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Clinical outcomes of catheter-directed thrombolysis compared with anticoagulation in acute haemodynamically stable pulmonary embolism: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Background:

The role of catheter-directed thrombolysis (CDT) in haemodynamically stable pulmonary embolism (PE) remains controversial with observational data supporting a mortality benefit for CDT. This meta-analysis aimed to assess the effect of CDT, compared with anticoagulation alone, on mortality, haemodynamic decompensation and major bleeding in haemodynamically stable PE.

Methods:

Randomised controlled trials comparing treatment with CDT versus anticoagulation in patients with acute haemodynamically stable pulmonary embolism were systematically searched in the PubMed/MEDLINE database. The primary outcome was all-cause mortality at 30 days. Secondary outcomes were haemodynamic decompensation (efficacy) and major bleeding, minor bleeding and intracranial haemorrhage (safety).

Results:

A total of 8 clinical trials comprising 1503 patients with acute haemodynamically stable pulmonary embolism were included. CDT was not associated with a significant difference in 30-day all-cause mortality compared with anticoagulation alone (OR, 0.83; 95% CI, 0.24–2.92). CDT reduced the risk of haemodynamic decompensation at 7 days (OR, 0.27; 95% CI, 0.08–0.87). Regarding safety, there was no significant difference in major bleeding between groups (OR, 1.39; 95% CI, 0.63–3.07), whereas minor bleeding occurred more frequently with CDT (OR, 2.77; 95% CI, 1.41–5.42). There were four reported cases of intracranial haemorrhage in the CDT arm.

Conclusions:

In patients with haemodynamically stable acute PE, CDT reduced early haemodynamic decompensation without a detectable difference in mortality. There was no significant increase in major bleeding, but minor bleeding was significantly increased. These findings might inform decisions of pulmonary embolism response teams.

Background

Pulmonary embolism (PE) is a common cardiovascular condition with an estimated annual incidence of 39 to 115 per 100,000 population [1]. Incidence has increased over the past few decades, probably reflecting the ageing of Western populations and the wider use of imaging techniques, which may be detecting cases that were previously missed [2]. Although PE-related mortality and length of hospital stay have decreased over time [3], mortality remains substantial, with 30-day all-cause mortality ranging from 5–10% in intermediate-risk PE to 22% in haemodynamically unstable, high-risk PE [4].

Early risk stratification is therefore essential to guide treatment [5]. Efforts to characterise these patients more precisely have driven a successive redefinition of PE severity, from the three strata proposed by the American Heart Association in 2011 (low risk, submassive, and massive) [6] to the four-category framework of the European Society of Cardiology (low, intermediate-low, intermediate-high, and high risk) [7]. Systemic thrombolysis is recommended in patients with haemodynamic instability [8], but in normotensive patients with right ventricular dysfunction and myocardial injury (intermediate-high risk), the PEITHO trial failed to demonstrate a net clinical benefit [9]. Intermediate-high risk PE therefore occupies a particularly uncertain position: approximately 5–10% of these patients develop haemodynamic instability under anticoagulation, with a corresponding increase in mortality occurring predominantly within the first 72 hours [10, 11]. These limitations have prompted a further revision of the risk classification. The 2026 AHA/ACC multisociety guideline replaced conventional risk tiers with a set of five PE Clinical Categories (A–E), graded according to the trajectory of cardiopulmonary compromise, and explicitly incorporating the pre-failure state (stage D) and respiratory compromise (R modifier) [12]. This framework provides a Class II indication for systemic thrombolysis or catheter-directed intervention in stages D1, D2 (IIb), and E1 (IIa). In the terms of that framework, the trial populations correspond broadly to categories C and D1, with HI-PEITHO enriching towards D.

Catheter-directed interventions for PE have emerged over the last two decades as a way of relieving pulmonary vascular resistance and right ventricular overload without the systemic exposure of full-dose lysis [13, 14]. They comprise two distinct strategies: catheter-directed thrombolysis (CDT), in which a reduced dose of fibrinolytic agent is infused through a catheter positioned in the pulmonary arteries, with or without ultrasound facilitation; and mechanical or aspiration thrombectomy, in which thrombus is physically removed without usually adding any lytic agent. Based on very limited randomised evidence[15–17], the uptake of intervention increased significantly over the last decade, reducing the number of patients treated with systemic thrombolysis [18]. However, since the beginning of 2026, five randomised trials comparing CDT with anticoagulation alone have been reported, including the first two powered for clinical endpoints [19–23]. We therefore performed a systematic review and meta-analysis restricted to randomised controlled trials, to estimate the effect of CDT compared with anticoagulation alone on mortality, haemodynamic decompensation and bleeding in patients with acute PE who are haemodynamically stable at randomisation.

Methods

We conducted and report this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [24] and the Cochrane Handbook for Systematic Reviews of Interventions [25]. The completed PRISMA 2020 checklist is provided as Additional file 1: Table S1. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD420261481735).

Because this study is a systematic review and meta-analysis of previously published data, Institutional Review Board approval and informed patient consent for study participation were not required.

Search strategy and data extraction

Two authors (X.P. and J.G.O.) independently performed a systematic search of the PubMed/Medline database on August 25, 2026. We also hand-searched the reference lists of all included trials and of previous systematic reviews and meta-analyses on the topic and screened major scientific conferences during 2026. Search terms combined “Pulmonary embolism”, “Catheter-directed thrombolysis”, “Anticoagulation”, and “Intermediate-high risk pulmonary embolism”. The complete search strategy is presented in the Additional file 1: Supplementary methods. Two authors (X.P. and J.G.O.) independently screened titles and abstracts, and then full texts against the eligibility criteria; disagreements were resolved by discussion with the senior author (P.S.). The selection process is summarised in the PRISMA flow diagram (Fig. 1).

Two authors (X.P. and J.G.O.) independently extracted the following data into a piloted spreadsheet: trial identifiers, catheter type and fibrinolytic regimen, comparator anticoagulation, follow-up duration, and definitions of the primary and secondary outcomes (Table 1). Further study definitions are detailed in Supplementary Tables S2 to S4. Data (event counts) were taken directly from the published articles and their supplementary appendices. Denominators were extracted at the level each trial itself used for the outcome in question rather than from the randomised total; where a trial reported an outcome in more than one analysis population, we used the intention-to-treat population for efficacy outcomes and the treated population for bleeding outcomes, following each trial's own definitions (Additional file 1: Table S5).

Table 1
General considerations of the included randomised clinical trials.

Study	Sample size (n)	Intervention	Control	Inclusion criteria	Primary outcome	Secondary outcome	Maximum reported follow-up (months)
ULTIMA 2014 [15]	30/ 29	USCDT (EKOS system) + UFH (10 mg rtPA) over 15 hours	UFH: 80 IU/kg, followed by an infusion of 18 IU/kg per hour (minimum duration of 24 hours)	Acute symptomatic PE and RV/LV ratio > = 1.0 (echocardiogram)	Difference RV/LV ratio from baseline to 24 h (echocardiogram)	Death Haemodynamic decompensation * Major or minor bleeding Recurrent VTE SAE	3
CANARY 2022 [16]	48 / 46	CDT (Cragg-McNamara) + alteplase + UFH (500 U/h) Unilateral: 12 mg/24 h Bilateral: 24 mg/ 24 h	Anticoagulation (enoxaparin 1 mg/kg twice per day)	Intermediate-high-risk PE (2019 ESC guidelines)	Proportion of patients with RV/LV ratio > 0.9 (echocardiogram) at 3-month follow-up.	All-cause mortality PE-related mortality Hospital length of stay (index hospitalisation) 6 minutes walk test Major bleeding (BARC type 3 or 5) Severe thrombocytopenia. Vascular access complications. Clinically relevant non-major bleeding (BARC type 2).	3
Kroupa J, et al. 2022 [17]	12 / 11	CDT (Cragg-McNamara) + alteplase 1mg/hr/catheter for 10 h (total dose 20 mg) + UFH	UFH or LMWH	Intermediate-high-risk PE (2019 ESC guidelines).	Effectiveness of CDT (Improved RV function): - Reduction of the RV/LV ratio by 25% (baseline – 48 h) (CTA) - Reduction of the sPAP by 30% (baseline-24 h) (echocardiogram) - Reduction of the Qanadli score by 30% (baseline-48 h). (CTA)	Absence of intracranial or life-threatening bleeding (BARC 5 or 3c) within 72 hours. Technical success of CDT: successful catheter placement followed by continuous infusion of alteplase. All bleeding complications (BARC classification). Haemodynamic instability during hospitalisation. * Length of hospitalisation. In-hospital mortality.	1
HI-PEITHO 2026 [19]	273 / 271	USCDT (EkoSonic) + alteplase (bolus 2 mg, infusion 1 mg/catheter/h for 7 hours) + UFH (300–600 U/h).	Anticoagulation (LMWH and/or UFH)	Intermediate-high risk PE (2019 ESC guidelines) plus additional risk parameters.	Composite outcome (PE-related death, cardiorespiratory decompensation or collapse, or non-fatal recurrent PE	Major bleeding at 72 h, 7 days, and 30 days. (ISTH criteria). Major bleeding at 7 days (GUSTO criteria).	12

BARC, Bleeding Academic Research Consortium; BP, blood pressure; CDT, catheter-directed thrombolysis; CT, computed tomography; CTA, computed tomography angiography; CTPA, computed tomography pulmonary angiography; EKOS, EkoSonic Endovascular System; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; ESC, European Society of Cardiology; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, heart rate; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; IU, international units; IV, intravenous; LMWH, low-molecular-weight heparin; LV, left ventricle; PE, pulmonary embolism; PEmb-QoL, Pulmonary Embolism Quality of Life questionnaire; rmMS, refined modified Miller score; RR, respiratory rate; rtPA, recombinant tissue plasminogen activator; RV, right ventricle; SAE, serious adverse event; 6MWT, 6-minute walk test; sPAP, systolic pulmonary artery pressure; TIMI, Thrombolysis in Myocardial Infarction; TR, tricuspid regurgitation; UFH, unfractionated heparin; USCDT, ultrasound-assisted catheter-directed thrombolysis; VTE, venous thromboembolism; WHO, World Health Organization.

*Definition in Table S3; ** Three arm study. + Data only available for patients undergoing invasive treatment.

Study	Sample size (n)	Intervention	Control	Inclusion criteria	Primary outcome	Secondary outcome	Maximum reported follow-up (months)
		Unilateral therapy: total dose 9 mg Bilateral therapy: total dose 18 mg			confirmed by CT) * at 7 days.	Ischaemic or haemorrhagic stroke at 7 and 30 days. Change in RV/LV ratio at 48 hours (CT/echocardiography). Death from any cause at 7 and 30 days. Recurrence PE at 30 days SAE at 30 days WHO functional class	
PRETHA 2026** [21]	13 / 13	CDT (PigTail catheter) + alteplase 1 mg/h for 24 h	Heparin IV for 3 days	Intermediate-high-risk PE (2019 ESC guidelines).	Early haemodynamic improvement: - Changes in echocardiographics and laboratory biomarkers (48 h, 1, 6 and 12 months) - Changes in direct systolic and mean pulmonary pressures.+	Surrogate endpoints of functional and quality of life improvements: - Changes in 6 MWT - Changes in PEmb-QoL questionnaire Treatment-related adverse events during hospitalisation: - Deaths - Major bleeding (WHO) - Periprocedural complications.	12
STRATIFY 2026** [20, 34]	71 / 69	USCDT (EKOS) + alteplase 20 mg/6h per catheter + 20 mg IV per 2 h more + heparin	Heparin	Intermediate-high-risk PE (2019 ESC guidelines).	Reduction in rmMS at 48–96 h (CT).	Duration of index admission (including hospital-based rehabilitation). Dyspnoea index (Visual analogue scale) after 48–96 h and 3 months. FiO2, BP, RR, HR at the time of follow-up CTPA. Incidence of TR gradient > 40 mmHg at 3 m 6MWT at 3 m PEmb-QoL and EQ-5D-5L 3 m Bleeding complications (major and minor according to TIMI classification). Mortality RV/LV ratio (post hoc analysis)	3

BARC, Bleeding Academic Research Consortium; BP, blood pressure; CDT, catheter-directed thrombolysis; CT, computed tomography; CTA, computed tomography angiography; CTPA, computed tomography pulmonary angiography; EKOS, EkoSonic Endovascular System; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; ESC, European Society of Cardiology; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, heart rate; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; IU, international units; IV, intravenous; LMWH, low-molecular-weight heparin; LV, left ventricle; PE, pulmonary embolism; PEmb-QoL, Pulmonary Embolism Quality of Life questionnaire; rmMS, refined modified Miller score; RR, respiratory rate; rtPA, recombinant tissue plasminogen activator; RV, right ventricle; SAE, serious adverse event; 6MWT, 6-minute walk test; sPAP, systolic pulmonary artery pressure; TIMI, Thrombolysis in Myocardial Infarction; TR, tricuspid regurgitation; UFH, unfractionated heparin; USCDT, ultrasound-assisted catheter-directed thrombolysis; VTE, venous thromboembolism; WHO, World Health Organization.

*Definition in Table S3; ** Three arm study. + Data only available for patients undergoing invasive treatment.

Study	Sample size (n)	Intervention	Control	Inclusion criteria	Primary outcome	Secondary outcome	Maximum reported follow-up (months)
BETULA 2026 [22]	29/ 30	CDT with AngioDynamics catheter, 4 mg rtPA per catheter over 2 h (2 mg/h, infusion of 25 mL/h) + UFH	UFH per 24 h	Intermediate-high-risk PE (2019 ESC guidelines).	Change in RV/LV ratio at 24 h (CT).	Change in thrombus burden (Qanadli score). Echocardiographic measure of RV function and load. All-cause mortality (30 d). Length of hospital stay. Recurrent symptomatic PE (90 days) Major and minor bleeding *	3
PRAGUE-26 2026 [23]	280 / 278	CDT (Cragg–McNamara), alteplase 1 mg per hour per catheter (total dose of 20 mg) + UFH	Anticoagulation (LMWH or UFH)	Intermediate-high-risk PE (2019 ESC guidelines).	Death from any cause, recurrence of PE, or cardiorespiratory decompensation or collapse within 7 days.	Individual components of the primary outcome. Failure of the assigned first-line therapy. Ischaemic or haemorrhagic stroke. Serious adverse events RV/LV ratio (echocardiogram). WHO functional class. Lengths of stay in ICU and hospital. GUSTO major bleeding. ISTH major bleeding. BARC 2 or higher: clinically relevant bleeding	1

BARC, Bleeding Academic Research Consortium; BP, blood pressure; CDT, catheter-directed thrombolysis; CT, computed tomography; CTA, computed tomography angiography; CTPA, computed tomography pulmonary angiography; EKOS, EkoSonic Endovascular System; EQ-5D-5L, EuroQol five-dimension five-level questionnaire; ESC, European Society of Cardiology; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, heart rate; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; IU, international units; IV, intravenous; LMWH, low-molecular-weight heparin; LV, left ventricle; PE, pulmonary embolism; PEmb-QoL, Pulmonary Embolism Quality of Life questionnaire; rmMS, refined modified Miller score; RR, respiratory rate; rtPA, recombinant tissue plasminogen activator; RV, right ventricle; SAE, serious adverse event; 6MWT, 6-minute walk test; sPAP, systolic pulmonary artery pressure; TIMI, Thrombolysis in Myocardial Infarction; TR, tricuspid regurgitation; UFH, unfractionated heparin; USCDT, ultrasound-assisted catheter-directed thrombolysis; VTE, venous thromboembolism; WHO, World Health Organization.

*Definition in Table S3; ** Three arm study. + Data only available for patients undergoing invasive treatment.

Eligibility criteria

We included in the meta-analysis studies that met all of the following criteria: (1) randomised design; (2) comparing CDT (defined as local delivery of a fibrinolytic agent through a catheter positioned in the pulmonary arteries, with or without ultrasound facilitation and at any dose or infusion duration) with anticoagulation alone; (3) enrolling adults with acute PE who were haemodynamically stable at randomisation; (4) reporting at least one outcome of interest. There were no restrictions regarding publication date or sample size. Although eligibility was defined by haemodynamic stability rather than by risk category, all included trials enrolled patients meeting criteria for intermediate-high risk PE; no trial enrolled low-risk or intermediate-low-risk patients (Table 1). In the two three-arm trials, we used only the CDT arm and the AC arm, so that no patient contributed more than once to the comparison.

We excluded: (1) Non-randomised studies, reviews, abstracts, case reports, letters and protocols; (2) studies not reporting clinical endpoints; (3) trials in which the comparator was systemic thrombolysis rather than anticoagulation alone; (4) trials in which the experimental arm was mechanical or aspiration thrombectomy without any local fibrinolysis arm; (5) trials in which patients with high-risk (haemodynamically unstable) PE were eligible for enrolment; and (6) publications not available in English.

Outcomes

The primary outcome was all-cause mortality at 30 days. Where a trial reported mortality at more than one time point, we used the estimate closest to 30 days; where only one time point was reported, we used it and recorded the window. Because some trials also reported the primary outcome at 7 days, we used a sensitivity analysis restricted to events at 7 days.

The secondary efficacy outcome was haemodynamic decompensation defined by each trial (Additional file 1: Table S3) and harmonised as any of the following: (1) cardiac arrest, (2) cardiogenic shock, (3) need for vasopressors, (4) mechanical ventilation, (5) extracorporeal membrane oxygenation, or (6) escalation to rescue reperfusion. This outcome is reported at 7 days, because PRAGUE-26 reports it only within that window.

Safety outcomes were major bleeding, minor bleeding, and intracranial haemorrhage. Trials used different bleeding definitions (Additional file 1: Table S4). Where a trial reported major bleeding under more than one scale, we prespecified the ISTH definition, because it was the classification most consistently available across the trials that reported more than one scale.

Although it was a primary outcome in some trials, we did not pool the change in right ventricle to left ventricle ratio. Trials measured it by different modalities (computed tomography and echocardiography), at different time points, and against different thresholds, and we judged that pooling it would produce a summary estimate that does not correspond to any single clinical measurement.

Quality assessment, risk of bias

Quality assessment of RCTs was performed using the Cochrane risk-of-bias tool for randomised trials (RoB 2), in which studies are rated as low risk, some concerns, or high risk of bias in five domains: the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [26]. RoB 2 assesses a specific result rather than a trial as a whole, so each trial was assessed separately for each of the five outcomes by two authors (X.P., J.G.O.) and resolved disagreements by discussion with senior author (P.S.). The traffic-light plot is provided as Additional file 1: Figure S1.

Statistical analysis

We pooled log odds ratios in random-effects models, estimating the between-trial variance by restricted maximum likelihood and deriving confidence intervals by the Hartung–Knapp–Sidik–Jonkman method [27]. Zero cells were handled with the treatment-arm continuity correction; trials with no events in either arm were excluded from odds-ratio analyses, and the number of contributing trials is reported with every estimate. Prespecified sensitivity analyses repeated the primary model using Peto odds ratios, a Mantel–Haenszel fixed-effect model, and a random-effects model with the conventional 0.5 correction.

Risk differences were pooled by the Mantel–Haenszel method and are reported with the corresponding number needed to treat or to harm; intracranial haemorrhage, for which no control-arm event occurred, was analysed on this scale only.

Heterogeneity was summarised with Cochran's Q, I^2 and τ^2. A 95% prediction interval is reported for outcomes with at least five contributing trials. We performed leave-one-out analyses and a sensitivity analysis restricted to outcomes reported at seven days. Publication bias was not assessed, since fewer than ten trials contributed to every outcome.

Analyses used Stata/BE 19.0 (StataCorp, College Station, TX). The extended statistical analysis plan is given in Additional file 1: Supplementary methods.

Results

Study selection

As shown in Fig. 1, the systematic search initially identified 1881 records. After removal of duplicates and ineligible studies, 24 full-text articles were assessed for eligibility. Ultimately, 8 randomised controlled trials comprising 1503 patients with acute PE who were haemodynamically stable at randomisation, all enrolled under criteria for intermediate-high risk, were included in the meta-analysis, of whom 756 (50.3%) were allocated to CDT therapy and 747 to anticoagulation alone (49.7%). Study characteristics are summarised in Table 1.

All-cause mortality.

Seven of the eight included trials contributed to the pooled analysis of 30-day all-cause mortality. Kroupa et al. reported zero deaths in both treatment groups and therefore did not contribute to the pooled effect estimate.

Among the 1480 randomised patients from the seven contributing trials, there were 22 mortality events: 10 of 744 (1.3%) in the CDT group and 12 of 736 (1.6%) in the anticoagulation-alone group. Treatment with CDT was not associated with a statistically significant difference in all-cause mortality

compared with anticoagulation alone (OR, 0.83; 95% CI, 0.24–2.92), Fig. 2A. Between-study heterogeneity was low (I^2 = 18.8%; τ^2 = 0.39), but the 95% prediction interval was wide (0.11 to 6.63), so the effect of CDT on mortality in a future trial remains largely undetermined.

Haemodynamic decompensation.

Three of the eight included trials contributed to the pooled analysis of haemodynamic decompensation at 7 days. Definitions of acute haemodynamic decompensation are provided in Additional file 1: Table S3. Of the five trials that did not contribute to the pooled estimate, three (STRATIFY, PRETHA, and BETULA) did not report haemodynamic decompensation, whereas ULTIMA [15] and Kroupa [17] reported no events in either treatment group and therefore did not contribute to the pooled effect estimate.

Across the three contributing trials, haemodynamic decompensation occurred in 12 of 601 patients (2.0%) in the CDT group and 44 of 595 patients (7.4%) in the anticoagulation-alone group. CDT was associated with significantly lower odds of haemodynamic decompensation compared with anticoagulation alone (OR, 0.27; 95% CI, 0.08–0.87), with low between-study heterogeneity (I^2 = 1.7%) (Fig. 2B). With only three contributing trials, between-trial variance was too imprecise to estimate a prediction interval.

Bleeding outcomes

Six of the eight included trials contributed to the pooled analysis of major bleeding. Definitions of bleeding across trials are provided in Additional file 1: Table S4. ULTIMA [15] and BETULA [22] trials reported no major bleeding events in either treatment group and therefore did not contribute to the pooled effect estimate. Major bleeding occurred in 26 of 695 patients (3.7%) receiving CDT and 17 of 688 (2.5%) receiving anticoagulation alone, with no statistically significant difference between groups (OR, 1.39; 95% CI, 0.63–3.07; I^2 = 0%; 95% prediction interval, 0.59 to 3.27), Fig. 2C.

Six of the eight included trials contributed to the pooled analysis of minor bleeding. The two largest trials, HI-PEITHO [19] and PRAGUE-26 [23], did not report minor bleeding as a separate outcome and therefore did not contribute to the pooled estimate, which was limited to 401 patients. Across the six contributing trials, minor bleeding occurred in 16 of 203 patients (7.9%) in the CDT group and 5 of 198 (2.5%) in the anticoagulation-alone group. CDT was associated with significantly higher odds of minor bleeding compared with anticoagulation alone (OR, 2.77; 95% CI, 1.41–5.42, Fig. 2D), with no evidence of between-study heterogeneity (I^2 = 0%; τ^2 = 0.00). The 95% prediction interval excluded one (1.34 to 5.71), indicating that a future trial would be expected to show an excess of minor bleeding.

Three trials recorded intracranial haemorrhage. All 4 events occurred in the CDT group (754 patients) and none in the 747 patients allocated to anticoagulation alone. Because no control arm recorded an event, the odds ratio is unbounded, and the outcome was analysed on the risk difference scale.

Risk differences

Risk differences were pooled by the Mantel–Haenszel common-effect method; every trial that reported the outcome contributes, including trials with no events in either arm, so the number of contributing trials is larger than in the corresponding odds-ratio analysis (Additional file 1: Table S6). Mortality (− 2.9 per 1000; 95% CI, − 14.9 to + 9.2) and major bleeding (+ 11.7 per 1000; 95% CI, − 5.0 to + 28.4) did not differ significantly. Haemodynamic decompensation favoured CDT (− 50.4 per 1000; 95% CI, − 72.6 to − 28.3), a number needed to treat of 20 (95% CI, 14 to 35). Minor bleeding favoured anticoagulation alone (+ 53.7 per 1000; 95% CI, + 10.8 to + 96.6), a number needed to harm of 19 (95% CI, 10 to 92). Intracranial haemorrhage favoured anticoagulation alone: +5.3 events per 1000 patients (95% CI, + 0.2 to + 10.4; P = 0.043), corresponding to a number needed to harm of 189 (95% CI, 96 to 5704).

Sensitivity analyses

Additional file 1: Table S7 shows pooled odds ratios under all four models. All sensitivity analyses were coherent with the primary analysis (Additional file 1: Figure S2 shows forest plots for the four models).

Additional file 1: Table S8 shows pooled odds ratios under all four models at 7 days for mortality and major bleeding. The results did not change any conclusion at 30 days.

In the leave-one-out analysis of all-cause mortality the pooled odds ratio ranged from 0.53 (omitting HI-PEITHO) to 1.17 (omitting PRAGUE-26); no omission produced a statistically significant result (Additional file 1: Table S9.)

Risk of bias

No trial was at high risk of bias for any outcome (Additional file 1: Figure S1). For all-cause mortality, six of the eight trials were at low risk of bias and two raised some concerns: Kroupa 2022 in the randomisation domain, and HI-PEITHO in deviations from intended interventions. For haemodynamic decompensation, among the five trials reporting it, only Kroupa et al. raised some concerns. For major bleeding, five trials were at low risk and three raised some concerns: Kroupa et al, HI-PEITHO, and STRATIFY in the domain covering measurement of the outcome, because we pooled major bleeding using the ISTH definition whereas that trial prespecified TIMI. Minor bleeding and intracranial haemorrhage followed the same distribution.

Discussion

The main finding of this systematic review and meta-analysis of eight randomised clinical trials is that catheter-directed thrombolysis prevents haemodynamic decompensation in patients with acute PE who are stable at randomisation (about one event avoided for every 20 patients treated), without any detectable effect on mortality. This benefit has to be balanced with an increase in minor bleeding, which almost tripled the anticoagulation alone arm, and a statistically fragile finding of four intracranial haemorrhages recorded in patients assigned to catheter treatment.

All-cause mortality was low: twenty-two deaths occurred among 1480 patients, 1.6% in the anticoagulation arm, in a population classified as intermediate-high risk. Registry and cohort data for the same risk category place 30-day mortality between 5% and 10% [3, 4]. The gap is likely due to eligibility criteria to trials. Trials evaluating fibrinolytic strategies commonly exclude patients with recent surgery, recent stroke, intracranial disease, thrombocytopenia and active bleeding, precisely the comorbidities that contribute to PE mortality. The selected trial population removes bleeding risk and competing mortality together. For example, about one in four PE patients have cancer: it is a dominant cause of death after intermediate-risk pulmonary embolism [28], however it is underrepresented in trials (CANARY reported no patient with active malignancy, BETULA two of 59, PRAGUE-26 reported cancer in 11% of its population with only 2.7% having active cancer under treatment). Also, improvement in PE care contributes as well: PE response teams, earlier risk stratification and readily available rescue reperfusion have lowered mortality across the whole spectrum of the disease [3, 5].

The patients excluded from these trials are precisely those at highest risk of PE-related mortality, for whom randomised evidence remains limited. Two strategies compete for that space: (i) large-bore mechanical thrombectomy has now been compared with anticoagulation alone in a randomised trial [29], and it is a potential candidate for a patient who needs the obstruction relieved but cannot be given a fibrinolytic, and (ii) anticoagulation with watchful waiting for decompensation. This evidence gap might be palliated with upcoming evidence from Peerless II [30].

Is it likely that further trials might establish a mortality benefit for CDT? With a control-arm mortality of 1.6%, detecting a 50% reduction would require close to 6000 randomised patients. The entire randomised literature on CDT comprises 1503, so our null result is therefore not evidence of equivalence, and it is not a failure of the intervention; we are just underpowered to answer the clinical question. This limited sample size likely explains the apparent discrepancy between the reduction in haemodynamic decompensation and lack of a detectable reduction in mortality. CDT prevented in the order of 32 decompensation events among the 601 patients in whom this outcome was measured. Even if a fifth of those events would otherwise have ended in death, the mortality benefit to be found would be about six deaths, roughly one percentage point, in an analysis that contains 22 deaths in total. The second reason is close monitoring and rapid access to rescue therapies characteristic of the tertiary centres in which these trials were conducted. In HI-PEITHO, rescue treatment was given to 25 of 271 patients (9.2%) in the control group and to 8 of 273 (2.9%) in the intervention group, while in PRAGUE-26, escalation was required in 12 of 278 control patients and in none of the thrombolysis group. Thus, effective rescue treatment after clinical deterioration may have attenuated any potential mortality consequence of haemodynamic decompensation. Although HI-PEITHO and PRAGUE-26 used objective criteria, the decision to escalate treatment in PRAGUE-26 was left to the treating clinicians rather than being determined by prespecified protocol criteria as in HI-PEITHO.

The efficacy benefit must also be considered alongside the bleeding profile. Major bleeding was not significantly increased with CDT (OR 1.39; 95% CI 0.63 to 3.07), suggesting that catheter-directed delivery of lower fibrinolytic doses may achieve haemodynamic benefit without the magnitude of bleeding observed with systemic thrombolysis in PEITHO trial [9]. Minor bleeding was increased to a similar magnitude compared to the haemodynamic benefit, and in these trials typically was represented by an access-site bleeding. Set against a deterioration event that means vasopressors, intubation, even rescue lysis or extracorporeal support and the extended intensive-care stay that follows, that is an exchange most clinicians and most patients would accept. However, that conclusion rests on weaker foundations than it should, and the reason is neither HI-PEITHO nor PRAGUE-26 reports a minor or clinically relevant non-major bleeding category that can be separated from major bleeding. The two trials that contribute nearly three-quarters of the randomised population therefore contribute nothing to our minor-bleeding estimate, which rests on 401 patients from six small trials. Future trials should use standardised bleeding definitions and report events by severity tier to allow more reliable assessment of the efficacy–safety trade-off.

Intracranial haemorrhage occurred in four patients, all assigned to CDT. The small number of events precludes a precise estimate of risk, and the finding should therefore be interpreted with caution. Nevertheless, intracranial haemorrhage remains a clinically important potential complication of fibrinolytic therapy and should be considered when selecting and informing patients for CDT.

Our findings also differ from previous observational evidence. Most of the prior evidence supporting catheter-based treatment is observational. Iannaccone et al. [31], pooling 76 studies, reported substantially lower 30-day mortality with interventional treatment (2.1% vs. 9.1%) compared with medical therapy. Similarly, Zhang et al. [32], in a network meta-analysis of 45 studies, found that CDT was associated with lower mortality but more bleeding compared with anticoagulation alone; with a more favourable safety profile than systemic thrombolysis. Both analyses were dominated by registries and single-arm series, in which patients selected for intervention differ systematically from those treated medically. In contrast, our randomised estimate for mortality was OR 0.83, with wide confidence intervals and no evidence of a mortality reduction. Thus, the magnitude of survival benefit reported in observational studies is not supported by the available randomised evidence.

However not everything is unaligned. The direction and approximate size of the effect on early clinical deterioration survived randomisation intact, as did the modest bleeding penalty. The pattern suggests that the physiological rationale for catheter-directed thrombolysis is likely genuine, and the

observational literature was measuring something real but it might have been attributing to the procedure a survival difference that belonged to the patients selected for it.

An important unresolved question is which patients within the intermediate-high-risk spectrum should be considered for CDT. HI-PEITHO selected a population with more pronounced cardiopulmonary compromise, requiring intermediate-high risk with at least two additional clinical “enrichment” criteria. This approach is consistent with the direction of contemporary risk stratification, including the 2026 ACC/AHA guideline, which emphasises the granularity in evaluating the incipient cardiopulmonary failure. Probably, those patients at the high-end of intermediate-high risk might benefit the most, with space for the local PE response team for individualising the decision evaluation and discussion with the patient, to contribute to the decision [12, 14, 33].

The main strength of this analysis is its restriction to randomised controlled trials, including the most recent evidence, which removes the confounding inherent to previous observational syntheses. Mortality was prespecified as the primary outcome, and clinically relevant efficacy and safety outcomes were evaluated. Sensitivity analyses addressing rare events and zero-event trials were prespecified and reported.

Several limitations warrant consideration. First, the number of trials and clinical events was small, particularly for mortality, and the resulting estimates are imprecise; the mortality prediction interval of 0.11 to 6.63 illustrates the substantial uncertainty around the pooled effect, which is the honest expression of how much remains unknown. Second, haemodynamic decompensation was reported in only five trials and was estimable in three, and the definitions differed across trials, so there is clinical heterogeneity that the low statistical heterogeneity index does not capture. Third, bleeding definitions and reporting differed across trials, and the two largest trials, HI-PEITHO and PRAGUE-26, do not report a separable minor-bleeding category, so this outcome rests on the smaller trials and cannot be extrapolated to the populations those two recruited. Fourth, all included trials enrolled intermediate-high risk patients, so these findings do not apply to low-risk or intermediate-low-risk PE, in whom the balance between preventing decompensation and bleeding is likely to be different. Fifth, none of the trials reports cause of death in a way that allows deaths from pulmonary embolism to be separated from deaths from bleeding or other causes. Sixth, we did not pool length of stay, intensive-care use or rescue therapy, outcomes that may be clinically and economically relevant consequences of preventing haemodynamic deterioration. Seventh, trials reported heterogeneous time points, and we defined the primary outcome at 30-days which was not always each trial’s primary outcome time point. Eighth, the trials used different catheter systems including ultrasound assisted catheters, fibrinolytic doses and infusion durations, and we cannot say whether the effect is a class effect. Finally, all trials were open-label and outcomes involving clinical judgement may therefore be susceptible to ascertainment bias.

Conclusions

In patients with acute pulmonary embolism who are haemodynamically stable at randomisation, catheter-directed thrombolysis reduced early haemodynamic decompensation without a detectable difference in mortality. There was no significant increase in major bleeding, but minor bleeding was significantly increased. Four cases of intracranial haemorrhage were described in the catheter arm. These findings might inform decisions of pulmonary embolism response teams.

Abbreviations

ACC, American College of Cardiology

AHA, American Heart Association

BARC, Bleeding Academic Research Consortium

CDT, catheter-directed thrombolysis

CI, confidence interval

ISTH, International Society on Thrombosis and Haemostasis

OR, Odds ratio

PE, pulmonary embolism

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;

PROSPERO, International Prospective Register of Systematic Reviews

RCT, randomised clinical trial

RR, risk ratio

Rob-2, Cochrane Risk of Bias tool version 2

TIMI, Thrombolysis In Myocardial Infarction

Declarations

Ethics approval and consent to participate

A Statement of Ethics is not applicable because this study is based exclusively on published literature. All methods were carried out according to relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

PS and HM received speaker honoraria from Stryker, Boston Scientific, Abbott Vascular. All other authors have no conflicts of interest to declare.

Supplementary information

Additional file 1. Supplementary material (.docx). Supplementary methods (statistical analysis plan and search strategies), Tables S1-S9 and Figures S1-S2.

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Author Contribution

XP and JGO did the literature search, data acquisition and drafted the article. PS designed the project, supervised the work and performed the statistical analysis. AT provided statistical consultation. All authors critically revised and contributed to the final version. All authors approved the final version for submission.

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Not applicable.

Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files. The extracted event-count dataset and the Stata code used for the analyses are available from the corresponding author on reasonable request.

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Figures

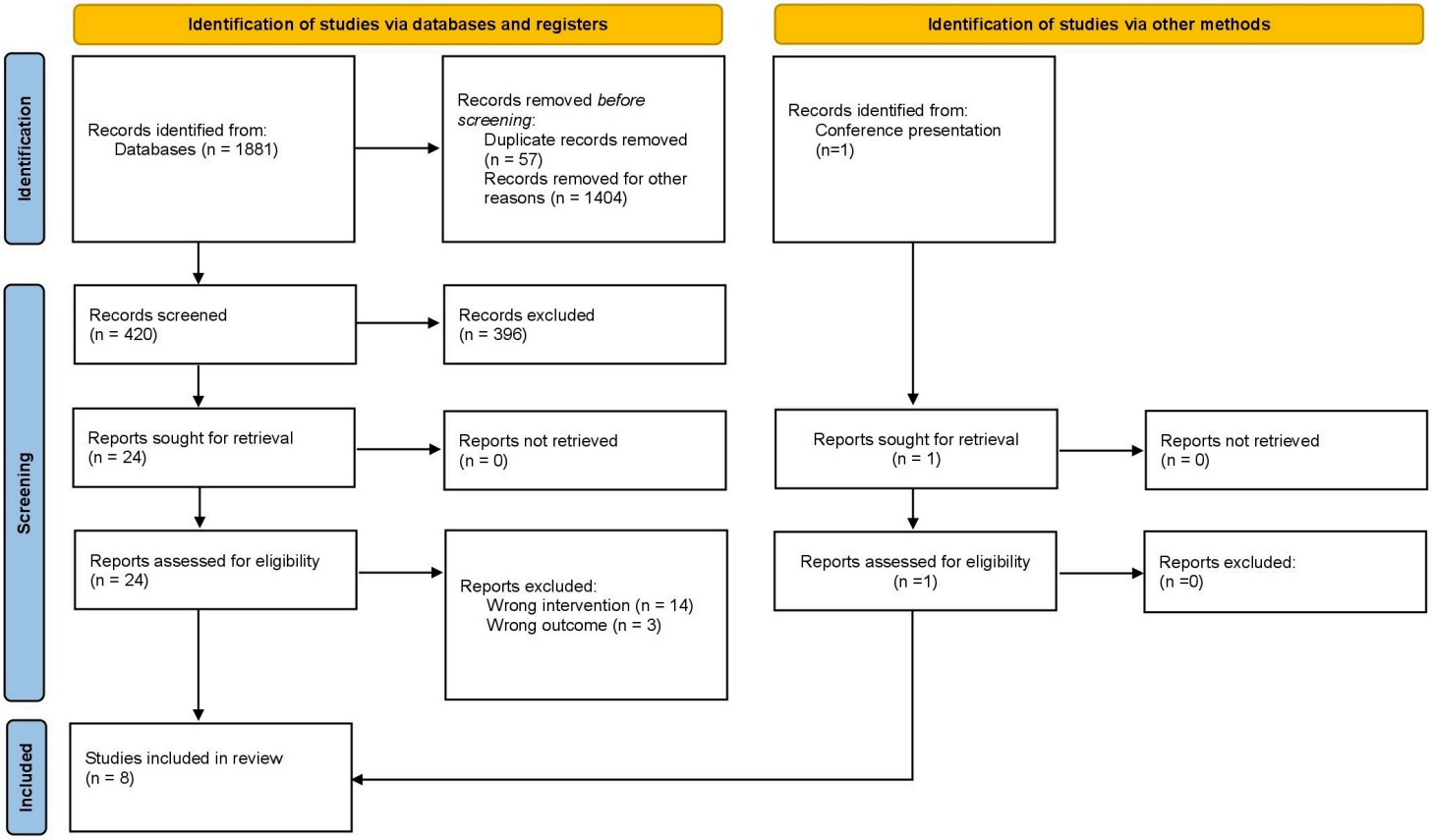


Figure 1

PRISMA 2020 flow diagram of study screening and selection.

Flow of records through identification, screening, full-text assessment and inclusion, with the reasons for exclusion at the full-text stage. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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