

## Critical Review Form

### Meta-analysis

[Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014 Jun.](#)

**Objectives:** "to ascertain associations of thrombolytic therapy with bleeding risk and potential mortality benefits, with special attention paid to the subpopulation of patients presenting with intermediate-risk PE." (p. 2415)

**Methods:** This systematic review and meta-analysis was performed according to the [PRISMA \(Preferred Reporting Items for Systematic reviews and Meta-Analyses\) statement](#). Two authors searched PubMed, the Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases from inception through April 10, 2014, without language restriction. Randomized controlled trials (RCTs) comparing thrombolytic therapy with a control (unfractionated heparin, low-molecular weight heparin [LMWH], vitamin K antagonist, or fondaparinux), and evaluating mortality outcomes were eligible for inclusion.

Two reviewers independently extracted data using a standardized protocol. Risk of bias was assessed according to the [Cochrane Handbook of Systematic Reviews](#). The primary efficacy outcome was all-cause mortality, and the primary safety outcome was major bleeding. Secondary outcomes included risk of recurrent PE and intracranial hemorrhage (ICH). Trial patients were individually classified into one of the following groups:

1. **Low-risk:** hemodynamically stable without evidence of right ventricular dysfunction.
2. **Intermediate-risk:** hemodynamically stable with evidence of RV dysfunction diagnosed by ECHO or abnormalities of cardiac biomarkers (troponin/BNP).
3. **High-risk:** hemodynamically unstable (systolic blood pressure [SBP] < 90 mm Hg).
4. **Unclassifiable** due to lack of patient information.

Out of 72 potentially eligible RCTs, 16 met inclusion criteria, with a total of 2115 patients. Of these, 210 patients (9.93%) had low-risk PE, 1499 (70.87%) had intermediate-risk PE, 31 (1.47%) had high-risk PE, and 385 (18.20%) were unclassifiable. Pre-specified subgroup analyses were performed as follows: mortality and major bleeding were evaluated in 8 studies that assessed thrombolytic therapy in hemodynamically stable patients with

objective evidence of RV dysfunction required for inclusion; the primary outcomes were assessed in studies published after 2009; an exploratory analysis was performed using trials with a mean age in the thrombolytic group > 65 years. Additionally, a net clinical benefit analysis was performed, in which the short-term risk of ICH (Ti) induced by thrombolytic therapy (multiplied by a weighting factor of 0.75) was subtracted from the short-term mortality (Tm) prevented by thrombolytic therapy.

Guide	Question	Comments
I	<i>Are the results valid?</i>	
1.	Did the review explicitly address a sensible question?	Yes. The authors wished to assess the bleeding risk and mortality benefit of thrombolytic therapy in patients with intermediate-risk PE.
2.	Was the search for relevant studies details and exhaustive?	Yes. "Two authors (S.C., J.G.) identified the relevant articles by searching the following data sources: PubMed, the Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases (from inception through April 10, 2014), without language restrictions." (p. 2415)
3.	Were the primary studies of high methodological quality?	Yes. The results of this assessment are reported in the online supplementary content. Errors in this assessment can be noted, principally that in the MOPETT trial, participants and personnel were not blinded as stated.
4.	Were the assessments of the included studies reproducible?	The authors state "risk of bias was assessed for the domains suggested by the Cochrane Handbook of Systematic Reviews, specifically emphasizing sequence generation, allocation concealment, blinding, outcomes assessment, and selective reporting." (2415) The results of this assessment are reported in the online supplementary content.
II.	<i>What are the results?</i>	
1.	What are the overall results of the study?	<ul style="list-style-type: none"> <li>• Mortality was lower in the thrombolytic group compared to the anticoagulant group (2.17% [23/1061] vs. 3.89% [41/1054]), with an odds ratio (OR) of 0.53 (95% CI 0.32-0.88) and a number needed to treat (NNT) of 59 (95% CI 31-380).</li> <li>• The rate of major bleeding was higher in the thrombolytic group compared to the anticoagulant group (9.24% vs. 3.42%) with an OR of 2.73 (95% CI 1.91-3.91) and a number needed to harm (NNH) of 18 (95% CI 13-27).</li> <li>• Thrombolysis demonstrated an association with a greater ICH rate (1.46% vs. 0.19%) with an OR of 4.63 (95% CI 1.78-12.04) and a NNH of 78 (95% CI 48-206)</li> <li>• The risk of recurrent PE was lower in the thrombolytic group (1.17% vs. 3.04%) with an OR of 0.40 (95% CI 0.22- 0.74) and a NNT of 54.</li> </ul>

		<ul style="list-style-type: none"> <li>For the 8 trials (n = 1775) specifically enrolling only patients who were hemodynamically stable with objective assessments of RV function, thrombolysis was associated with lower mortality (OR 0.48; 95% CI 0.25-0.92), as well as higher rates of major bleeding (OR 3.19, 95% CI 2.07-4.92). These results yield a NNT of 65 and NNH of 18.</li> <li>For patients &gt; 65 years old, there was a nonsignificant decrease in mortality (OR 0.55; 95% CI 0.29-1.05) and an increased risk of major bleeding (OR, 3.10; 95% CI 2.10-4.56).</li> </ul>
2.	How precise are the results?	See above.
3.	Were the results similar from study to study?	Yes. "All outcomes were associated with negligible heterogeneity ( $I^2 < 25\%$ )." (p. 2416)
<b>III.</b>	<b><i>Will the results help me in caring for my patients?</i></b>	
1.	How can I best interpret the results to apply them to the care of my patients?	These data suggest that the use of thrombolytics in pulmonary embolism reduces mortality, while also increasing the risk of bleeding complications. The vast majority of patients included were classified as either intermediate or high-risk, and the results should only be applied to these subgroups. Caution should be used when applying these results to those over age 65, as the reduction in mortality did not achieve statistical significance in this subgroup, while a significant increase in bleeding risk was observed. When only studies specifically evaluating patients who were hemodynamically stable with objective evidence of RV dysfunction (i.e. "submassive PE" were included, analysis demonstrated a significant reduction in mortality (NNT 65), as well as an increase in risk of major bleeding (NNH 18).
2.	Were all patient important outcomes considered?	No. The authors were not able to evaluate other important long-term outcomes, such as functional capacity and quality of life.
3.	Are the benefits worth the costs and potential risks?	Uncertain. In patients with intermediate-risk PE, thrombolytic therapy demonstrated a small but statistically significant decrease in the risk of mortality (NNT 65), balanced by a much larger increase in the risk of major bleeding (NNH 18). Given the significant clinical heterogeneity inherent to these studies (different types and doses of thrombolytic, different modes of thrombolytic administration, different criteria for diagnosis of "intermediate-risk", poorly defined and differing criteria for

		<p>“major bleeding”), it is difficult to draw any firm conclusions. A careful discussion with patient and family will need to occur on a case by case basis in order to include patients’ values in the decision of whether to administer thrombolytics or anticoagulants alone.</p>
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**Limitations:**

1. Significant [clinical heterogeneity](#) for the included studies:
  - a. Different inclusion criteria were used resulting in different levels of risk
  - b. Follow-up duration for mortality differed significantly among studies
  - c. Different dosages and methods of delivery of thrombolytics were used (including catheter-directed delivery in one study).
  - d. Different thrombolytic drugs were used in different studies.
  - e. Definitions for hemodynamic instability or shock, major bleeding, and minor bleeding were not standardized.
2. Many of the included studies did not define major bleeding.
3. The results of the meta-analysis were driven largely by the results of a single study ([PEITHO](#)) that comprised nearly half of the patients in the overall meta-analysis and nearly 60% of the “intermediate-risk” patients.
4. Despite improved mortality, this meta-analysis was unable to assess functional outcomes, which would be particularly important for those patients with intracranial hemorrhage from thrombolytic administration.

**Bottom Line:**

This meta-analysis of thrombolytics for PE demonstrated an improvement in mortality, with a NNT of 59 for all patients. This mortality benefit was balanced by an increased risk of major bleeding, with a NNH of 18. Specifically, for patients with “intermediate-risk” PE, the mortality benefit was slightly smaller (NNT 65) while the risk of major bleeding was the same (NNH 18). The degree of heterogeneity in the included studies, poorly defined criteria for “intermediate-risk,” and poorly defined criteria for “major bleeding” limit our ability to draw firm conclusions from the meta-analysis.