

ORIGINAL ARTICLE

Comparative analysis of safety and efficacy of different advanced therapeutic strategies for acute pulmonary embolism: A Bayesian network meta-analysis

Prakash Raj Oli¹, Dhan Bahadur Shrestha^{2*}, Sagun Dawadi³, Jurgen Shtembari⁴, Jishanth Mattumpuram⁵, and Daniel H. Katz²¹Department of Internal Medicine, Mount Sinai Hospital, Chicago, Illinois, United States of America²Division of Cardiology, Department of Internal Medicine, Bassett Medical Center, Cooperstown, New York, United States of America³Department of Internal Medicine, Nepalese Army Institute of Health Sciences, Kathmandu, Bagmati, Nepal⁴Division of Cardiology, Department of Internal Medicine, Carle Foundation Hospital, Urbana, Illinois, United States of America⁵Division of Cardiology, Department of Internal Medicine, University of Louisville, Louisville, Kentucky, United States of America

***Corresponding author:**
Dhan Bahadur Shrestha
(Dhan.shrestha@bassett.org)

Citation: Oli PR, Shrestha DB, Dawadi S, Shtembari J, Mattumpuram J, Katz DH. Comparative analysis of safety and efficacy of different advanced therapeutic strategies for acute pulmonary embolism: A Bayesian network meta-analysis. *J Clin Transl Res*.2026;12(2):025340056. doi: 10.36922/JCTR025340056

Received: August 20, 2025

Revised: January 13, 2026

Accepted: January 30, 2026

Published online: April 17, 2026

Copyright: © 2026 Author(s). This is an open-access article distributed under the terms of the Creative Commons AttributionNon-Commercial 4.0 International (CC BY-NC 4.0), which permits all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract

Background: Pulmonary embolism (PE) is a major global health concern and the third leading cause of cardiovascular mortality in the U.S. There are various treatment options available for the treatment of intermediate-to-high risk acute PE, including catheter-based treatments, surgical embolectomy, and systemic thrombolysis. **Objective:** To perform a systematic review and Bayesian network meta-analysis (NMA) comparing the safety and efficacy of advanced therapies in patients with intermediate-to-high risk acute PE. **Methods:** We searched PubMed/Medline, Embase, and Scopus for relevant studies published until August 30, 2024, and performed a Bayesian NMA to synthesize direct and indirect evidence using the Bayesian inference Using Gibbs Sampling to conduct a Network meta-analysis package in R. **Results:** Of 1,586 studies, 47 met the inclusion criteria, of which 45 were non-randomized. A total of 267,695 acute intermediate-to-high risk PE patients were included in the analysis, receiving one of five advanced interventions: ultrasound-assisted thrombolysis (USAT), standard catheter-directed thrombolysis (sCDT), catheter-based embolectomy, surgical pulmonary embolectomy (SE), or systemic thrombolysis. USAT had the lowest risk of short-term (94.11), long-term mortality (94.67), major bleeding (90.38), and risk of blood transfusions (91); sCDT had the lowest risk of intracranial hemorrhage (86.2), and SE had the lowest risk of any bleeding (99.37) and gastrointestinal bleeding (87.46) based on Surface Under the Cumulative Ranking values. **Conclusion:** In our study, USAT offers significant short- and long-term mortality benefits with the lowest risk of major bleeding and transfusion requirements, while sCDT is ideal for patients at high-risk for intracranial hemorrhage. **Relevance for patients:** Among catheter-based therapies for acute intermediate-to-high-risk PE, USAT offered the best clinical and safety outcomes.

Keywords: Pulmonary embolism; Ultrasound-assisted thrombolysis; Standard catheter-directed thrombolysis; Catheter-based embolectomy; Surgical pulmonary embolectomy; Systemic thrombolysis

1. Introduction

Pulmonary embolism (PE) causes significant morbidity and mortality across the globe¹ and is the third leading cause of cardiovascular mortality in the USA.² Across the globe, the annual incidence of PE is approximately 1 in 1000 persons, and approximately 20% of patients die within 90 days despite treatment, making PE one of the fatal cardiovascular diseases.³ PE accounts for seven million disability-adjusted life years worldwide, underscoring its significant health and financial burden.⁴ In the USA, the annual incidence rate was 1.15 per 1000 people, with more than 300,000 cases yearly.^{1,5} Despite efforts to reduce its fatality, PE-related mortality remains high, ranging from 19.4 to 32.3 per 100,000 across the USA. For all PE patients, in-hospital mortality may reach up to 7%, rising to 33% among patients with hemodynamic instability, underscoring the need for risk stratification to guide management. Acute PE patients primarily face mortality due to right heart failure from right ventricular (RV) dysfunction or hemodynamic instability, categorizing them as intermediate-risk or high-risk.⁶

For all acute PE patients, both the American Heart Association (AHA) 2011⁷ and the European Society of Cardiology (ESC) 2019⁸ recommend therapeutic anticoagulation unless contraindicated. According to AHA 2011, systemic thrombolysis (ST) is reasonable or may be considered for massive or submassive acute PE ([Class IIa; Level of Evidence B] [Class IIb; Level of Evidence C]), while catheter embolectomy, fragmentation, or surgical embolectomy should be considered if patients cannot receive thrombolysis.⁷ ESC 2019 recommends ST for high-risk acute PE (Class I; Level of Evidence B) and surgical pulmonary embolectomy only if ST is contraindicated or has failed (Class I; Level of Evidence C), while percutaneous catheter-directed treatment may be considered as an alternative (Class IIa; Level of Evidence C).⁸

Although ST is recommended for the management of intermediate and high-risk acute PE, its utilization is limited due to its potential complications, mainly bleeding complications, including major bleeding (MB) and intracranial hemorrhage.⁹ This has prompted a search for alternative options, including catheter-based therapies (CDT) such as ultrasound-assisted thrombolysis (USAT), standard catheter-directed thrombolysis (sCDT), catheter-based embolectomy (CBE), and surgical pulmonary embolectomy (SE) to overcome the shortcomings

associated with ST. In recent years, there has been a leap forward in biomedical engineering, including the use of nanomaterials to manage various diseases, such as pulmonary embolism. Magnetic nanoparticles provide a platform for targeted delivery of the active thrombolytic agent to specific blood clots, enabling more precise targeting and minimizing the risk of off-target effects and damage to healthy tissue. However, this technology has not been tested in humans and was therefore excluded from our analysis.¹⁰ Each of these advanced therapies has a distinct mode of action, resulting in differences in clinical efficacy and safety profiles. A previous network meta-analysis (NMA) comparing systemic anticoagulation (AC), ST, and CDT showed that CDT was superior to AC alone and ST in reducing death and MB, including intracranial hemorrhage.¹¹ However, no updated meta-analysis or network meta-analysis has compared the safety and efficacy of different CDTs and SE with ST, despite recent advances. Thus, we conducted this systematic review and Bayesian network meta-analysis to compare the safety and efficacy of different advanced therapies in patients with intermediate/high-risk or submassive/massive acute PE.

2. Methods

2.1. Study design

The NMA was conducted and reported in accordance with the NMA extension of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).¹² Literature search was performed using the PICO framework¹³: population (patients with intermediate- to high-risk or submassive/massive acute pulmonary embolism), interventions (sCDT, USAT, CBE, SE), comparison (ST), and outcomes (short-term mortality, long-term mortality, any bleeding, MB, gastrointestinal [GI] bleeding, intracranial hemorrhage [ICH], and blood transfusion [BT]). This study was registered in the International Prospective Register of Systematic Reviews with registration number CRD42024548182.¹⁴

2.2. Literature search and study selection

We conducted an initial database search in PubMed/Medline, Embase, and Scopus for relevant studies from inception to August 30, 2024, using predefined keywords. Citation lists within each study were also screened to identify additional studies. The search was updated on October 30, 2024, to identify any additional publications;

however, no new relevant studies meeting the inclusion criteria were found. The detailed search strategy is provided in the supplementary file.

For this NMA, eligible studies included all randomized clinical trials (RCTs), quasi-RCTs, and non-randomized studies comparing the sCDT, USAT, CBE, ST, and SE strategies for treating intermediate- to high-risk/high-risk or submassive/massive acute PE. Intermediate-high risk/high-risk or submassive/massive acute PE were defined according to ESC 2019⁸ and AHA 2011⁷ PE guidelines. No restrictions were applied regarding date, publication status, or year of publication. The inclusion criteria were: (i) studies comparing sCDT, USAT, CBE, ST, and SE interventions in acute PE patients, (ii) studies meeting good study criteria according to the Grading of Recommendations Assessment, Development and Evaluation Working Group, and (iii) studies reporting clinical efficacy and safety outcomes of interest. The exclusion criteria were: (i) study conducted in non-human participants, (ii) study not reporting outcomes of interest, (iii) studies including patients with low-risk acute PE, and (iv) study without clear differentiation of catheter-directed intervention types (sCDT, USAT, and CBE).

2.3. Primary and secondary outcomes

The primary outcome was short-term mortality. Secondary outcomes included long-term mortality, any bleeding, MB, GI bleeding, ICH, and BT. Short-term mortality was defined as an in-hospital or 30-day all-cause mortality. Long-term mortality was defined as death from any cause at the longest follow-up of participants in the study. MB was defined as overt bleeding associated with a fall in hemoglobin level of at least 2.0 g/dL, transfusion of ≥ 2 units of packed red blood cells, involvement of a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or requiring operating room intervention.¹⁵

2.4. Data collection

Covidence was used for data screening. Two reviewers (PRO and SD) independently screened the titles and abstracts, with conflicts resolved by a third reviewer (DS). A full-text review was also performed independently by two reviewers, PRO and SD, with DS resolving the conflicts.

Data were extracted using a standardized electronic form in Microsoft Excel, including study and patient demographics, baseline comorbidities, predisposing factors, clinical presentation, Pulmonary Embolism Severity Index score on admission, echocardiographic findings, cardiac biomarkers (Tables S1–S4), and clinical

outcomes (Table 1). Two reviewers independently extracted data from the included studies to reduce bias from missing data, and a third reviewer verified the extracted data to minimize extraction errors and avoid duplicate study inclusion. Any discrepancies in study inclusion or data collection were carefully examined and resolved through discussion with PRO and DS.

2.5. Quality assessment: Risk of bias and grading the certainty of evidence

Randomized studies were assessed for bias using the Cochrane risk of bias tool¹⁶, whereas the quality of non-randomized studies was evaluated using the Risk Of Bias In Non-randomized Studies of Interventions tools for non-randomized studies.¹⁷ RevMan 5.4¹⁸ was used to create the graph and summary for the included studies (Figure S1).

We used the Confidence in Network Meta-Analysis web application¹⁹ to examine the confidence in the findings from the NMA for the primary outcome, short-term mortality, as shown in Figure S2.

2.6. Network meta-analysis

For each outcome of interest, a Bayesian NMA was performed using a generalized linear model with a logit link and binomial likelihood. The analysis utilized the Bayesian inference Using Gibbs Sampling to conduct a Network meta-analysis (BUGSnet) package²⁰ in R and RStudio (version 2023.12.1 build 402).²¹ Bayesian analysis employed Markov Chain Monte Carlo with four concurrent chains and a random-effect model to account for study-level variance. Following NICE-DSU guidelines, we ran 50,000 burn-in iterations and 100,000 further iterations with 10,000 adaptations. Network diagrams showed patient counts by node size and the number of studies by line width.²²

Effect sizes were reported using posterior medians of odds ratios (OR) and 95% credible intervals (CrI). NMA forest plots and league tables illustrated the network estimates. Surface under the cumulative ranking (SUCRA) values and mean ranks indicated treatment ranking probabilities, with higher SUCRA reflecting greater effectiveness.²³ A league table displayed relative odds ratios among comparisons via a heatmap.

Inconsistency refers to differences between direct and indirect evidence. We used an NMA model, comparing Deviance Information Criterion (DIC) values and inspecting leverage plots to detect inconsistencies. Consistency was defined as DIC values within 5 points and a 3-point difference on visual inspection. We also plotted the contributions to the posterior mean deviation for each data point to systematically assess the degree of

inconsistency.

Bayesian NMA was performed using a random-effects framework to account for heterogeneity among studies. Single-arm zero-event studies were included in the analysis for each outcome of interest, with appropriate continuity corrections. In contrast, both-armed zero-event studies were excluded from the analysis because the outcomes of interest were not rare. Two models were used: random-effect consistency and inconsistency. Model fit was assessed with the DIC (lower values are better), while convergence was evaluated using the potential scale reduction factor (PSRF) (acceptable range: 1.00 and 1.05). If PSRF exceeded this range, larger parameters were applied until convergence was satisfactory. Weakly informative priors were chosen for treatment effects and heterogeneity to avoid bias and ensure model convergence. Non-informative priors were used for relative treatment effects, and vague priors were set for between-study variance, following standard Bayesian NMA methods.

We assessed homogeneity of direct evidence using Higgins & Thompson's I^2 statistic from pairwise comparisons of intervention pairs across multiple studies. I^2 values of $\leq 25\%$, $\leq 50\%$, and $\geq 75\%$ indicate low, moderate, and high, respectively.²⁴ Network meta-regression was performed using the MetaInsight: Interactive Network Meta-Analysis and Visualization tool to assess potential between-study heterogeneity and inconsistency, while

incorporating study-level covariates.²⁵ Additionally, this study focused on estimating the relative treatment effect using a Bayesian NMA, and heterogeneity was addressed through standard random-effects assumptions.

3. Results

An initial database search identified 1,586 studies. After removing 640 duplicates, 946 studies remained for title and abstract screening. Subsequently, 150 studies were selected for full-text review, of which 47 were chosen for data extraction. Of these, two were RCTs^{15,26}, and the remaining 45 studies^{15,24,26–71} were non-randomized studies. The PRISMA flow diagram illustrating this review is presented in Figure 1.

3.1. Qualitative summary

A total of forty-seven studies encompassing 267,695 patients with intermediate-high risk/high risk or submassive/massive acute PE were included in this Bayesian NMA. Of these, two randomized controlled trials included 131 (0.049%) acute PE patients, while 45 observational studies accounted for 267,564 (99.951%) cases. Among 196,410 patients with gender identification, 96,482 (49.12%) patients were female. The mean age of participants was 61.26 ± 17.48 years. Patients were assigned to one of five advanced management strategies for acute PE: 135,129 ST (50.48%), 106,001 sCDT (39.60%), 11,431 USAT (4.27%),

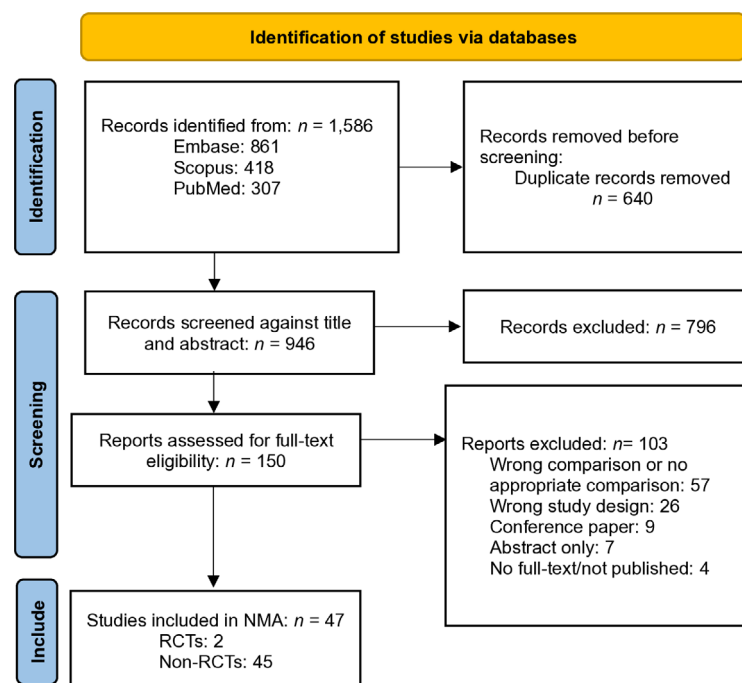


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for relevant study search and screening
Abbreviations: NMA: Network meta-analysis; RCT: Randomized controlled trials.

Table 1. Characteristics of included studies and demographic characteristics of included patients with intermediate-to-high risk PE

Study, publication year	Study type	Interventions, n	Gender, Female n (%)	Age, mean (SD), years	BMI, mean (SD), kg/ m ²	Race, n (%)		African American	Hispanic	Others
Tated <i>et al.</i> , 2021 ²⁶	Randomized prospective study	sCDT, n = 25	7 (28)	46.92 (14.65)	25.80 (1.6)	NA	NA	NA	NA	NA
		ST, n = 25	3 (12)	46.88 (13.79)	26.07 (1.41)	NA	NA	NA	NA	NA
Avgerinos <i>et al.</i> , 2021 ¹⁵	Multicenter, randomized single-blind trial	USAT, n = 40	17 (42)	(52.13)	37 (8)	NA	NA	NA	NA	NA
		sCDT, n = 41	21 (51)	55 (14)	37 (9)	NA	NA	NA	NA	NA
Sekulic <i>et al.</i> , 2020 ²⁷	Multicenter, observational, retrospective study	ST, n = 91	46 (51)	62.3 (15.3)	NA	NA	NA	NA	NA	NA
		USAT, n = 24	10 (42)	59.2 (10)	NA	NA	NA	NA	NA	NA
Lin <i>et al.</i> , 2009 ²⁸	Retrospective, observational study	USAT, n = 11	6 (55)	59 (17)	NA	NA	NA	NA	NA	NA
		sCDT, n = 14	7 (50)	62 (18)	NA	NA	NA	NA	NA	NA
Macovei <i>et al.</i> , 2020 ²⁹	Retrospective observational study	sCDT, n = 37	18 (48.65)	61 (13.6)	NA	NA	NA	NA	NA	NA
		ST, n = 36	19 (52.78)	54 (13)	NA	NA	NA	NA	NA	NA
Tran <i>et al.</i> , 2023 ³⁰	Multicenter, retrospective, observational study	USAT, n = 226	105 (46)	57 (21)	34.1 (11.9)	127 (56)	86 (38)	NA	NA	13 (6)
		CBE, n = 146	83 (57)	59.5 (21)	32.5 (11.5)	71 (49)	56 (38)	NA	NA	19 (13)
Monteleone <i>et al.</i> , 2024 ³¹	Multicenter, retrospective, observational study	USAT, n = 1,577	684 (43.4)	62.3 (15.3)	NA	1295 (82.1)	183 (11.6)	55 (3.5)	27 (1.7)	
		CBE, n = 682	326 (47.8)	59.2 (10)	NA	542 (79.5)	64 (9.4)	55 (8.1)	11 (1.6)	
Feroze <i>et al.</i> , 2023 ³²	Retrospective observational study	CBE, n = 97	44 (45.4)	63.94 (15.8)	NA	NA	NA	NA	NA	NA
		USAT, n = 97	27 (54)	58.88 (15.27)	NA	NA	NA	NA	NA	NA
Wahood <i>et al.</i> , 2023 ³³	National Readmission Database (NRD) (from 2016 to 2019)	sCDT, n = 18,702	8,741 (46.74)	60.2 (10.8)	NA	NA	NA	NA	NA	NA
		ST, n = 18,414	8,786 (47.71)	57.4 (11.9)	NA	NA	NA	NA	NA	NA
Graif <i>et al.</i> , 2020 ³⁴	Retrospective cohort study	sCDT, n = 26	14 (53.8)	59.7 (14.2)	34.4 (10.5)	15 (57.7)	8 (30.8)	1 (3.8)	3 (11.5)	
		CBE, n = 26	14 (53.8)	60.2 (17.1)	38.6 (10.2)	18 (69.2)	8 (30.8)	2 (7.7)	0	
Yoo <i>et al.</i> , 2016 ³⁵	Retrospective study	ST, n = 44	35 (79.5)	65.5 (16.8)	NA	NA	NA	NA	NA	NA
		sCDT, n = 28	15 (53.6)	61.5 (17.3)	NA	NA	NA	NA	NA	NA
Cho <i>et al.</i> , 2015 ³⁶	Single-center retrospective study	ST, n = 19	11 (58)	68.47 (16.82)	NA	NA	NA	NA	NA	NA
		SE, n = 26	17 (65)	63 (16.63)	NA	NA	NA	NA	NA	NA
Beyer <i>et al.</i> , 2020 ³⁷	NRD between January 2016 and December 2016	USAT, n = 417	219 (52.5)	59.8 (15.3)	NA	NA	NA	NA	NA	NA
		sCDT, n = 1,643	796 (48.4)	60.1 (15.20)	NA	NA	NA	NA	NA	NA
		ST, n = 3,376	1,652 (48.9)	59.2 (15.9)	NA	NA	NA	NA	NA	NA

(Contd...)

Table 1. (Continued)

Study, publication year	Study type	Interventions, <i>n</i>	Gender, Female <i>n</i> (%)	Age, mean (SD), years	BMI, mean (SD), kg/ m ²	Race, <i>n</i> (%)			
						White	African American	Hispanic	Others
Avgerinos <i>et al.</i> , 2019 ³⁸	Retrospective observational study	USAT, <i>n</i> = 54	32 (59.3)	63.5 (14.2)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 18	9 (50)	64.1 (14.1)	NA	NA	NA	NA	NA
Avgerinos <i>et al.</i> , 2018 ³⁹	Retrospective observational study	USAT, <i>n</i> = 213	107 (50.2)	60.2 (14.9)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 104	58 (55.8)	55.9 (17.3)	NA	NA	NA	NA	NA
Pietrasik <i>et al.</i> , 2024 ⁴⁰	Retrospective observational study	ST, <i>n</i> = 11	7 (63.6)	60.5 (16.5)	NA	NA	NA	NA	NA
		SE, <i>n</i> = 15	9 (60)	50.2 (16.9)	NA	NA	NA	NA	NA
		sCDT, <i>n</i> = 4	8 (46.1)	61.5 (16)	NA	NA	NA	NA	NA
		CBE, <i>n</i> = 13		59.2 (13.5)	NA	NA	NA	NA	NA
Macovei <i>et al.</i> , 2015 ⁴¹	Retrospective observational study	sCDT, <i>n</i> = 28	15 (53.71)	56.3 (13.2)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 24	14 (58.33)	53.2 (13)	NA	NA	NA	NA	NA
Kolkallah <i>et al.</i> , 2016 ⁴²	Retrospective observational study	USAT, <i>n</i> = 62	29 (46.8)	57.4 (16.2)	31.9 (8.1)	NA	NA	NA	NA
		SE, <i>n</i> = 71	20 (28.2)	57.3 (13.5)	30.6 (6.9)	NA	NA	NA	NA
Lin <i>et al.</i> , 2021 ⁴³	Prospective open cohort study	sCDT, <i>n</i> = 145	89 (61.4)	61.5 (16)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 1,158	631 (54.5)	62.9 (15.7)	NA	NA	NA	NA	NA
Azari <i>et al.</i> , 2015 ⁴⁴	Non-randomized prospective study	SE, <i>n</i> = 30	17 (56.7)	54.93 (12.67)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 78	47 (60.3)	53.82 (10.16)	NA	NA	NA	NA	NA
Klevanets <i>et al.</i> , 2017 ⁴⁵	Prospective study	ST, <i>n</i> = 102	50 (49)	57 (15.7)	NA	NA	NA	NA	NA
		sCDT, <i>n</i> = 107	49 (46)	55 (15.5)	NA	NA	NA	NA	NA
Arora <i>et al.</i> , 2017 ⁴⁶	Retrospective cohort study based on the NRD of 2013–2014	ST, <i>n</i> = 2,256	1,086 (48.14)	62.9 (15.7)	NA	NA	NA	NA	NA
		sCDT, <i>n</i> = 1,128	535 (47.43)	54.93 (12.67)	NA	NA	NA	NA	NA
Geller <i>et al.</i> , 2020 ⁴⁷	Retrospective analysis	sCDT, <i>n</i> = 629	286 (45.5)	57.3 (16.3)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 629	284 (45.2)	57.5 (16.6)	NA	NA	NA	NA	NA
Lehnert <i>et al.</i> , 2016 ⁴⁸	Longitudinal cohort study	SE, <i>n</i> = 50	28 (46)	50.15 (48.08)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 86	40 (46.51)	55.25 (45.24)	NA	NA	NA	NA	NA
Aymarda <i>et al.</i> , 2013 ⁴⁹	Retrospective observational study	SE, <i>n</i> = 28	12 (44)	56.3 (2.7)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 52	29 (56)	56.5 (2)	NA	NA	NA	NA	NA
Elheet <i>et al.</i> , 2024 ⁵⁰	Observational retrospective study	sCDT, <i>n</i> = 58	31 (53.4)	58 (10)	NA	NA	NA	NA	NA
		USAT, <i>n</i> = 77	43 (55.8)	60 (10)	NA	NA	NA	NA	NA

(Cont'd...)

Table 1. (Continued)

Study, publication year	Study type	Interventions, <i>n</i>	Gender, Female <i>n</i> (%)	Age, mean (SD), years	BMI, mean (SD), kg/ m ²	Race, <i>n</i> (%)			
						White	African American	Hispanic	Others
Jiang <i>et al.</i> , 2020 ⁵¹	Retrospective cohort analysis	ST, <i>n</i> = 52	23 (44.23)	58.6 (15.4)	NA	26 (50)	18 (32.14)	4 (7.14)	4 (7.14)
		USAT, <i>n</i> = 47	30 (63.83)	59.4 (15.1)	NA	33 (70.21)	13 (27.66)	1 (2.13)	0
Guan <i>et al.</i> , 2023 ⁵²	Retrospective cohort analysis	ST, <i>n</i> = 37	20 (54.05)	56.72 (11.15)	NA	NA	NA	NA	NA
		sCDT, <i>n</i> = 37	15 (40.54)	56.91 (10.42)	NA	NA	NA	NA	NA
Al-Terki <i>et al.</i> , 2024 ⁵³	Multicenter, retrospective study	USAT, <i>n</i> = 69	38 (55)	66 (4.02)	29.2 (6.628)	NA	NA	NA	NA
		CBE, <i>n</i> = 26	9 (35)	68 (2.93)	29.7 (4.63)	NA	NA	NA	NA
Bradley <i>et al.</i> , 2021 ⁵⁴	Retrospective, single-center cohort study	sCDT, <i>n</i> = 21	7 (33.33)	55.3 (18.1)	34.9 (8.7)	12 (57.1)	9 (42.9)	0	NA
		ST, <i>n</i> = 21	10 (47.62)	52.6 (18.3)	31.6 (10)	11 (52.4)	8 (38.1)	2 (9.5)	NA
Hobohm <i>et al.</i> , 2020 ⁵⁵	German Diagnosis-Related Groups (DRG) system-based study	sCDT, <i>n</i> = 1,175	602 (51.2)	65.54 (17.07)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 40,728	21 371 (52.5)	67.6 (18.27)	NA	NA	NA	NA	NA
Sharifi <i>et al.</i> , 2019 ⁵⁶	Retrospective analysis	USAT, <i>n</i> = 47	20 (42.55)	59 (14)	37.1 (5)	NA	NA	NA	NA
		ST, <i>n</i> = 50	21 (42)	61 (13)	36 (4)	NA	NA	NA	NA
Hassan <i>et al.</i> , 2021 ⁵⁷	Non-randomized controlled trial	CBE, <i>n</i> = 25	13 (52)	49.6 (13.13)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 25	17 (68)	42.92 (12.3)	NA	NA	NA	NA	NA
Kuebel <i>et al.</i> , 2023 ⁵⁸	Multicenter, exploratory, retrospective, cohort study	USAT, <i>n</i> = 105	42 (40)	59.7 (18.04)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 105	54 (51.4)	59.64 (14.28)	NA	NA	NA	NA	NA
Iskandar <i>et al.</i> , 2022 ⁵⁹	Non-randomized Pulmonary Embolism Response Team (PERT)- based study	USAT, <i>n</i> = 47	22 (46.8)	59.06 (15.33)	NA	NA	NA	NA	NA
		CBE, <i>n</i> = 17	7 (41.2)	65.39 (16.06)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 71	53 (60)	61 (13)	NA	NA	NA	NA	NA
Gulba <i>et al.</i> , 1994 ⁶⁰	Prospective observational study	SE, <i>n</i> = 13	5 (38.46)	52.19 (19.93)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 24	6 (25)	56.86 (28.37)	NA	NA	NA	NA	NA
Rothschild <i>et al.</i> , 2019 ⁶¹	A retrospective analysis	sCDT, <i>n</i> = 36	19 (52.8)	60.4 (15.7)	34.5 (9.7)	NA	NA	NA	NA
		USAT, <i>n</i> = 62	32 (51.6)	57.7 (15.4)	36.6 (8.7)	NA	NA	NA	NA
Rao <i>et al.</i> , 2019 ⁶²	Retrospective study	sCDT, <i>n</i> = 33	18 (54.5)	57.4 (12.7)	33 (6)	NA	11 (33.3)	NA	NA
		USAT, <i>n</i> = 37	15 (40.5)	65.2 (12.8)	38 (15)	NA	5 (13.5)	NA	NA
(Contd...									

(Contd...)

Table 1. (Continued)

Study, publication year	Study type	Interventions, <i>n</i>	Gender, Female <i>n</i> (%)	Age, mean (SD), years	BMI, mean (SD), kg/ m ²	Race, <i>n</i> (%)			
						White	African American	Hispanic	Others
Shatla <i>et al.</i> , 2024 ⁶³	National Inpatient Sample (NIS) years 2016-2020	sCDT, <i>n</i> = 26,710	12,405 (46.5)	60.5 (14.7)	NA	19,105 (74.0)	4,640 (18.0)	1,355 (5.2)	725 (2.9)
		USAT, <i>n</i> = 8,060	3,910 (48.5)	60.7 (14.6)	NA	5705 (73.0)	1,510 (9.3)	350 (4.5)	245 (3.1)
Lee <i>et al.</i> , 2017 ⁶⁴	Retrospective cohort analysis	ST, <i>n</i> = 1,854	1,051 (57)	58.5 (16.7)	NA	134 (52)	67 (26)	10 (4)	46 (18)
		SE, <i>n</i> = 257	110 (43)	58.7 (16.1)	NA	1,175 (64)	363 (22)	88 (5)	228 (12)
Percy <i>et al.</i> , 2020 ⁶⁵	NIS from 2010 to 2014	ST, <i>n</i> = 33,553	16,646 (49.6)	58 (23)	NA	22,653 (73.3)	5,211 (16.9)	1,805 (5.8)	1,226 (4.0)
		sCDT, <i>n</i> = 22,336	11,054 (49.5)	62 (24)	NA	14,845 (72.6)	3,844 (18.8)	1,003 (4.9)	756 (3.7)
Chan <i>et al.</i> , 2023 ⁶⁶	Retrospective cohort study	SE, <i>n</i> = 3,085	1,414 (45.8)	56 (25)	NA	1,993 (68.3)	602 (20.6)	129 (4.4)	196 (6.7)
		CBE, <i>n</i> = 14	8 (57.1)	58.6 (19.6)	NA	NA	NA	NA	NA
Lin <i>et al.</i> 2022 ⁶⁷	Retrospective cohort study	USAT, <i>n</i> = 14	6 (42.9)	58.1 (13.8)	NA	NA	NA	NA	NA
		sCDT, <i>n</i> = 169	98 (58)	60.9 (16.4)	NA	NA	NA	NA	NA
Krishnan <i>et al.</i> , 2022 ⁶⁸	Retrospective cohort study	SE, <i>n</i> = 220	120 (54.5)	59.3 (16.4)	NA	NA	NA	NA	NA
		sCDT, <i>n</i> = 2,460	1,200 (48.8)	61.5 (1.92)	NA	1,805 (73.4)	428 (17.4)	48 (2)	NA
Weekes <i>et al.</i> , 2024 ⁶⁹	Observational registry-based study	ST, <i>n</i> = 1,340	555 (41.4)	61.4 (2.894)	NA	922 (68.8)	300 (22.4)	70 (5.2)	NA
		USAT, <i>n</i> = 145	71 (49.0)	56 (25)	NA	79 (54.5)	62 (42.8)	2 (1.4)	4 (2.8)
Mahar <i>et al.</i> , 2018 ⁷⁰	Cleveland Clinic PERT	ST, <i>n</i> = 154	77 (50.0)	58.6 (19.6)	NA	90 (58.4)	61 (39.6)	4 (2.6)	3 (1.9)
		SE, <i>n</i> = 9	NA	58.1 (13.8)	NA	NA	NA	NA	NA
Sedhom <i>et al.</i> , 2022 ⁷¹	NRD between 2016 and 2019	sCDT, <i>n</i> = 14	NA	60 (14)	NA	NA	NA	NA	NA
		SE, <i>n</i> = 6	NA	60 (14)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 22	NA	60 (14)	NA	NA	NA	NA	NA
		CBE, <i>n</i> = 4	NA	60 (14)	NA	NA	NA	NA	NA
		ST, <i>n</i> = 3,570	NA	63 (16.63)	NA	NA	NA	NA	NA
		sCDT, <i>n</i> = 30,395	NA	59.8 (15.3)	NA	NA	NA	NA	NA
		CBE, <i>n</i> = 8,089	NA	60.1 (15.2)	NA	NA	NA	NA	NA
		SE, <i>n</i> = 2,185	NA	59.2 (15.9)	NA	NA	NA	NA	NA

Note: NA: Not available.

Abbreviations: CBE: Catheter-based embolectomy; PE: Pulmonary embolism; sCDT: Standard catheter-directed thrombolysis; SE: Surgical pulmonary embolectomy; ST: Systemic thrombolysis; USAT: Ultrasound-assisted thrombolysis.

9,139 CBE (3.41%), 5,995 SE (2.24%).

3.2. Quantitative summary

Short-term mortality, long-term mortality, any bleeding, MB, GI bleeding, ICH, and BTs showed good convergence.

3.2.1. Short-term mortality

A total of 44 studies evaluated short-term mortality among 267,471 patients with acute PE across five interventions. All ten pairwise treatment comparisons are supported by direct data. Of the 44 studies, 37 were two-arm, and seven were multi-arm. There were 41,187 short-term mortality events, and 10 studies included at least one arm with zero events. The network plot is presented in [Figure 2A](#).

Analysis of NMA forest plot demonstrated that USAT (OR: -1.34; 95% CrI: -1.94 to -0.77), sCDT (OR: -0.89; 95% CrI: -1.37 to -0.48), CBE (OR: -0.89; 95% CrI: -1.74 to -0.04), and SE (OR: -0.60; 95% CrI: -1.28 to -0.005) were associated with significant reductions in short-term mortality relative to ST, as illustrated in [Figure S4A](#).

Regarding short-term mortality reduction, USAT achieved the highest SUCRA (94.11), whereas ST had the lowest (1.12). Sequentially lower SUCRA values were observed for sCDT (59.7), CBE (57.84), and SE (37.23) as detailed in [Figures 3A](#) and [S6A](#).

The heatmap from the league plot of the network estimates corroborated the results obtained from both the NMA forest and SUCRA plots. Compared to ST, each of the four strategies: USAT, sCDT, CBE, and SE, demonstrated statistically significant reductions in the occurrence of short-term mortality events, as shown in [Figures 4A](#) and [Table S5](#).

Network meta-regression showed a decreasing trend in short-term mortality with increasing baseline risk across interventions, as shown in [Figure S7](#).

3.2.2. Long-term mortality

A total of 10 studies reported long-term mortality outcomes and included 3,739 patients with acute PE across five interventions. Of the 10 possible pairwise comparisons, only five had direct comparative data. All included studies were two-arm studies. There were 747 long-term mortality events in total, with at least one zero event in each arm. The network plot was connected as depicted in [Figure 2B](#).

In the NMA forest plot, compared with ST, both USAT (OR: -15.27; 95% CrI: -53.67 to -1.87) and CBE (OR: -14.66; 95% CrI: -53.13 to -1.49) demonstrated a statistically significant reduction in long-term mortality events, but not by sCDT and SE, as shown in [Figure S4B](#).

Regarding reductions in long-term mortality, USAT

had the highest SUCRA (94.67), whereas ST had the lowest (9.88). Following the USAT, CBE (79.37), sCDT (45.2), and SE (20.9) were ranked in descending order, as shown in [Figures 3B](#) and [S6B](#).

The heatmap of the league plot further corroborated the findings from the NMA forest plot and SUCRA rankings. Compared with ST, treatment of acute PE with USAT was associated with a significant reduction in long-term mortality, as shown in [Figure 4B](#) and [Table S5](#).

3.2.3. Any bleeding

A total of 25 studies reported any bleeding events, enrolling 117,706 patients with acute PE across 10 interventions. Of the 10 possible pairwise comparisons, all had direct comparison data. Of 25 studies, 22 were two-arm, while the remaining three included multiple arms. There were 12,879 bleeding events, with seven studies reporting at least one arm with zero events. The network plot was connected as shown in [Figure 2C](#).

In the NMA forest plot, compared to ST, only SE (OR: -3.34; 95% CrI: -5.79 to -1.48) showed a significant reduction in the occurrence of any bleeding events, as illustrated in [Figure S4C](#).

Regarding reducing bleeding events, SE had the highest SUCRA (99.37), while ST had the lowest (17.88). Following SE, sCDT (50.72), CBE (49), and USAT (33.03), ranked in decreasing order, as illustrated in [Figures S5A](#) and [S6C](#).

Additionally, the heatmap of the league plot of the network estimates corroborated the findings from the NMA forest plot and SUCRA plot. Treatment of acute PE with SE is associated with a significantly lower incidence of any bleeding events compared to USAT, sCDT, and CBE, as illustrated in [Figure S8A](#) and [Table S5](#).

3.2.4. Major bleeding

A total of 33 studies reported MB events and included 115,411 patients with acute PE assigned to five interventions. Among the 10 possible pairwise comparisons, all had direct comparison data. Of these 33 studies, 27 were two-arm, with the remaining being six multi-arm. There were 20,208 MB events, and 11 studies included at least one zero-event arm. The network plot was connected as shown in [Figure 2D](#).

In the NMA forest plot, compared to ST, none of the other interventions: sCDT, USAT, CBE, and SE showed significant differences in the occurrence of the MB events, as illustrated in [Figure S4D](#).

Regarding the reduction in MB events, USAT (90.38) has the highest SUCRA value, whereas SE (11.85) has the lowest. Following the USAT, sCDT (74.7), ST (38.39),

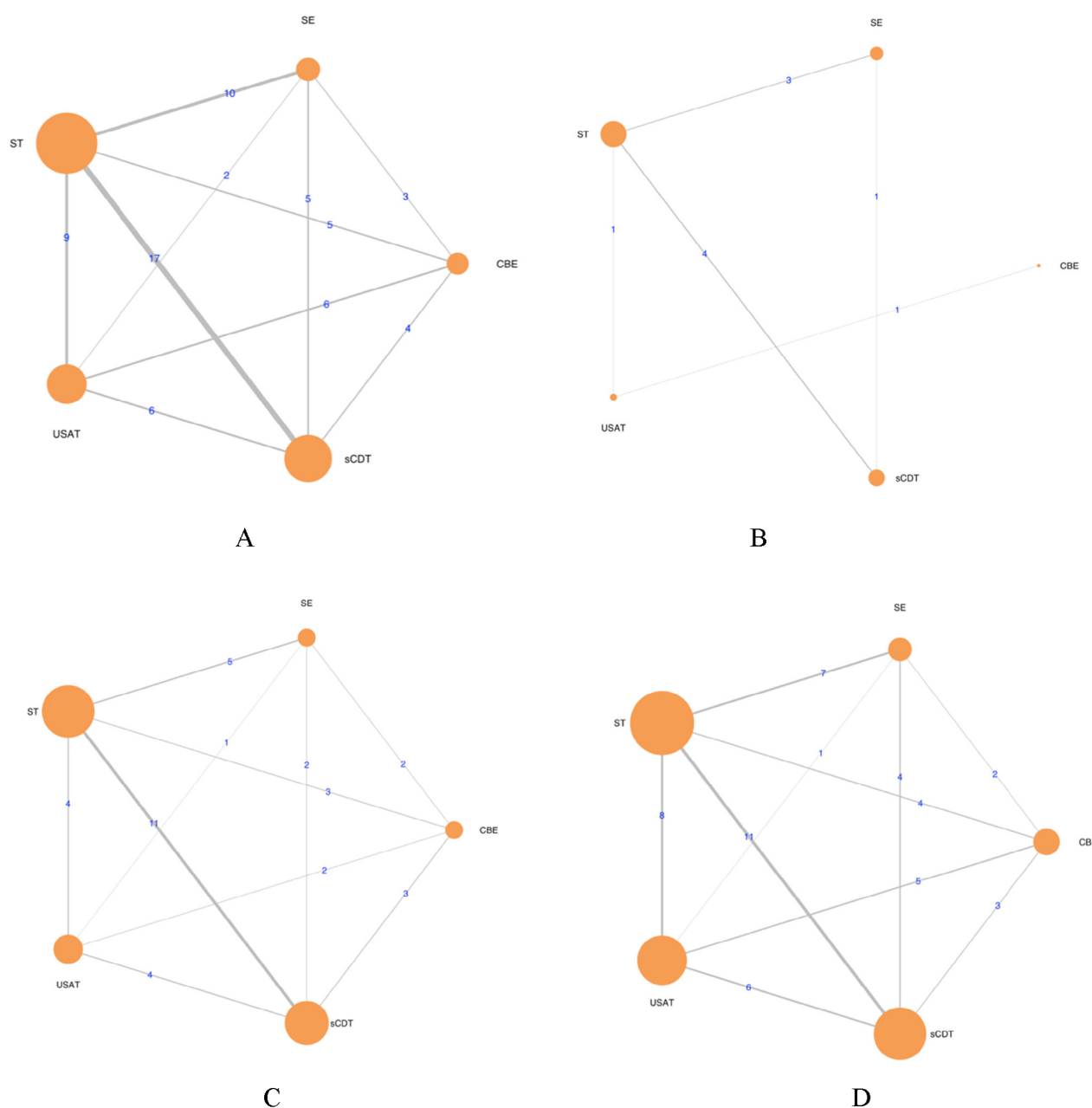


Figure 2. Network plot for included interventions: (A) For short-term mortality, (B) For long-term mortality, (C) For any bleeding, (D) For major bleeding. Abbreviations: CBE: Catheter-based embolectomy; sCDT: Standard catheter-directed thrombolysis; SE: Surgical pulmonary embolectomy; ST: Systemic thrombolysis; USAT: Ultrasound-assisted thrombolysis.

and CBE (34.67), ranked in decreasing order as shown in Figure 3C and S6D.

The heatmap of league plots of the network estimates confirmed the findings of the NMA forest plot and SUCRA plot. Treatment of acute PE with USAT may significantly reduce the risk of MB events compared to SE, as shown in Figure 4D.

3.2.5. Gastrointestinal bleeding

A total of nine studies reported GI bleeding events and included 91,012 patients with acute PE assigned to four interventions. Of the six possible pairwise comparisons, only six had direct comparison data. Of the nine studies, eight were two-arm while the remaining one was a multi-arm study. There were a total of 2,493 GI bleeding events,

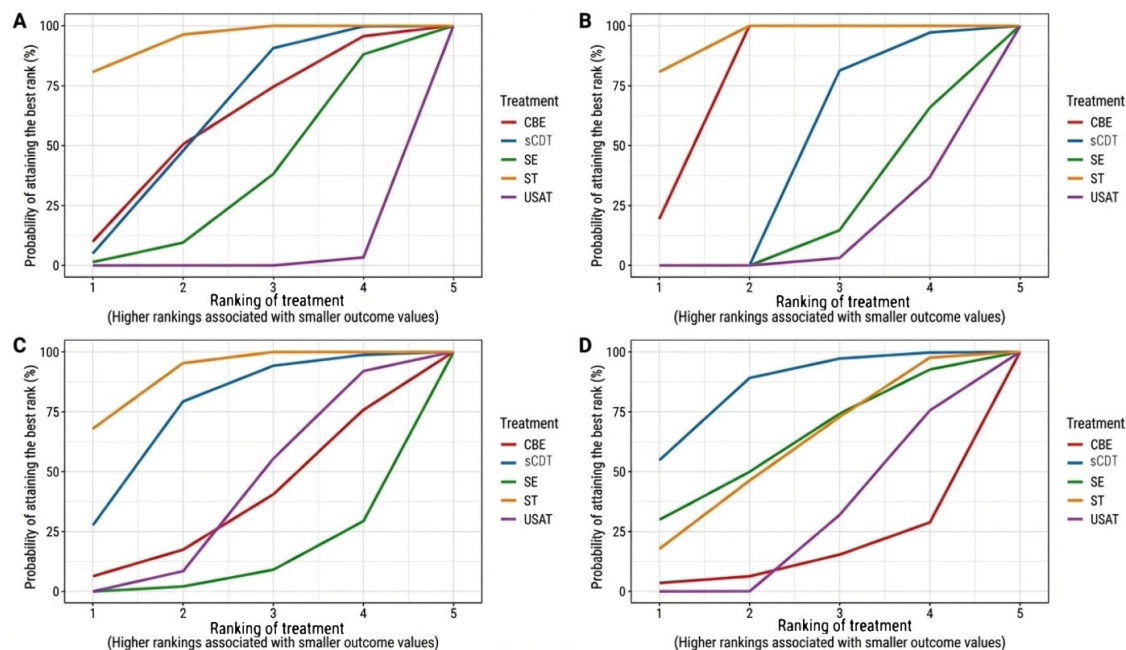


Figure 3. Cumulative probability SUCRA ranking chart for included interventions. The SUCRA intuitively displays the sorting probability of each intervention group in the form of a curve: (A) For short-term mortality, (B) For long-term mortality, (C) For major bleeding, (D) For intracranial hemorrhage.

Abbreviations: CBE: Catheter-based embolectomy; sCDT: Standard catheter-directed thrombolysis; SE: Surgical pulmonary embolectomy; ST: Systemic thrombolysis; SUCRA: Surface under the cumulative ranking curve; USAT: Ultrasound-assisted thrombolysis.

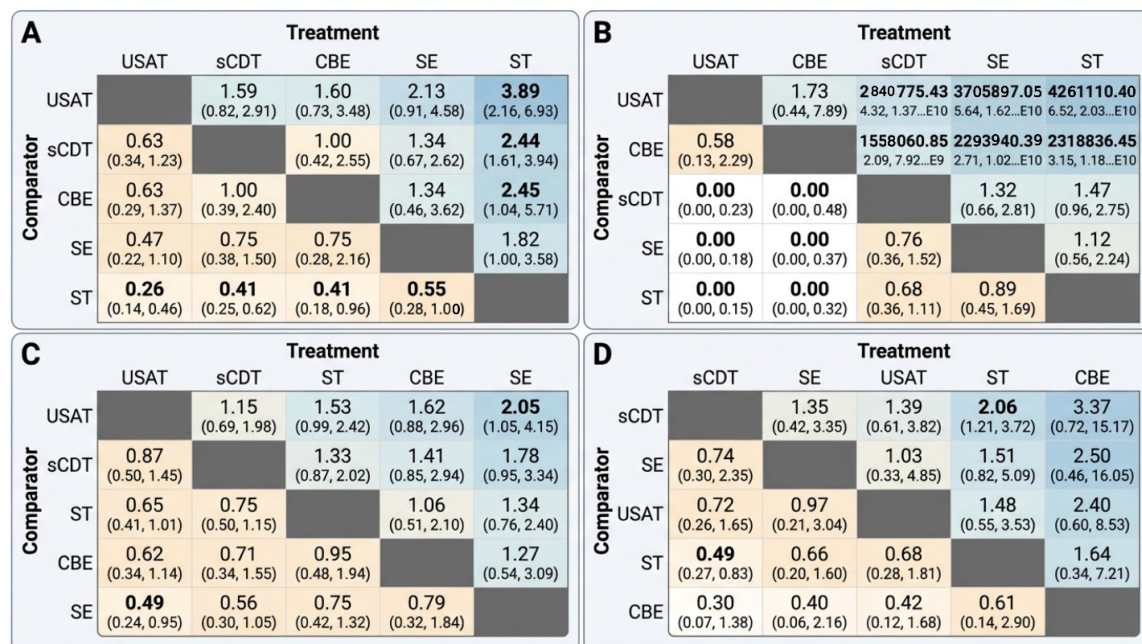


Figure 4. Ranking chart heat maps for included interventions. Data are ORs (95% CrI) of the treatment on the top, compared with the comparator on the left. OR > 1.0 shows an advantage for the treatment, whereas OR < 1.0 shows an advantage for the comparator. Statistically significant results ($p < 0.05$) are marked by double asterisks (**): (A) For short-term mortality, (B) For long-term mortality, (C) For major bleeding, (D) For intracranial hemorrhage.

Abbreviations: CBE: Catheter-based embolectomy; CrI: Credible interval; sCDT: Standard catheter-directed thrombolysis; OR: Odds ratio; SE: Surgical pulmonary embolectomy; ST: Systemic thrombolysis; USAT: Ultrasound-assisted thrombolysis.

with one study having at least one zero-event arm. The network plot was connected as shown in Figure S3A.

In the NMA forest plot, compared to ST, none of the other interventions: sCDT, USAT, and SE showed significant differences in the occurrence of the GI bleeding events, as illustrated in Figure S4E.

Regarding reducing the occurrence of GI bleeding events, SE (87.46) has the highest SUCRA value, and ST (11.76) has the lowest. Following the SE, USAT (56.1) and sCDT (44.69) ranked in decreasing order, as illustrated in Figures S5B and S6E.

The heatmap of league plots of the network estimates confirmed the findings of the NMA forest plot and SUCRA plot. There was no significant difference among USAT, sCDT, SE, and ST in the occurrence of GI bleeding events, as illustrated in Figure S8B.

3.2.6. Intracranial hemorrhage

A total of 23 studies reported ICH events and included 259,575 patients with acute PE assigned to five interventions. Of the 10 possible pairwise comparisons, all had direct comparison data. Of 23 studies, 19 were two-arm, while the remaining four were multi-arm. There were a total of 3,286 ICH events, with 10 studies having at least one zero-event arm. The network plot was connected as shown in Figure S3B.

In the NMA forest plot, compared to ST, sCDT (OR: -0.72 ; 95% CrI: -1.31 to -0.19) may significantly lower the occurrence of ICH events, but not with other interventions, as illustrated in Figure S4F.

Regarding the reduction of ICH events, sCDT (86.2) has the highest SUCRA value, whereas CBE (13.66) has the lowest. Following the sCDT, SE (61.85), USAT (59.99), and ST (28.29) ranked in decreasing order as shown in Figures 3D and in S6F.

The heatmap of league plots of the network estimates confirmed the findings of the NMA forest plot and SUCRA plot. Treatment of acute PE with sCDT may significantly reduce the incidence of ICH compared to ST, as shown in Figure 4D.

3.2.7. Blood transfusion

A total of 21 studies reported the BT events and included 155,655 patients with acute PE assigned to five interventions. Of the 10 possible pairwise comparisons, six had direct comparison data. Of 21 studies, 19 were two-arm, while the remaining two were multi-arm. There were a total of 19,830 BT events, with five studies including at least one zero-event arm. The network plot was connected as shown in Figure S3C.

In NMA forest plot, compared to ST, sCDT (OR: -0.43 ; 95% CrI: -0.76 to -0.11) shown to lower the occurrence of BT events significantly whereas SE (OR: 0.76 ; 95% CrI: 0.20 to 1.23) might increase the occurrence of BT events significantly but not with other interventions, as illustrated in Figure S4G.

Regarding the need for BT risk, SUCRA values ranked USAT (91) highest, and SE (6.43) lowest. Following the USAT, sCDT (82.54), ST (47.72), and CBE (22.29) ranked in decreasing order, as illustrated in Figures S5C and S6G.

The heatmap of league plots of the network estimates confirmed the findings of the NMA forest plot and SUCRA plot. Treatment of acute PE with USAT might significantly reduce the need for BT compared with CBE and ST. Similarly, treatment with sCDT might significantly reduce BT events compared with ST, CBE, and SE, as illustrated in Figure S8C.

3.2.8. Pairwise meta-analysis comparing sCDT and USAT

In a pairwise meta-analysis comparing sCDT versus USAT, the USAT group had significantly more BTs but no differences in short-term mortality, any bleeding, or significant bleeding. Heterogeneity was low for MB and BT, and medium to high for short-term mortality and any bleeding, as illustrated in Figure S9.

3.2.9. Consistency of direct and indirect evidence

The possibility of global inconsistency was none for long-term mortality and GI bleeding, and very low for short-term mortality, any bleeding, MB, ICH, and BT, as illustrated in Figure S10.

4. Discussion

Our Bayesian NMA of 47 studies involving 267,695 intermediate-to-high risk acute PE patients showed with moderate certainty that USAT is associated with a lower risk of short-term (SUCRA 94.11) and long-term all-cause mortality (SUCRA 94.67), MB (SUCRA 90.38), and risk of BTs (SUCRA 91) compared to other advanced PE interventions. Additionally, sCDT has a lower risk of ICH (SUCRA 86.2) than other interventions, including USAT. Regarding the risk of any bleeding and GI bleeding, surgical embolectomy has a lower risk profile than other interventions, with SUCRA scores of 99.37 and 87.46, respectively. These findings are primarily based on non-randomized studies, as randomized studies accounted for less than 1% of the total patient population. The better BT risk profile of USAT compared to sCDT in NMA was also supported by a pairwise comparison between sCDT and USAT.

PE management can be categorized into three phases based on the timing of onset: initial treatment (within the first week), primary treatment (3–6 months), and secondary prevention (after 3–6 months). Anticoagulation therapy is the cornerstone of PE management across all phases; it is essential during the initial and primary treatment periods, and its continuation during the secondary prevention stage depends on underlying risk factors. Anticoagulant options include unfractionated heparin, low-molecular-weight heparin, vitamin K antagonists, and direct oral anticoagulants, each targeting a distinct point in the coagulation cascade by either inhibiting clotting factor synthesis or directly blocking their action. In patients with PE, anticoagulants prevent thrombus extension and recurrence, enabling endogenous fibrinolysis. Achieving optimal clinical outcomes takes several days, making this approach suitable for low-risk PE but insufficient for acute intermediate- or high-risk cases due to the risk of rapid clinical deterioration and mortality. Advanced therapies are therefore indicated for acute intermediate- to high-risk PE.⁷² ST employs lytic agents that convert plasminogen to plasmin, facilitating fibrinolysis.⁷³ This leads to rapid reversal of hemodynamic compromise, right ventricular dysfunction, and gas exchange abnormalities associated with intermediate- and high-risk PE.⁶ However, standard-dose fibrinolytics carry a significant risk of bleeding complications, including those involving intracranial and gastrointestinal bleeding. Efforts to reduce bleeding risk using low-dose thrombolytics have shown some promise but do not eliminate this concern.^{6,73} The pulmonary circulation compensates for hypoxia resulting from ventilation/perfusion (V/Q) mismatch via the von Euler-Liljestrand mechanism, redirecting blood flow to better ventilated regions. Fibrinolytic-induced clot lysis releases vasoconstrictors such as thromboxane A2 and serotonin, which can precipitate pulmonary vasoconstriction, exacerbate V/Q mismatch, and promote intrapulmonary shunting. While the clinical significance of these effects in acute PE is still being investigated, they may influence outcomes associated with fibrinolytic-based therapies.⁷⁴

To achieve a more favorable bleeding risk profile without compromising the mortality benefits seen with ST, there is increasing support for catheter-based interventions, including standard catheter-directed thrombolysis, ultrasound-assisted thrombolysis, and catheter-based embolectomy. In sCDT, fibrinolytics are delivered directly to the thrombus via a catheter, achieving even higher local drug concentrations and promoting mechanical disruption of the embolus, thereby increasing the surface area susceptible to fibrinolysis. These synergistic mechanisms lower the overall dose of fibrinolytics required. They may reduce the risk of hemorrhage, suggesting that sCDT may

be a preferable alternative to ST.⁶ USAT builds upon sCDT by incorporating ultrasonic waves, which disrupt the fibrin architecture of the thrombus, expose additional binding sites for thrombolytics, and further reduce the required dosage. USAT has demonstrated a superior bleeding risk profile compared to both ST and sCDT, alongside improved mortality rates, likely attributable to reduced bleeding complications.⁷⁵ CBE and SE address PE pathophysiology via direct embolus removal; CBE uses large-bore devices to extract thrombi mechanically, and SE necessitates surgical access to the pulmonary artery or trunk for thrombus retrieval.⁶

Systemic thrombolysis is considered a recommended or reasonable therapeutic option for intermediate- or high-risk acute PE, as outlined by both the ESC 2019⁸ and AHA 2011⁷ guidelines, due to its potential mortality benefit and acceptable bleeding risk. In a meta-analysis of 15 RCTs involving 2,057 acute PE patients, Marti *et al.* compared systemic thrombolytic therapy with anticoagulation versus anticoagulation alone and found that systemic thrombolytic therapy combined with anticoagulation was associated with a statistically significant reduction in early all-cause and PE-related mortality, death or treatment escalation, and PE recurrence compared to anticoagulation alone. However, these benefits were not observed after stratification by PE severity, and there was a notable increase in MB, including intracranial or fatal hemorrhage, irrespective of PE severity.⁷⁶ Similarly, Mathew *et al.*, in a meta-analysis of nine RCTs that included intermediate-risk PE, found no significant differences between ST and anticoagulation for in-hospital mortality and MB. However, ST was associated with a higher risk of intracranial hemorrhage.⁷⁷ Furthermore, in a meta-analysis of seven RCTs by Xu *et al.*, ST was effective in preventing clinical deterioration and PE recurrence but was associated with an increased risk of any bleeding without a significant improvement in mortality.⁷⁸ Consequently, there is an ongoing search for alternate treatment options that offer a more favorable bleeding risk profile while maintaining comparable or superior mortality outcomes relative to ST.

A meta-analysis of 12 observational studies by Su *et al.* compared standard CDT plus anticoagulation with anticoagulation only. The authors found sCDT with AC was associated with a significant reduction in in-hospital, 30-day, and one-year mortality; however, it was linked to an increased risk of MB, with no significant difference in minor bleeding risk. Additionally, ST compared to AC alone did not demonstrate any bleeding risk benefits.⁷⁹ In a Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism trial, sCDT showed a significantly lower risk of all-cause mortality or RV/left ventricular

ratio > 0.9 at 3 months compared with AC alone, while MB risk remained similar between groups.⁸⁰ The ULTIMA trial evaluated USAT versus AC alone in 59 patients with intermediate risk PE; USAT was superior to AC alone in reversing RV dilatation at 24 h without increasing bleeding complications, although intervention-related mortality was not assessed.⁸¹ In the Standard vs Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism trial, USAT was compared with sCDT in 81 patients with acute intermediate-risk (submassive) PE and demonstrated no additional benefit in mortality, bleeding risk, or pulmonary obstruction compared with sCDT.¹⁵ Recent non-randomized and randomized studies continue to report variable CDT.

Consistent with our findings, Ishisaka *et al.* in their NMA of 157,454 intermediate-to-high risk PE patients demonstrated that CDT was associated with significantly lower in-hospital mortality than AC, SE, and ST, and with significantly lower long-term mortality than AC only, but not compared to SE or ST. Additionally, CDT showed a lower long-term mortality risk than AC alone, but not when compared to both AC and CDT. Regarding the risk of MB, ST had a notably higher risk relative to both AC and CDT. Minor bleeding was lowest with AC, and highest with ST. The same NMA reported that ST was also associated with an increased risk of ICH compared with AC alone and CDT. A notable distinction between NMA by Ishisaka *et al.* and our Bayesian NMA is our inclusion of specific CDT subtypes—USAT, sCDT, CBE—which were not examined in Ishisaka *et al.*'s analysis. Conversely, we did not include the AC-alone arm, unlike Ishisaka *et al.*, because our focus was on patients requiring advanced PE therapies in addition to acute intermediate-to-high-risk PE management, where maximal clinical benefits are observed.⁸² Another NMA evaluating 45 studies with a total of 81,705 acute PE patients compared CDT, ST, and AC alone, and found that AC alone ranked best at minimizing MB and intracranial bleeding risks. In contrast, CDT offered the most favorable short-term mortality outcomes.⁸³ Similarly, Planer *et al.* performed an NMA of 44 studies involving 20,006 patients. They showed that CDT was associated with reduced all-cause mortality compared to ST (OR 0.43; 95% CI: 0.32–0.57) and AC alone (OR 0.36; 95% CI: 0.25–0.52), and had superior outcomes to ST regarding MB (OR 0.61; 95% CI: 0.53–0.70) and ICH (OR 0.44; 95% CI: 0.29–0.64), which aligns with our findings.¹¹ Furthermore, Mathew *et al.* conducted a Bayesian NMA of 14 RCTs comprising 2,132 submassive PE patients to compare USAT, AC, full-dose ST, low-dose thrombolytics, and sCDT. Their findings, in agreement with ours, indicated that USAT conferred the lowest in-hospital mortality risk (SUCRA 85.15) and recurrent PE risk (SUCRA 82.6). CDT was associated

with the lowest MB risk (SUCRA 80.04); however, this intervention was excluded from our analysis.⁸⁴

In addition to conducting Bayesian NMA, we performed pairwise meta-analyses comparing USAT and sCDT for short-term mortality, any bleeding, MB, and BT requirements. No significant differences were observed between these interventions across all outcomes except BT requirements, where sCDT was associated with a higher risk than USAT (OR 1.39; CI: 1.19–1.62; $I^2 = 0$). The increased transfusion risk linked to sCDT in a pairwise meta-analysis may differ from that in an NMA, as the latter combines direct and indirect evidence, addresses between-study heterogeneity, and pools data across studies, thereby reducing differences observed in individual comparisons. Consistent with our findings, Bruno *et al.* did not observe differences between USAT and sCDT for major or minor bleeding risk, intensive care unit stay, or hospital length of stay in their meta-analysis of 543 patients with acute PE across eight studies.⁸⁵ Our analysis also revealed no superiority of catheter-based embolectomy for any outcome of interest. Similarly, the recently published Pulmonary Embolism Endovascular Removal With Large-Bore Mechanical Thrombectomy Compared With Catheter-Directed Thrombolysis (PEERLESS) trial reported no significant difference between CBE (large-bore mechanical thrombectomy) and other CDTs (USAT, sCDTs) regarding MB, ICH risk, and 30-day all-cause mortality.⁸⁶ In our study, surgical embolectomy for acute PE demonstrated favorable outcomes only for any bleeding and GI bleeding. Furthermore, an observational study by Winters *et al.* comparing surgical pulmonary embolectomy with CDT in patients with acute PE found no significant differences in mortality or bleeding profiles.⁸⁷

We acknowledge that our NMA had several limitations. First, almost all included studies are non-randomized, which, while offering real-world insights, are inherently prone to confounding by indication and selection bias, as treatment selection is influenced by patient condition, underlying comorbidities, bleeding risk, and institutional protocols or available experts; these factors may not be fully adjusted for in observational study designs. Furthermore, between-study variations in the definitions of outcomes, mainly for long-term outcome/any bleeding/others, follow-up duration, and adjustment methods across studies, also further hamper the direct comparability within them. Additionally, several studies relied on administrative databases, which are retrospective and can introduce coding errors, misclassification, and a lack of comprehensive clinical information, thereby decreasing certainty. Thus, observed differences in mortality and bleeding outcomes may reflect these underlying patient

characteristics rather than being genuine. Second, SUCRA values used to summarize cumulative ranking probabilities rather than treatment effects should be interpreted cautiously. Due to limitations in observational data, potential confounding, and overlapping credible intervals, it may not provide a definitive ranking of treatments. Instead, it might supplement effect estimates and clinical judgment, especially when differences are smaller and uncertainty is high. Third, the included studies had substantial differences in patient numbers, raising the possibility that different studies may have different effects on the outcome of interest. Fourth, there were significant differences in the numbers and types of underlying comorbidities, predisposing factors, and acute PE types among patients included in the studies, creating substantial heterogeneity; thus, interpreting results from the NMA may require caution. Lastly, most of the included studies are from North American and European countries; they may have limited generalizability to patient populations from other geographic regions. Nevertheless, despite these constraints, our Bayesian NMA remains robust. Despite these limitations, our Bayesian NMA is the first NMA to our knowledge that has compared different types of CDT: sCDT, USAT, and CBE; ST and SE for acute intermediate-to-high risk PE management along with anticoagulation therapy. Also, our study is strengthened by a large number of included studies.

We hope that the ongoing randomized clinical trials: PEITHO-3 trial (NCT04430569)⁸⁸, HI-PEITHO trial (NCT04790370)⁸⁹, PEERLESS II trial (NCT06055920)⁹⁰, PE-TRACT trial (NCT05591118)⁹¹, STRATIFY trial (NCT04088292)⁹², STORM-PE trial (NCT05684796)⁹³ will provide us with more insight into the management of acute, intermediate-to-high-risk PE patients. Results of these trials may solidify evidence supporting the aggressive management of intermediate to high-risk PE, compare different available strategies, and provide further insight into the evidence on USAT and sCDT in PE management compared with other strategies.

5. Conclusion

This Bayesian NMA addresses an important question in acute intermediate-to-high-risk PE management: which advanced PE therapy offers the greatest mortality benefit with the least bleeding risk when used as an adjunct to anticoagulation therapy. For the management of acute intermediate-to-high risk PE patients, when expertise and resources are available, and there are no contraindications to fibrinolysis, USAT should be utilized to achieve maximal mortality benefit in the short- and long-term, with the lowest MB risk and thus BT risk. sCDT should be considered for those patients who are at high risk for

intracranial hemorrhage. ST should be pursued if no alternative advanced PE therapies are available for acute, intermediate-to-high-risk PE patients. Thus, the findings of this NMA will encourage more studies focused on USAT and sCDT strategies and their comparison with other approaches for the acute management of intermediate-to-high risk PE in the near future, providing more definitive answers to this debated topic.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Prakash Raj Oli, Dhan Bahadur Shrestha, Sagun Dawadi, Jurgen Shtembari

Formal analysis: Prakash Raj Oli

Methodology: Prakash Raj Oli, Dhan Bahadur Shrestha, Sagun Dawadi

Writing—original draft: Prakash Raj Oli, Dhan Bahadur Shrestha, Sagun Dawadi

Writing—review & editing: All authors

Ethics approval and consent to participate

This is a meta-analysis; therefore, it did not require an ethical review committee approval.

Consent for publication

Not applicable.

Availability of data

All data related to the study are presented in the study and supplementary files.

Further disclosure

We would like to disclose that the abstract of this manuscript was presented as a poster at American Heart Association (AHA), Scientific Sessions 2024, Chicago, IL, USA, November 16-18, 2024.

References

1. Hsu SH, Ko CH, Chou EH, *et al.* Pulmonary embolism in United States emergency departments, 2010–2018. *Sci Rep.* 2023;13(1).
doi: 10.1038/s41598-023-36123-2

2. Giri J, Sista AK, Weinberg I, *et al.* Interventional therapies for acute pulmonary embolism: Current status and principles for the development of novel evidence. *Circulation*. 2019;140(20):E774-E801.
doi: 10.1161/CIR.0000000000000707
3. Kahn SR, de Wit K. Pulmonary Embolism. *N Engl J Med*. 2022;387(1):45-57.
doi: 10.1056/nejmcp2116489
4. Patel U, Sakariya DC, Kondamuri NSRM, *et al.* Abstract P3155: Socio-Demographic Disparities in the Management Modalities of Pulmonary Embolism Amongst COVID-19 Patients: A Retrospective Population-Based Study. *Circulation*. 2025;151(Suppl_1).
doi: 10.1161/CIR.151.SUPPL_1.P3155
5. Burton JR, Madhavan M V., Finn M, *et al.* Advanced Therapies for Acute Pulmonary Embolism: A Focus on Catheter-Based Therapies and Future Directions. *Struct Heart*. 2021;5(2):103-119.
doi: 10.1080/24748706.2020.1853860
6. Piazza G. Advanced Management of Intermediate- and High-Risk Pulmonary Embolism: JACC Focus Seminar. *J Am Coll Cardiol*. 2020;76(18):2117-2127.
doi: 10.1016/j.jacc.2020.05.028
7. Jaff MR, McMurtry MS, Archer SL, *et al.* Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation*. 2011;123(16):1788-1830.
doi: 10.1161/CIR.0b013e318214914f
8. Konstantinides S V., Meyer G, Bueno H, *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;41(4):543-603.
doi: 10.1093/eurheartj/ehz405
9. Finocchiaro S, Mauro MS, Rochira C, *et al.* Percutaneous interventions for pulmonary embolism. *EuroIntervention*. 2024;20(7):E408-E424.
doi: 10.4244/EIJ-D-23-00895
10. Zhang B, Jiang X. Magnetic Nanoparticles Mediated Thrombolysis-A Review. *IEEE Open J Nanotechnol*. 2023;4:109-132.
doi: 10.1109/OJNANO.2023.3273921
11. Planer D, Yanko S, Matok I, *et al.* Catheter-directed thrombolysis compared with systemic thrombolysis and anticoagulation in patients with intermediate- or high-risk pulmonary embolism: systematic review and network meta-analysis. *Can Med Assoc J*. 2023;195(24):E833-E843.
doi: 10.1503/cmaj.220960
12. Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *Br Med J*. 2015;349.
doi: 10.1136/bmj.g7647
13. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak*. 2007;7.
doi: 10.1186/1472-6947-7-16
14. Oli P, Shrestha D, Dawadi S, Regmi L. Efficacy and Safety of different treatment strategies for acute pulmonary embolism: A Systematic Review and Network Meta-Analysis. PROSPERO International prospective register of systematic reviews. Published online 2024. Available from: <https://www.crd.york.ac.uk/PROSPERO/view/CRD42024548182> [Last accessed on 17 April, 2025].
15. Avgerinos ED, Jaber W, Lacomis J, *et al.* Randomized Trial Comparing Standard Versus Ultrasound-Assisted Thrombolysis for Submassive Pulmonary Embolism: The SUNSET sPE Trial. *JACC Cardiovasc Interv*. 2021;14(12):1364-1373.
doi: 10.1016/j.jcin.2021.04.049
16. Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br Med J*. 2011;343(7829).
doi: 10.1136/bmj.d5928
17. JBI Critical Appraisal Tools|JBI. Available from: <https://jbi.global/critical-appraisal-tools> [Last accessed on 17 April, 2025].
18. RevMan. Available from: <https://revman.cochrane.org/myReviews> [Last accessed on 17 April, 2025].
19. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al.* Cinema: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020;17(4).
doi: 10.1371/JOURNAL.PMED.1003082
20. Béliveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: An R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. *BMC Med Res Methodol*. 2019;19(1).
doi: 10.1186/s12874-019-0829-2
21. Allaire JJ. RStudio: Integrated Development Environment for R. Available from: <http://www.rstudio.org/> [Last accessed on 17 April, 2025].
22. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework For Pairwise And Network Meta-Analysis Of Randomised Controlled Trials Report By The Decision

- Support Unit. 2011. Available from: www.nicesdu.org.uk [Last accessed on 29 December, 2025].
23. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163-171.
doi: 10.1016/j.jclinepi.2010.03.016
24. Ioannidis JPA, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *Br Med J*. 2007;335(7626):914.
doi: 10.1136/BMJ.39343.408449.80
25. MetaInsight R App | Largest R and Python Shiny App Store|Grow Your Shiny App Userbase. Available from: <https://shinyappstore.com/a/MetaInsight> [Last accessed on 9 January, 2026].
26. Tated S, Joshi D, Shukla A, *et al*. A simple randomized prospective study comparing catheter-directed thrombolysis versus systemic thrombolysis in patients with massive and submassive pulmonary embolism. *Heart India*. 2021;9(3):169-173.
doi: 10.4103/heartindia.heartindia_96_21
27. Sekulic I, Dzudovic B, Matijasevic J, *et al*. Ultrasound assisted thrombolysis in intermediate-risk patients with pulmonary thromboembolism. *Acta Cardiol*. 2020;75(7):623-630.
doi: 10.1080/00015385.2019.1646850
28. Lin PH, Annambhotla S, Bechara CF, *et al*. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. *Vascular*. 2009;17(SUPPL. 3).
doi: 10.2310/6670.2009.00063
29. Macovei L, Presura RM, Magopet R, *et al*. Local Thrombolysis in High-Risk Pulmonary Embolism—13 Years Single-Center Experience. *Clin Appl Thromb/Hemost*. 2020;26.
doi: 10.1177/1076029620929764
30. Tran A, Toma C, Jaber W, *et al*. Cost-Comparison of Mechanical Thrombectomy and Catheter-Directed Thrombolysis in Intermediate-Risk Pulmonary Embolism. *J Soc Cardiovasc Angiogr Interv*. 2024;3(2).
doi: 10.1016/j.jscai.2023.101187
31. Monteleone P, Ahern R, Banerjee S, *et al*. Modern Treatment of Pulmonary Embolism (USCDT vs MT): Results From a Real-World, Big Data Analysis (REAL-PE). *J Soc Cardiovasc Angiogr Interv*. 2024;3(1).
doi: 10.1016/j.jscai.2023.101192
32. Feroze R, Arora S, Tashtish N, *et al*. Comparison of Large-Bore Thrombectomy With Catheter-Directed Thrombolysis for the Treatment of Pulmonary Embolism. *J Soc Cardiovasc Angiogr Interv*. 2023;2(1).
doi: 10.1016/j.jscai.2022.100453
33. Wahood W, Sista AK, Paul JD, Ahmed O. Unplanned 30-Day Readmissions after Management of Submassive and Massive Acute Pulmonary Embolism: Catheter-Directed versus Systemic Thrombolysis. *J Vasc Interv Radiol*. 2023;34(1):116-123.e14.
doi: 10.1016/j.jvir.2022.09.017
34. Graif A, Patel KD, Wimmer NJ, *et al*. Large-Bore Aspiration Thrombectomy versus Catheter-Directed Thrombolysis for Acute Pulmonary Embolism: A Propensity Score-Matched Comparison. *J Vasc Interv Radiol*. 2020;31(12):2052-2059.
doi: 10.1016/j.jvir.2020.08.028
35. Yoo JW, Choi HC, Lee SJ, Cho YJ, Lee JD, Kim HC. Comparison between systemic and catheter thrombolysis in patients with pulmonary embolism. *Am J Emerg Med*. 2016;34(6):985-988.
doi: 10.1016/j.ajem.2016.02.037
36. Cho YH, Sung K, Kim WS, *et al*. Management of acute massive pulmonary embolism: Is surgical embolectomy inferior to thrombolysis? *Int J Cardiol*. 2016;203:579-583.
doi: 10.1016/j.ijcard.2015.10.223
37. Beyer SE, Shanafelt C, Pinto DS, *et al*. Utilization and Outcomes of Thrombolytic Therapy for Acute Pulmonary Embolism: A Nationwide Cohort Study. *Chest*. 2020;157(3):645-653.
doi: 10.1016/j.chest.2019.10.049
38. Avgerinos ED, Abou Ali A, Toma C, *et al*. Catheter-directed thrombolysis versus suction thrombectomy in the management of acute pulmonary embolism. *J Vasc Surg Venous Lymphat Disord*. 2019;7(5):623-628.
doi: 10.1016/j.jvsv.2018.10.025
39. Avgerinos ED, Abou Ali AN, Liang NL, *et al*. Catheter-directed interventions compared with systemic thrombolysis achieve improved ventricular function recovery at a potentially lower complication rate for acute pulmonary embolism. *J Vasc Surg Venous Lymphat Disord*. 2018;6(4):425-432.
doi: 10.1016/j.jvsv.2017.12.058
40. Pietrasik A, Kurzyrna P, Szwed P, *et al*. Treatment of high- and intermediate-high-risk pulmonary embolism by the Pulmonary Embolism Response Team: Focus on catheter-directed therapies. *Cardiol J*. 2024;31(2):215-225.
doi: 10.5603/CJ.a2023.0047
41. Macovei L, Presura RM, Georgescu CA. Systemic or local thrombolysis in high-risk pulmonary embolism. *Cardiol J*. 2015;22(4):467-474.
doi: 10.5603/CJ.a2014.0103
42. Kolkailah AA, Hirji S, Piazza G, *et al*. Surgical pulmonary

- embolectomy and catheter-directed thrombolysis for treatment of submassive pulmonary embolism. *J Card Surg.* 2018;33(5):252-259.
doi: 10.1111/jocs.13576
43. Lin DSH, Lin YS, Wu CK, Lin HH, Lee JK. Midterm prognosis of patients with pulmonary embolism receiving catheter-directed thrombolysis or systemic thrombolysis: A nationwide population-based study. *J Am Heart Assoc.* 2021;10(7).
doi: 10.1161/JAHA.120.019296
44. Azari A, Beheshti AT, Moravvej Z, Bigdeli L, Salehi M. Surgical embolectomy versus thrombolytic therapy in the management of acute massive pulmonary embolism: Short and long-term prognosis. *Heart Lung J Acute Crit Care* 2015;44(4):335-339.
doi: 10.1016/j.hrtlng.2015.04.008
45. Klevanets J, Starodubtsev V, Ignatenko P, Voroshilina O, Ruzankin P, Karpenko A. Systemic Thrombolytic Therapy and Catheter-Directed Fragmentation with Local Thrombolytic Therapy in Patients with Pulmonary Embolism. *Ann Vasc Surg.* 2017;45:98-105.
doi: 10.1016/j.avsg.2017.05.003
46. Arora S, Panaich SS, Ainani N, *et al.* Comparison of In-Hospital Outcomes and Readmission Rates in Acute Pulmonary Embolism Between Systemic and Catheter-Directed Thrombolysis (from the National Readmission Database). *Am J Cardiol.* 2017;120(9):1653-1661.
doi: 10.1016/j.amjcard.2017.07.066
47. Geller BJ, Adusumalli S, Pugliese SC, *et al.* Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: A real-world analysis of national administrative claims. *Vasc Med.* 2020;25(4):334-340.
doi: 10.1177/1358863X20903371
48. Lehnert P, Möller CH, Mortensen J, Kjaergaard J, SkovOlsen P, Carlsen J. Surgical embolectomy compared to thrombolysis in acute pulmonary embolism: Morbidity and mortality. *Eur J Cardio-Thorac Surg.* 2017;51(2):354-361.
doi: 10.1093/ejcts/ezw297
49. Aymard T, Kadner A, Widmer A, Basciani R, Tevaearai H, Weber A, *et al.* Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy—should surgical indications be revisited? *Eur J Cardio-Thorac Surg.* 2012;43(1):90-94.
doi: 10.1093/ejcts/ezs123
50. Elheet A, Elhadidy AF, Farrag MH, *et al.* Ultrasound-Facilitated, Catheter-Directed Thrombolysis for Acute Pulmonary Embolism. *Cureus.* 2024;16(3): e57345.
doi: 10.7759/cureus.57345
51. Jiang C, Xie M. Clinical Outcomes of Intermediate-Risk Pulmonary Embolism Across a Northeastern Health System: A Multi-Center Retrospective Cohort Study. *Cureus.* 2021;13(6):e15888.
doi: 10.7759/cureus.15888
52. Guan Q, Liu C, Li W, *et al.* Comparison of therapeutic effect of catheter direct thrombolysis and peripheral venous thrombolysis on acute pulmonary embolism. *Medicine.* 2023;102(21):E33696.
doi: 10.1097/MD.00000000000033696
53. Al-Terki H, Lauder L, Mügge A, Göttinger F, Elhakim A, Mahfoud F. Ultrasound-assisted endovascular thrombolysis versus large-bore thrombectomy in acute intermediate-high risk pulmonary embolism: The propensity-matched EKNARI cohort study. *Catheter Cardiovasc Interv.* 2024;103(5):758-765.
doi: 10.1002/ccd.30998
54. Bradley M, Bull T, Hountras P, MacLaren R. Pragmatic Use of Catheter-Directed Thrombolysis in Venous Thromboembolism and a Comparative Evaluation With Traditional Therapies in Submassive Pulmonary Embolism. *J Pharm Pract.* 2022;35(5):738-746.
doi: 10.1177/08971900211004833
55. Hobohm L, Schmidt FP, Gori T, *et al.* In-hospital outcomes of catheter-directed thrombolysis in patients with pulmonary embolism. *Eur Heart J Acute Cardiovasc Care.* 2021;10(3):258-264.
doi: 10.1093/ehjacc/zuua026
56. Sharifi M, Awdisho A, Schroeder B, Jiménez J, Iyer P, Bay C. Retrospective comparison of ultrasound facilitated catheter-directed thrombolysis and systemically administered half-dose thrombolysis in treatment of pulmonary embolism. *Vasc Med.* 2019;24(2):103-109.
doi: 10.1177/1358863X18824159
57. Hassan AKM, Ahmed H, Ahmed Y, Elfadl AEA, Omar A. Efficacy and safety of hydro-mechanical defragmentation in intermediate- and high-risk pulmonary embolism. *Egypt Heart J.* 2021;73(1).
doi: 10.1186/s43044-021-00204-2
58. Kuebel D, Winter J, Martin L, *et al.* Systemic thrombolytic and ultrasound-assisted catheter-directed thrombolysis for treatment of acute pulmonary embolism: a 7-year, multicenter experience. *J Thromb Thrombolysis.* 2023;55(3):545-552.
doi: 10.1007/s11239-022-02760-z
59. Iskandar JP, Hariri E, Kanaan C, *et al.* The safety and efficacy of systemic versus catheter-based therapies: application of a prognostic model by a pulmonary embolism response team. *J Thromb Thrombolysis.* 2022;53(3):616-625.

- doi: 10.1007/s11239-021-02576-3
60. Gulba DC, Lichtlen P, Schmid C, Borst HG, Dietz R, Luft FC. Medical compared with surgical treatment for massive pulmonary embolism. *Lancet*. 1994;343(8897):576-577.
doi: 10.1016/S0140-6736(94)91523-7
 61. Rothschild DP, Goldstein JA, Ciacci J, Bowers TR. Ultrasound-accelerated thrombolysis (USAT) versus standard catheter-directed thrombolysis (CDT) for treatment of pulmonary embolism: A retrospective analysis. *Vasc Med*. 2019;24(3):234-240.
doi: 10.1177/1358863X19838350
 62. Rao G, Xu H, Wang JJ, *et al*. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute pulmonary embolism: A multicenter comparison of patient-centered outcomes. *Vasc Med*. 2019;24(3):241-247.
doi: 10.1177/1358863X19838334
 63. Shatla I, El Iskandarani M, Khan MZ, *et al*. Ultrasound-Assisted Versus Standard Catheter-Directed Thrombolysis for Acute Pulmonary Embolism: Insights From National Inpatient Sample. *J Soc Cardiovasc Angiogr Interv*. 2024;3(5).
doi: 10.1016/j.jscai.2024.101360
 64. Lee T, Itagaki S, Chiang YP, Egorova NN, Adams DH, Chikwe J. Survival and recurrence after acute pulmonary embolism treated with pulmonary embolectomy or thrombolysis in New York State, 1999 to 2013. *J Thorac Cardiovasc Surg*. 2018;155(3):1084-1090.e12.
doi: 10.1016/j.jtcvs.2017.07.074
 65. Percy ED, Shah R, Hirji S, *et al*. National Outcomes of Surgical Embolectomy for Acute Pulmonary Embolism. *Ann Thorac Surg*. 2020;110:441-447.
doi: 10.1016/j.athoracsur.2020.02.024
 66. Chan LTH, Wong CW, Lam H, Chan YH, Yan BPY, Tan GM. Outcomes of Catheter-Based Interventions for the Treatment of Intermediate to High-Risk Pulmonary Embolism in Patients With High Bleeding Risk: A Single-Centre Experience. *J Hong Kong Coll Cardiol*. 2023;30(3):6-11.
doi: 10.55503/2790-6744.1504
 67. Lin DSH, Lin YS, Lee JK, Chen WJ. Short- and Long-Term Outcomes of Catheter-Directed Thrombolysis versus Pulmonary Artery Embolectomy in Pulmonary Embolism: A National Population-Based Study. *J Endovasc Ther*. 2022;29(3):409-419.
doi: 10.1177/15266028211054763
 68. Krishnan AM, Gadela NV, Ramanathan R, Jha A, Perkins ME, Metersky ML. A Comparative Analysis of Catheter Directed Thrombolysis with Anticoagulation Alone or Systemic tPA in Acute Pulmonary Embolism with Cor Pulmonale. *J Intensive Care Med*. 2022;37(10):1336-1343.
doi: 10.1177/08850666221083241
 69. Weekes AJ, Trautmann A, Hambright PL, *et al*. Comparison of Treatment Approaches and Subsequent Outcomes within a Pulmonary Embolism Response Team Registry. *Crit Care Res Pract*. 2024;2024.
doi: 10.1155/2024/5590805
 70. Mahar JH, Haddadin I, Sadana D, *et al*. A pulmonary embolism response team (PERT) approach: initial experience from the Cleveland Clinic. *J Thromb Thrombolysis*. 2018;46(2):186-192.
doi: 10.1007/s11239-018-1686-2
 71. Sedhom R, Megaly M, Elbadawi A, *et al*. Contemporary National Trends and Outcomes of Pulmonary Embolism in the United States. *Am J Cardiol*. 2022;176:132-138.
doi: 10.1016/j.amjcard.2022.03.060
 72. Roy PM, Douillet D, Penaloza A. Contemporary management of acute pulmonary embolism. *Trends Cardiovasc Med*. 2022;32(5):259-268.
doi: 10.1016/j.tcm.2021.06.002
 73. Stewart LK, Kline JA. Fibrinolytics for the treatment of pulmonary embolism. *Transl Res*. 2020;225:82.
doi: 10.1016/J.TRSL.2020.05.003
 74. Lyhne MD, Kline JA, Nielsen-Kudsk JE, Andersen A. Pulmonary vasodilation in acute pulmonary embolism—a systematic review. *Pulm Circ*. 2020;10(1).
doi: 10.1177/2045894019899775
 75. Schultz J, Andersen A, Kabrhel C, Nielsen-Kudsk JE. Catheter-based therapies in acute pulmonary embolism. *EuroIntervention*. 2018;13(14):1721-1727.
doi: 10.4244/EIJ-D-17-00437
 76. Marti C, John G, Konstantinides S, *et al*. Systemic thrombolytic therapy for acute pulmonary embolism: A systematic review and meta-analysis. *Eur Heart J*. 2015;36(10):605-614.
doi: 10.1093/eurheartj/ehu218
 77. Mathew D, Seelam S, Bumrah K, Sherif A, Shrestha U. Systemic thrombolysis with newer thrombolytics vs anticoagulation in acute intermediate risk pulmonary embolism: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2023;23(1).
doi: 10.1186/s12872-023-03528-w
 78. Xu Q, Huang K, Zhai Z, Yang Y, Wang J, Wang C. Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: A meta-analysis. *J Thorac Dis*. 2015;7(5):810-821.
doi: 10.3978/j.issn.2072-1439.2015.04.51
 79. Su Y, Zou D, Liu Y, Wen C, Zhang X. Anticoagulant Impact on Clinical Outcomes of Pulmonary Embolism Compared

- With Thrombolytic Therapy; Meta-Analysis. *Clin Cardiol.* 2024;47(9).
doi: 10.1002/clc.70016
80. Sadeghipour P, Jenab Y, Moosavi J, *et al.* Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High-risk Pulmonary Embolism: The CANARY Randomized Clinical Trial. *JAMA Cardiol.* 2022;7(12):1189-1197.
doi: 10.1001/JAMACARDIO.2022.3591
 81. Kucher N, Boekstegers P, Müller OJ, *et al.* Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation.* 2014;129(4):479-486.
doi: 10.1161/CIRCULATIONAHA.113.005544
 82. Ishisaka Y, Watanabe A, Fujisaki T, *et al.* Comparison of interventions for intermediate to high-risk pulmonary embolism: A network meta-analysis. *Catheter Cardiovasc Interv.* 2023;102(2):249-265.
doi: 10.1002/CCD.30745
 83. Zhang RS, Maqsood MH, Sharp ASP, *et al.* Efficacy and Safety of Anticoagulation, Catheter-Directed Thrombolysis, or Systemic Thrombolysis in Acute Pulmonary Embolism. *JACC Cardiovasc Interv.* 2023;16(21):2644-2651.
doi: 10.1016/j.jcin.2023.07.042
 84. Mathew D, Kim J, Kosuru BP, *et al.* Mortality and bleeding associated with the management of sub-massive pulmonary embolism: a systematic review and Bayesian network meta-analysis. *Sci Rep.* 2023;13(1).
doi: 10.1038/s41598-023-34348-9
 85. Bruno ES, Mujer MTP, Desai P V., Brailovsky Y, Darki A. A Meta-analysis of Standard Versus Ultrasound-Assisted Catheter-Directed Thrombolysis in the Management of Acute Pulmonary Embolism. *J Soc Cardiovasc Angiogr Interv.* 2023;2(1).
doi: 10.1016/j.jscai.2022.100514
 86. Jaber WA, Gonsalves CF, Stortecky S, *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.* 2024;151:260-273.
doi: 10.1161/CIRCULATIONAHA.124.072364/FORMAT/EPUB
 87. Winters AA, McDaniel MJ, Binongo JN, *et al.* A comparison of surgical pulmonary embolectomy and catheter-directed lysis for life-threatening pulmonary emboli. *Interact Cardiovasc Thorac Surg.* 2020;30(3):388-393.
doi: 10.1093/icvts/ivz288
 88. Sanchez O, Charles-Nelson A, Ageno W, *et al.* Reduced-Dose Intravenous Thrombolysis for Acute Intermediate-High-risk Pulmonary Embolism: Rationale and Design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial. *Thromb Haemost.* 2021;122(05):857-866.
doi: 10.1055/a-1653-4699
 89. Klok FA, Piazza G, Sharp ASP, *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;251:43-53.
doi: 10.1016/J.AHJ.2022.05.011
 90. Giri J, Mahfoud F, Gebauer B, *et al.* PEERLESS II: A Randomized Controlled Trial of Large-Bore Thrombectomy Versus Anticoagulation in Intermediate-Risk Pulmonary Embolism. *J Soc Cardiovasc Angiogr Interv.* 2024;3(6):101982.
doi: 10.1016/j.jscai.2024.101982
 91. Sista AK, Troxel AB, Tarpey T, *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;281:112-122.
doi: 10.1016/J.AHJ.2024.11.016
 92. Kjærgaard J, Carlsen J, Sonne-Holm E, *et al.* A randomized trial of low-dose thrombolysis, ultrasound-assisted thrombolysis, or heparin for intermediate-high risk pulmonary embolism-the STRATIFY trial: design and statistical analysis plan. *Trials.* 2024;25(1).
doi: 10.1186/S13063-024-08688-4
 93. Rosovsky RP, Konstantinides S V., Moriarty JM, *et al.* A prospective, multicenter, randomized controlled trial evaluating anticoagulation alone vs anticoagulation plus computer assisted vacuum thrombectomy for the treatment of intermediate-high-risk acute pulmonary embolism: Rationale and design of the STORM-PE study. *Am Heart J.* 2025.
doi: 10.1016/J.AHJ.2025.03.018