Critical Review Form
Meta-analysis

Thrombolysis Compared With Heparin for the Initial Treatment of Pulmonary Embolism: A Meta-Analysis of the Randomized Controlled Trials
Circ 2004; 110:744-749

Objective: **"To further clarity the role of thrombolysis for the treatment of pulmonary embolism". (p. 744)**

Methods: **The authors conduced an electronic search of MEDLINE and EMBAE (January 1980 to January 2003), and the Cochrane library using the following search terms: pulmonary embolism, thromboembolism, thrombolysis, fibrinolysis, randomized controlled trial, controlled clinical trial, and random "in conjunction with generic and trade names of individual thrombolytic agents" (p. 745). Additionally, they hand-searched journal article bibliographies and abstracts from major international meetings.**

Studies were included if they had proper randomization, included patients with objectively diagnosed symptomatic PE, compared thrombolysis to heparin alone, and used objective outcome measures for recurrent PE, death, and bleeding. Study quality was assessed using the Schulz method that included proper generation of treatment allocation sequence, concealment of allocation sequence, blinding of patient and investigator assessing clinical outcomes, and completeness of follow-up.

Two investigators abstracted individual study data on efficacy and safety outcomes for up to 30-days post- randomization including recurrent PE, death, major bleeding, non-major bleeding and intracranial hemorrhage. The primary outcome was the composite of recurrent PE or death. Secondary outcomes included hemorrhagic complications.

Meta-analysis was conducted using a fixed-effects model although the authors report a random-effects model that did not differ significantly and which they do not detail. They assessed for publication bias using a funnel plot and for heterogeneity using only χ^2 (Cochrane's Q). They conducted a sensitivity analysis by removing each of the 11,

including studies sequentially and re-analyzing the fixed effects model for any significant change.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes does thrombolytic therapy augment heparin alone in the acute treatment of unselected PE patients.
2.	Was the search for relevant studies details and exhaustive?	Yes. MEDLINE and EMBASE in addition to the Cochrane library and a hand search of bibliographies and abstracts.
3.	Were the primary studies of high methodological quality?	Uncertain. The meta-analysis authors used an atypical quality metric rather than the better accepted Jadad scale. Nonetheless, "reporting of study quality data was incomplete" and "the number of patients lost to follow-up was not reported in any of the trials". (p. 745)
4.	Were the assessments of the included studies reproducible?	Uncertain since the authors did not use a validated quality metric like the Jadad scale that has demonstrated reproducibility. Furthermore, the authors do not report the proportion of study quality rating disagreements or the raw results for their Schulz scores.

<table>
<tr><th>II.</th><th>What are the results?</th><th></th></tr>
<tr><td>1.</td><td>What are the overall results of the study?</td><td>

Authors identified 700 potentially eligible citations but ultimately excluded all but 11, of which five included subjects with hemodynamic instability.
7/11 included studies suggested a non-statistically significant reduction in recurrent PE or death with thrombolysis (Fig 2, p 746) but the meta-analysis of 374 subjects in each arm) did not demonstrate a significant reduction in these events (below)

<table>
<tr><th>Event</th><th>Thrombolysis (%)</th><th>Heparin (%)</th><th>OR</th><th>χ^2</th></tr>
<tr><td>Recurrent PE or death</td><td>25/374 (6.7)</td><td>36/374 (9.7)</td><td>0.67(0.4-1.12)</td><td>0.48</td></tr>
<tr><td>Recurrent PE</td><td>10/374 (2.7)</td><td>16/374 (4.3)</td><td>0.67 (0.33-1.37)</td><td>1.0</td></tr>
<tr><td>Death</td><td>16/374 (4.3)</td><td>22/374 (5.9)</td><td>0.70 (0.37-1.30)</td><td>0.72</td></tr>
</table>

Subgroup analysis of the five trials enrolling a portion of hemodynamically unstable patients (5 trials) demonstrated a significant benefit for thrombolysis to prevent the primary outcome (9.4% vs. 19%, OR 0.45 95% CI 0.22-0.92, NNT = 10) without benefit in the other six trials (OR 1.07, 95% CI 0.50-2.30).
Pooled data demonstrated significantly increased non-major bleeding risk (below) with NNH= 8:

<table>
<tr><th>Event</th><th>Thrombolysis (%)</th><th>Heparin (%)</th><th>OR 95% CI</th><th>χ^2</th></tr>
<tr><td>Major bleeding</td><td>34/374 (9.1)</td><td>23/374 (6.1)</td><td>1.42(0.81-2.46)</td><td>0.92</td></tr>
<tr><td>Non-major bleeding</td><td>53/233 (22.7)</td><td>22/221 (1.0)</td><td>2.63 (1.53-4.54)</td><td>1.53</td></tr>
<tr><td>Intracranial hemorrhage</td><td>2/374 (0.5)</td><td>1/374 (0.3)</td><td>1.04 (0.36-3.04)</td><td>1.00</td></tr>
</table>

Sensitivity analysis did not significantly alter the primary outcome.
Funnel plot (Fig 3, p. 748) did not demonstrate evidence of publication bias.

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<tr><td>2.</td><td>How precise are the results?</td><td>See 95% CI’s above</td></tr>
</table>

3.	Were the results similar from study to study?	Although most of the χ^2 heterogeneity assessments are above the a priori defined p-value of 0.10 (i.e., not significant), the Cochrane's Q-test (χ^2) is underpowered to detect heterogeneity and ought to be coupled with I^2 which is more sensitive for heterogeneity (defined as $I^2 > 25\%$ where $I^2 = Q\text{-}df/Q$). Another way to assess heterogeneity is to visually inspect the Forest Plot (Fig 2, p 746) for qualitative (i.e. point estimate benefit vs. no benefit for individual trials) and quantitative (i.e. 95% CI's between trials do not overlap) differences. When one does so with this meta-analysis it does appear that there is heterogeneity and it would have been useful to include an I^2 value.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	Patients with PE and hemodynamic instability benefit from thrombolytic therapy, plus heparin compared with heparin alone as manifest by decreased recurrent PE or death (NNT = 10). Unfortunately, we do not know which proportion of patients in these five trials had hemodynamic instability or the NNH in this subset. Among unselected PE patients there is no evidence of benefit for thrombolytics and the NNH = 8.
2.	Were all patient important outcomes considered?	No assessment of recovery times or hospital length of stay. Also "non-major bleed" is poorly defined.
3.	Are the benefits worth the costs and potential risks?	No, not based on this meta-analysis although "the present meta-analysis has limited statistical power to reliably detect clinically worthwhile differences between thrombolytic therapy and heparin or among thrombolytic agents". (p 748)

Limitations

1) **No I^2 heterogeneity assessment.**

2) **No reference do or use of QUADROM.**

3) **No reporting of study quality assessment inter-rater reliability or use of validated metric like the Jadad scale.**

4) **No reporting of NNH for hemodynamically unstable subset.**

Bottom Line

There is insufficient evidence to support thrombolysis in addition to heparin for unselected PE patients. However, hemodynamically unstable PE patients have a significant benefit with thrombolysis with NNT = 10 to prevent recurrent PE or death at 30-days. Further research is needed to better understand the NNH for massive PE thrombolysis and the potential role of thrombolytics in well-defined submassive PE since some trials have demonstrated improved outcomes.