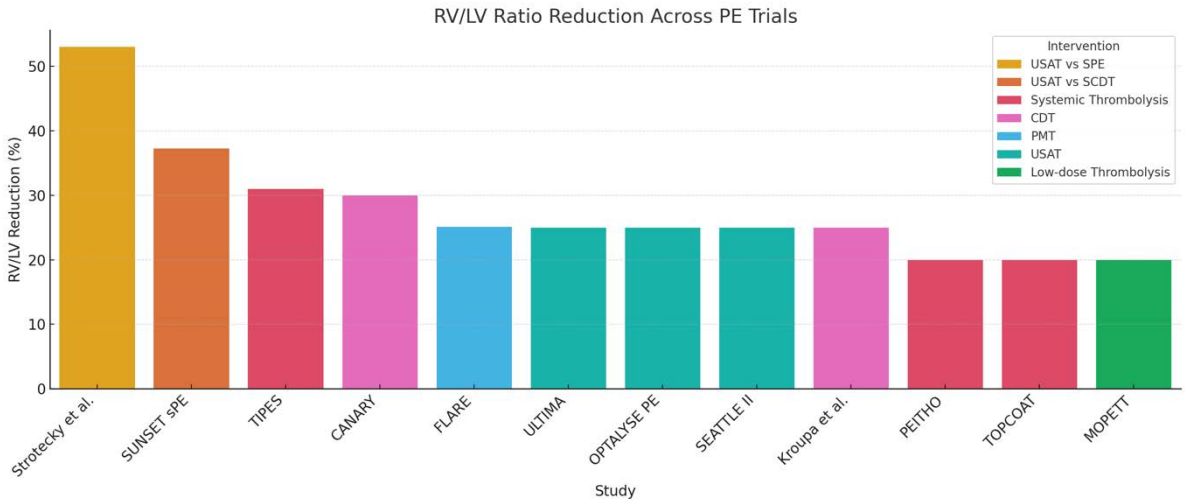

Figure 6: RV/LV reduction ratio across PE Trials, stratified by intervention type.
Note: Highlights 12 trials with clearly reported RV/LV reduction data, grouped and color-coded by intervention type. This figure focuses on trials with directly comparable, prospective data.

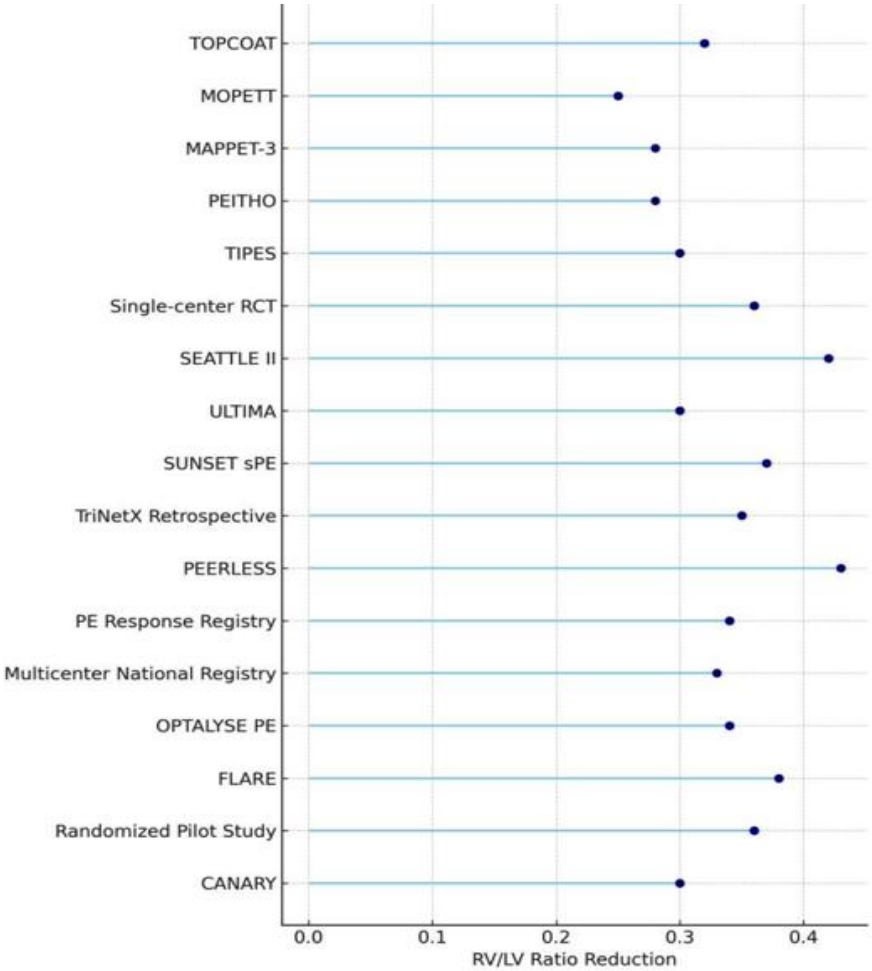

Figure 7: RV/LV Ratio Reduction by Study
This plot displays the mean reduction in RV/LV ratio reported across selected studies. It illustrates the relative efficacy of various PE therapies (systemic thrombolysis, catheter-directed thrombolysis, ultrasound-assisted thrombolysis, and mechanical thrombectomy) in improving right ventricular function as assessed by RV/LV ratio reduction.

Note: includes a broader set of studies (including retrospective analyses, registries, and pilot studies) to show variability across the literature. These studies were not always included in the main quantitative synthesis due to incomplete baseline/post-treatment data, non-standardized definitions, or inconsistent follow-up times, but were still visualized for reference.

This stratification supports the conclusion that catheter-based therapies—particularly USAT and PMT—are effective at rapidly reversing RV dysfunction in intermediate-risk PE with a favorable safety profile, especially in patients where systemic thrombolysis poses a high bleeding risk.

5.4.3 Mortality Benefit

Most studies on treatments for intermediate- and high-risk PE have focused on improving heart function or reducing symptoms rather than directly lowering the risk of death.
Among the trials reviewed, only the PEERLESS trial showed a clear benefit in reducing serious outcomes, including death, by using a combined score of different health events (36). Some other studies, like MOPETT, TOPCOAT, CANARY, and the retrospective analysis using TriNetX, suggested a possible benefit in lowering death rates, but these results were not strong enough to be considered conclusive (19),(20),(26),(35). In larger trials like PEITHO and TIPES, thrombolysis helped reduce strain on the heart but did not lower death rates (17),(21). Several catheter-based therapy studies—such as ULTIMA, SEATTLE II, and SUNSET sPE—did not measure mortality as a primary outcome (23),(27),(32).
While CDT show strong potential for reducing clinical deterioration and improving functional recovery, robust evidence of mortality benefit remains limited. It highlights the need for large-scale, long-term randomized controlled trials powered specifically for hard clinical endpoints.

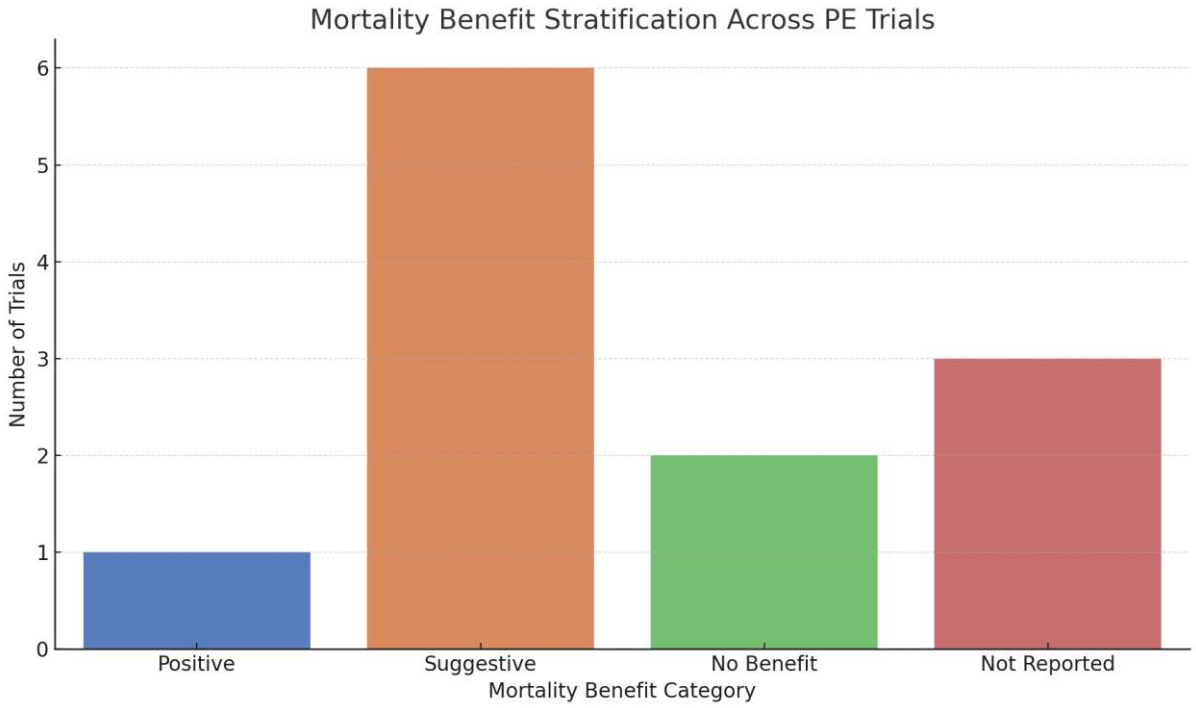

Figure 8: Mortality benefit stratification across PE Trial
Note: Most studies provided suggestive or inconclusive data, and only one demonstrated a statistically significant mortality reduction.

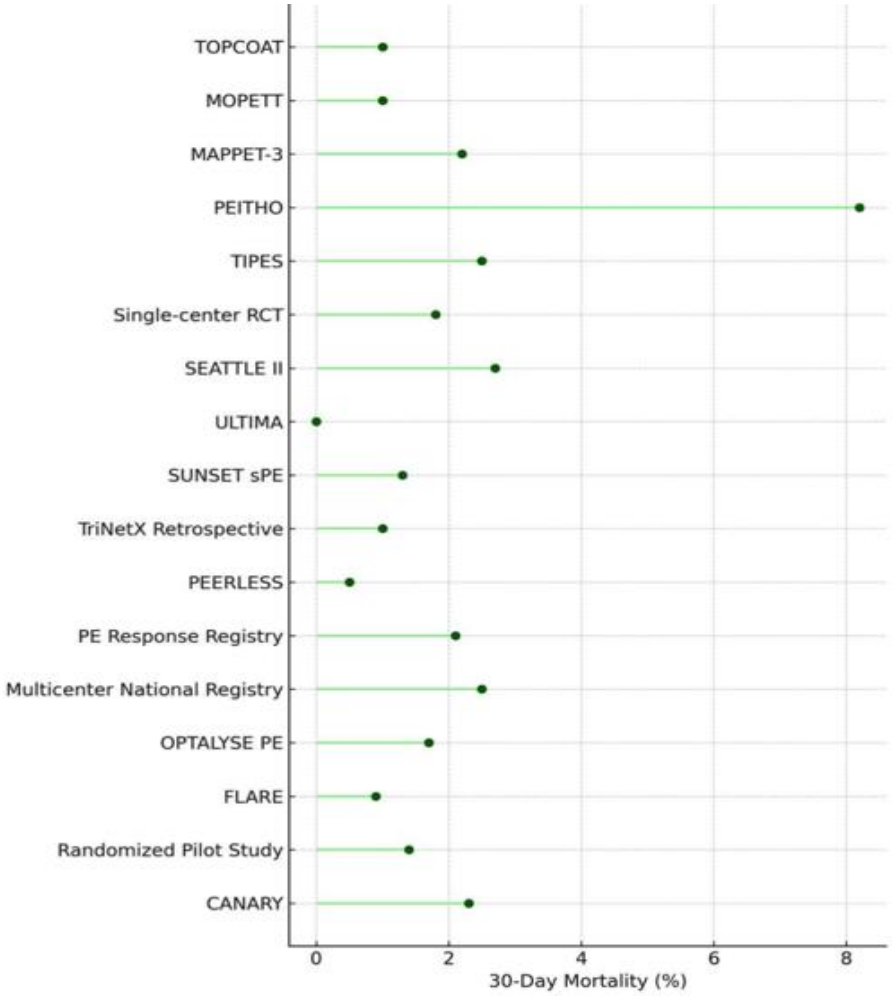

Figure 9: 30-day Mortality Rate by study
This plot presents reported 30-day mortality rates from individual studies, ranging from <1% in catheter-based trials to over 8% in PEITHO, highlighting variation in study populations and risk profiles.

5.4.4 ICU stay

ICU stay duration and utilization are important secondary outcomes in PE trials, reflecting treatment safety and healthcare burden.
This review found that catheter-based interventions, especially PMT and low-dose thrombolysis, were often associated with reduced or avoided ICU use. For instance, in the FLARE trial, over 40% of patients avoided ICU admission, while the PEERLESS and the retrospective analysis using TriNetX reported shorter ICU stays and fewer admissions in the PMT groups (36),(37),(35). Conversely, the PEITHO trial, which employed full-dose systemic thrombolysis, showed increased ICU use due to monitoring requirements for bleeding risk (17). Some trials, like ULTIMA and CANARY, did not report ICU-related outcomes, limiting comparison. Overall, therapies with lower bleeding risk and faster recovery, such as PMT and targeted CDL, appear to support more efficient ICU resource utilization.

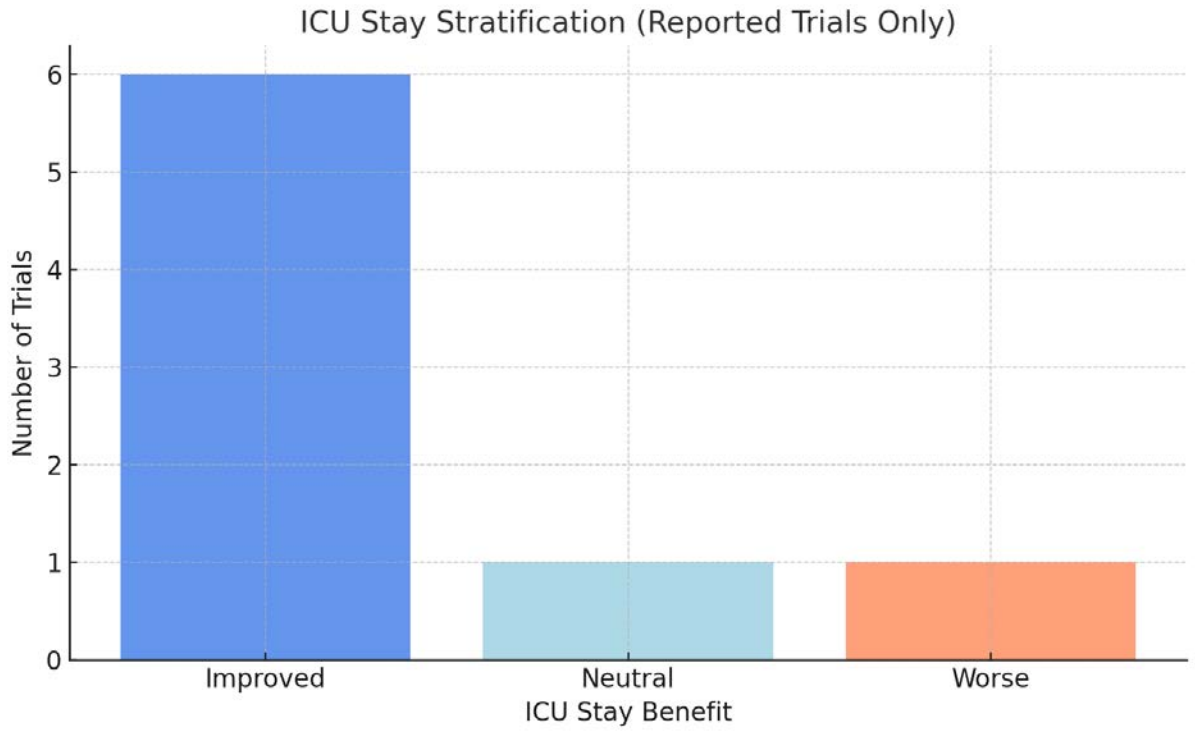

Figure 10: ICU stay stratification across PE trials
This bar chart categorizes the reported impact of clot-dissolving therapies on intensive care unit (ICU) length of stay across clinical trials for intermediate- and high-risk pulmonary embolism (PE). Trials were stratified into four categories based on reported outcomes:

- Improved: The intervention resulted in a reduced ICU stay.
- Neutral: No significant difference in ICU stay duration was observed.
- Worse: ICU stay duration was prolonged.

However, variability in reporting standards persists, as trials did not report ICU outcomes.

5.4.5 Long term outcomes

Long-term outcomes, including recurrence of PE, development of CTEPH, and sustained RV recovery were inconsistently reported across studies, however, are essential for evaluating the lasting impact of the PE treatments.
Only a few trials—including MOPETT, TOPCOAT, CANARY, the retrospective analysis using TriNetX, and PEERLESS—provided meaningful long-term data, focusing on parameters like PH, RV function, QoL, or 5-year follow-up outcomes (19),(20),(26),(35),(36). Other trials, such as PEITHO and FLARE, included limited long-term data, primarily indirect or short-term observations (17),(37). Many trials (ULTIMA, SEATTLE II, SUNSET sPE) did not assess long-term outcomes, focusing instead on acute hemodynamic or safety endpoints (23),(27),(32). This gap highlights the need for future studies to include standardized, patient-centred long-term outcomes to understand better the durability and real-world impact of clot-dissolving therapies for PE. It is being addressed by ongoing trials such as the Hi-PEITHO and PE-TRACT studies.

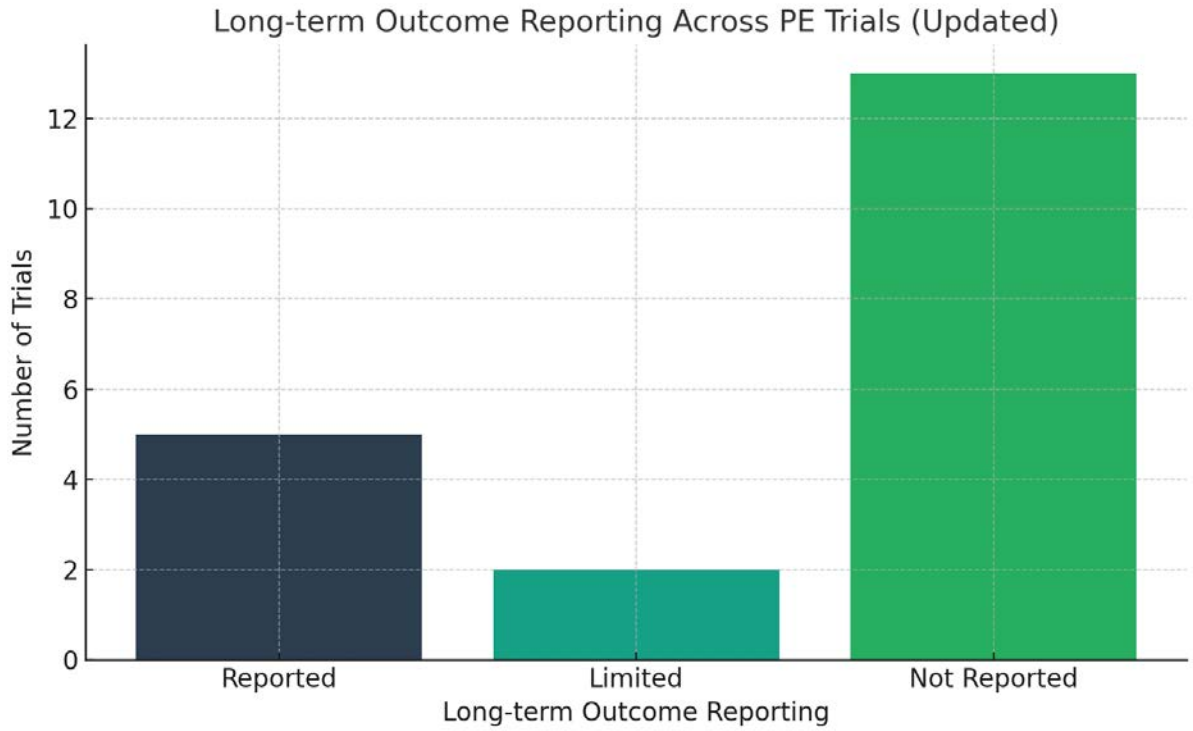

Figure 11: Long term Outcomes across PE trials
Note: This visualization highlights a critical evidence gap in PE research, underscoring the need for future trials to systematically assess long-term clinical and patient-centered outcomes.

6. Discussion

In this systematic review of 20 studies evaluating thrombolytic therapies for intermediate- and high-risk PE, catheter-based interventions demonstrated efficacy comparable to systemic thrombolysis in reducing RV strain while offering a substantially lower risk of major bleeding. PMT and USAT consistently showed favourable safety profiles.

USAT achieved approximately 25–30% reductions in RV/LV ratio across multiple trials (ULTIMA, OPTALYSE PE, SEATTLE II), with major bleeding rates ranging from 2% to 10%, markedly safer than systemic thrombolysis, which showed 10–20% major bleeding in PEITHO and registry studies (moderate certainty). PMT (e.g., FLARE, PEERLESS) produced similar hemodynamic benefits with even lower bleeding rates (~1–3%) (low to moderate certainty due to lack of long-term data and observational designs).

These findings align with a recent systematic review and meta-analysis comparing CDT and thrombectomy**,** which found that CDL was associated with significantly lower in-hospital mortality than thrombectomy (low certainty due to the observational nature of included studies). Both strategies showed similar rates of major bleeding, stroke, blood transfusion, and ICU length of stay. Both treatments led to comparable improvements in RV/LV ratios and readmission rates, confirming their clinical utility in managing submassive and massive PE (39) (moderate certainty).

Systemic thrombolysis consistently reduces early clinical deterioration but is associated with higher bleeding risk**,** particularly for ICH (high certainty for bleeding risk, moderate certainty for efficacy).

A 2020 systematic review evaluating thrombolysis for intermediate-risk PE found that thrombolytics reduced treatment escalation and hemodynamic collapse but at the cost of increased bleeding complications. The authors concluded that the benefit of thrombolysis in stable intermediate-risk patients remains limited by its bleeding profile (40) (moderate certainty).

Additionally, a Bayesian network meta-analysis of randomized controlled trials found systemic thrombolysis reduced mortality and recurrent PE compared to anticoagulation alone. However, it also increased minor bleeding events (high certainty for efficacy, moderate certainty for bleeding). The same study reported no significant difference between SCDT and USAT**,** suggesting similar efficacy between these catheter-based techniques (41) (moderate certainty).

These reviews reinforce the conclusion that catheter-directed therapies—especially when thrombolytic doses are reduced or omitted—can preserve clinical efficacy while offering improved safety (moderate to high certainty). This observation is particularly relevant for intermediate-high-risk patients, where the balance of risk and benefit is narrow. Trials such as CANARY, Kroupa et al., and PEERLESS suggest that advanced therapies lead to meaningful clinical improvements, including RV function and QoL, without increasing bleeding risk (low to moderate certainty due to heterogeneous designs and incomplete long-term data).

However, economic and health system considerations are critical to implementation. While PMT and USAT offer safety advantages, their feasibility is constrained by institutional resources, operator expertise, and equipment availability. High devices and procedural costs, such as those associated with the FlowTriever or EKOS Endovascular systems, may limit access in low-resource settings or smaller

hospitals, where systemic thrombolysis remains the only option. Health systems must weigh the clinical benefits against economic realities, especially in settings with constrained budgets or limited interventional capabilities.

Moreover, heterogeneity in study design, inconsistent outcome definitions (particularly for bleeding), and variable follow-up durations limit trial comparability. Furthermore, few studies evaluated long-term outcomes like CTEPH, functional capacity, or health-related QoL—key metrics for understanding sustained recovery after PE (very low to low certainty).

These findings, supported by high-quality systematic reviews and moderate to high certainty evidence, strengthen the growing adoption of catheter-based interventions for PE. Large-scale, long-term randomized controlled trials, like the ongoing HI-PEITHO and PE-TRACT, are still required to determine the optimal therapeutic approach, particularly in intermediate-risk patients. These trials should include standardized outcome measures**,** patient-reported endpoints**,** and cost-effectiveness analysis to better inform individualized treatment strategies.

Future research must also address key evidence gaps for high-risk subpopulations often excluded from clinical trials. These include elderly patients, pregnant women, patients with renal impairment, and those with absolute contraindications to anticoagulation. These groups may benefit most from PMT due to its non-thrombolytic nature and favorable bleeding profile. Expanding the evidence base for these vulnerable cohorts is critical for ensuring equity and safety in PE management.

Limitations of this review should be acknowledged.

While the synthesis included a broad range of interventions, only 12 of the 20 studies reported major bleeding risk and RV/LV ratio reduction as a quantitative endpoint, limiting the scope of hemodynamic comparisons. Many trials were single-center or lacked blinding, increasing risk of bias. Additionally, bleeding definitions varied widely across studies, complicating direct comparisons of safety outcomes. Long-term endpoints were inconsistently reported, and key subgroups, such as elderly patients, pregnant individuals, those with renal impairment, or contraindications to anticoagulation, were underrepresented or excluded. Lastly, publication bias and language restrictions may have led to omission of relevant unpublished or non-English trials.

7. Conclusion

In patients with intermediate- and high-risk PE, clot-dissolving therapies show important differences in efficacy, safety, and long-term outcomes—differences that directly inform clinical decision-making. Systemic thrombolysis remains the gold standard for patients with high-risk PE and hemodynamic compromise, offering rapid hemodynamic relief but at the cost of a significantly increased risk of major bleeding, particularly ICH.

CDL and PMT have emerged as effective and safer alternatives, particularly in patients at elevated bleeding risk or with relative or absolute contraindications to systemic thrombolysis. These modalities substantially improve RV function and thrombus clearance with lower rates of major bleeding. Significantly, PMT platforms—such as the FlowTriever system—are rapidly evolving and have shown promising short-term outcomes, including reduced ICU stays and improved safety, even without thrombolytics.

Given the growing number of therapeutic options, multidisciplinary Pulmonary Embolism Response Teams (PERTs) are critical for optimizing individualized therapy. PERTs combine critical care, cardiology, pulmonology, radiology, vascular surgery, haematology, and pharmacy specialists to provide real-time, collaborative decision-making. PERTs use real-time evaluation of patient-specific factors such as RV function, bleeding risk, thrombus burden, comorbidities, and hemodynamic status. Core principles of the PERT approach include immediate initiation of anticoagulation unless contraindicated, structured team activation protocols, and integration into institutional care pathways to stratify patients and select the most appropriate intervention. PERT integration with driven clinical algorithms into institutional PE protocols has been shown to improve coordination, reduce care delays, and potentially enhance outcomes while streamlining resource utilization. Ongoing efforts by the PERT Consortium aim to evaluate the impact of these teams on clinical outcomes, cost-efficiency, and system-wide practices in PE management.

Despite the advances in catheter-based strategies, there remains a lack of RCTs comparing PMT with USAT or SCDT. These trials are essential to determine comparative effectiveness, cost-efficiency, and long-term outcomes such as CTEPH, recurrent PE, exercise tolerance and QoL.

Therefore, while current evidence supports CDT and PMT as viable and often preferable alternatives to systemic thrombolysis in selected patients, robust, multicenter studies with standardized endpoints are needed to guide future practice. These studies should also incorporate PERT-led decision algorithms and patient-centred outcomes to build a precision-medicine framework for acute PE management in the modern era.

8. References

1. MSD Manual Professional Edition. Pulmonary Embolism (PE) - Pulmonary Disorders. Available from: https://www.msdmanuals.com/professional/pulmonary-disorders/pulmonary-embolism/pulmonary-embolism-pe

2. CDC. Venous Thromboembolism (Blood Clots). 2025. Data and Statistics on Venous Thromboembolism. Available from: https://www.cdc.gov/blood-clots/data-research/facts-stats/index.html

3. Yuriditsky E, Horowitz JM, Lau JF. Chronic thromboembolic pulmonary hypertension and the post-pulmonary embolism (PE) syndrome. Vasc Med. 2023 Aug;28(4):348–60. Available from: https://journals.sagepub.com/doi/10.1177/1358863X231165105

4. Naoum JJ. Anticoagulation Management Post Pulmonary Embolism. Methodist DeBakey Cardiovasc J. 2024 May 16;20(3):27–35. Available from: https://journal.houstonmethodist.org/articles/10.14797/mdcvj.1338/

5. Marti C, John G, Konstantinides S, Combescure C, Sanchez O, Lankeit M, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2015 Mar 7;36(10):605–14. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehu218

6. MSD Manual Professional Edition. Pulmonary Embolism (PE) - Pulmonary Disorders. Available from: https://www.msdmanuals.com/professional/pulmonary-disorders/pulmonary-embolism/pulmonary-embolism-pe

7. Shah IK, Merfeld JM, Chun J, Tak T. Pathophysiology and Management of Pulmonary Embolism. Int J Angiol. 2022 Sep;31(03):143–9. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0042-1756204

8. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020 Jan 21;41(4):543–603. Available from: https://academic.oup.com/eurheartj/article/41/4/543/5556136

9. Carroll BJ, Larnard EA, Pinto DS, Giri J, Secemsky EA. Percutaneous Management of High-Risk Pulmonary Embolism. Circ Cardiovasc Interv. 2023 Feb;16(2):e012166. Available from: https://www.ahajournals.org/doi/10.1161/CIRCINTERVENTIONS.122.012166

10. www.bostonscientific.com. EKOS™ Endovascular System. Available from: https://www.bostonscientific.com/en-EU/products/thrombectomy-systems/ekosonic-endovascular-system.html

11. Endovascular Today. Bryn Mawr Communications; The Search for the Holy Grail of New PE Devices. Available from: https://evtoday.com/articles/2020-july-supplement/the-search-for-the-holy-grail-of-new-pe-devices

12. Bunc M, Steblovnik K, Zorman S, Popovic P. Percutaneous mechanical thrombectomy in patients with high-risk pulmonary embolism and contraindications for thrombolytic therapy. Radiol Oncol. 2020 Feb 14;54(1):62–7. Available from: https://www.sciendo.com/article/10.2478/raon-2020-0006

13. Pruszczyk P, Klok FK, Kucher N, Roik M, Meneveau N, Sharp AS, et al. Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention. 2022 Oct;18(8):e623–38. Available from: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00246

14. Naidu SG, Knuttinen MG, Kriegshauser JS, Eversman WG, Oklu R. Rationale for catheter directed therapy in pulmonary embolism. Cardiovasc Diagn Ther. 2017 Dec;7(S3):S320–8. Available from: http://cdt.amegroups.com/article/view/16780/18092

15. Avgerinos ED, Abou Ali AN, Liang NL, Genovese E, Singh MJ, Makaroun MS, et al. Predictors of failure and complications of catheter-directed interventions for pulmonary embolism. J Vasc Surg Venous Lymphat Disord. 2017 May;5(3):303–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213333X17300732

16. ResearchGate. Comparison of the most used bleeding classifications. Available from: https://www.researchgate.net/figure/Comparison-of-the-most-used-bleeding-classifications-ISTH-classifies-bleeding-according_fig1_362735459

17. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014 Apr 10;370(15):1402–11.

18. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus Alteplase Compared with Heparin Alone in Patients with Submassive Pulmonary Embolism. N Engl J Med 2002 Oct 10;347(15):1143–50. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa021274

19. Kline JA, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost JTH. 2014 Apr;12(4):459–68.

20. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M, “MOPETT” Investigators. Moderate pulmonary embolism treated with thrombolysis (from the “MOPETT” Trial). Am J Cardiol. 2013 Jan 15;111(2):273–7.

21. Becattini C, Agnelli G, Salvi A, Grifoni S, Pancaldi LG, Enea I, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res. 2010 Mar;125(3):e82-86.

22. Klok FA, Piazza G, Sharp ASP, Ní Ainle F, Jaff MR, Chauhan N, et al. Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: Rationale and design of the HI-PEITHO study. Am Heart J. 2022 Sep;251:43–53.

23. Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014 Jan 28;129(4):479–86.

24. Tapson VF, Sterling K, Jones N, Elder M, Tripathy U, Brower J, et al. A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism. JACC Cardiovasc Interv. 2018 Jul 23;11(14):1401–10. Available from: https://www.jacc.org/doi/10.1016/j.jcin.2018.04.008

25. Kroupa J, Buk M, Weichet J, Malikova H, Bartova L, Linkova H, et al. A pilot randomised trial of catheter-directed thrombolysis or standard anticoagulation for patients with intermediate-high risk acute pulmonary embolism. EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol. 2022 Oct 7;18(8):e639–46.

26. Sadeghipour P, Jenab Y, Moosavi J, Hosseini K, Mohebbi B, Hosseinsabet A, et al. Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High-risk Pulmonary Embolism: The CANARY Randomized Clinical Trial. JAMA Cardiol. 2022 Dec 1;7(12):1189–97.

27. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. JACC Cardiovasc Interv. 2015 Aug 24;8(10):1382–92.

28. Sista AK, Troxel AB, Tarpey T, Parpia S, Goldhaber SZ, Stringer WW, et al. Rationale and design of the PE-TRACT trial: A multicenter randomized trial to evaluate catheter-directed therapy for the treatment of intermediate-risk pulmonary embolism. Am Heart J. 2025 March; 281:112–22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002870324003193

29. The HI-PEITHO Study of Ultrasound-Facilitated, Catheter-Directed Thrombolysis Versus Anticoagulation - Endovascular Today. Available from: https://evtoday.com/articles/2021-july-supplement/the-hi-peitho-study-of-ultrasound-facilitated-catheter-directed-thrombolysis-versus-anticoagulation

30. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early

cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation. 2013 Apr;84(4):465–70.

31. news2-final-report_0_0.pdf [Internet]. Available from: https://www.rcp.ac.uk/media/a4ibkkbf/news2-final-report_0_0.pdf

32. Avgerinos ED, Jaber W, Lacomis J, Markel K, McDaniel M, Rivera-Lebron BN, et al. Randomized Trial Comparing Standard Versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism: The SUNSET sPE Trial. JACC Cardiovasc Interv. 2021 Jun 28;14(12):1364–73.

33. Shatla I, El Iskandarani M, Khan MZ, Elkaryoni A, Elbadawi A, Goel SS, et al. Ultrasound-Assisted Versus Standard Catheter-Directed Thrombolysis for Acute Pulmonary Embolism: Insights From National Inpatient Sample. J Soc Cardiovasc Angiogr Interv [Internet]. 2024 May;3(5):101360. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2772930324001467

34. Stortecky S, Barco S, Windecker S, Heg D, Kadner A, Englberger L, et al. Ultrasound-assisted catheter-directed thrombolysis versus surgical pulmonary embolectomy for intermediate-high or high-risk pulmonary embolism: a randomized phase II non-inferiority trial. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2024 Jul 1;66(1):ezae252.

35. Tsukagoshi J, Wick B, Karim A, Khanipov K, Cox MW. Perioperative and intermediate outcomes of patients with pulmonary embolism undergoing catheter-directed thrombolysis vs percutaneous mechanical thrombectomy. J Vasc Surg Venous Lymphat Disord [Internet]. 2024 Nov;12(6):101958. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213333X24003536

36. Jaber WA, Gonsalves CF, Stortecky S, Horr S, Pappas O, Gandhi RT, et al. Large-Bore Mechanical Thrombectomy Versus Catheter-Directed Thrombolysis in the Management of Intermediate-Risk Pulmonary Embolism: Primary Results of the PEERLESS Randomized Controlled Trial. Circulation. 2025 Feb 4;151(5):260–73.

37. Tu T, Toma C, Tapson VF, Adams C, Jaber WA, Silver M, et al. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study. JACC Cardiovasc Interv. 2019 May 13;12(9):859–69.

38. Salinas P, Vázquez-Álvarez ME, Salvatella N, Ruiz Quevedo V, Velázquez Martín M, Valero E, et al. Catheter-directed therapy for acute pulmonary embolism: results of a multicenter national registry. Rev Esp Cardiol Engl Ed. 2024 Feb;77(2):138–47. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1885585723001664

39. Ismayl M, Ismayl A, Hamadi D, Aboeata A, Goldsweig AM. Catheter-directed thrombolysis versus thrombectomy for submassive and massive pulmonary embolism: A systematic review and meta-analysis. Cardiovasc Revascularization Med Mol Interv. 2024 Mar;60:43–52.

40. Alcedo PE, García-Perdomo HA, Rojas-Hernandez CM. The net benefit of thrombolysis in the management of intermediate risk pulmonary embolism: Systematic review and meta-analysis. EJHaem. 2020 Nov;1(2):457–66.

41. Mathew D, Kim J, Kosuru BP, Devagudi D, Sherif A, Shrestha U, et al. Mortality and bleeding associated with the management of sub-massive pulmonary embolism: a systematic review and Bayesian network meta-analysis. Sci Rep [Internet]. 2023 May 3;13(1):7169. Available from: https://www.nature.com/articles/s41598-023-34348-9