Critical Review Form
Meta-analysis

Thrombolytic therapy for pulmonary embolism, Cochrane Database Syst Review 2006; Issue 2. Art No.: CD004437. DOI: 10.1002/14651858. CD004437 pub 2

Objective: **"To assess the effectiveness and safety of thrombolytic therapy in patients with acute massive pulmonary embolism". (p. 3)**

Methods: **Authors searched for RCT's comparing thrombolytics to heparin via an electronic search (through 2006) of CENTRAL, Cochrane library, MEDLINE, EMBASE, Both Information Database Service, CINAHL, LILACS, and SCISEARCH. Additionally, authors checked reference lists of primary studies, review articles and text books. They contacted primary study investigators and industry to identify unpublished research. They applied no language or data of publication restrictions.**

Quality was assessed by method of Jadad and Schulz . Primary outcomes were analyzed by intention-to-treat and included all-course mortality, survival time, PE recurrence, and hemorrhagic events. They also sought QOL and healthcare cost comparisons of thrombolytic and heparin to heparin alone.

Heterogeneity was assessed with χ^2 and I^2. When significant heterogeneity (as defined by χ^2 $p > 0.10$ or $I^2 > 50\%$) was identified a random-effects model was used for pooled data.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Compared with heparin alone for PE can thrombolytics reduce mortality, recurrent PE's, or speed radiological resolution without significantly increasing bleeding risks?
2.	Was the search for relevant studies details and exhaustive?	Yes. (see above)

3.	Were the primary studies of high methodological quality?	Yes. "Five of the eight trials had well reported methodological quality and were classified as category A….three were classified as category B". (p 5)
4.	Were the assessments of the included studies reproducible?	Although the authors do not report any rating reliability assessment, they used the Jadad score which is a valid, reliable RCT quality metric.
II.	***What are the results?***	

1.	What are the overall results of the study?	• Eight trials of 679 participants were included in this meta-analysis.
		• None of the trials assessed quality of life or healthcare costs.
		• Thrombolytics did not reduce mortality (8 trials): OR 0.89, 95% CI 0.45-1.78, I^2 = 0%.
		• Ratio of recurrent PE was not reduced (5 trials): OR 0.63; 95% CI 0.33-1.20, I^2 = 0%.
		• Major bleeding complications were not increased (8 trials): OR 1.61; 95% CI 0.91-2.86, I^2= 0%.
		• Minor bleeding complications showed a non-significant trend towards increased bleeding with thrombolytics with significant heterogeneity (5 trials): OR 1.98; 95% CI 0.68 – 5.75, I^2 = 57%.
		• Only one trial (Konstantinides - see PGY-II critical appraisal) assessed escalation of therapy and that trial favored thrombolytics.
		• Thrombolytics may (or may not) also improve:
		  ○ Pulmonary arterial systolic pressure (urokinase WMD -4.4mmHg 95% CI -4.6 to 4.2 and streptokinase -11.6 mmHg 95% CI -20.8 to 2.4).
		  ○ Mean pulmonary arterial pressure = streptokinase (WMD – 4.4 mmHg) or urokinase (WMD -4.6 mmHg) but not t-PA.
		  ○ Urokinase improves pulmonary resistance (WMD -0.33 dyne.s.cm^{-5} 95% CI-0.35 to -0.31 @ 24 hours more than streptokinase or rt-PA.
		  ○ Lung perfusion @ 30-days (rt-PA WMD --2.80, 95% CI 0.35 to 5.25) while streptokinase improves 72h pulmonary angiograms (WMD -10.5; 95% CI -15.3 to -57).

2.	How precise are the results?	See 95% CI above.

3.	Were the results similar from study to study?	No. The eight studies used different inclusion/exclusion criteria, represented heterogeneous geographic (and likely clinical practice) locales, and used different thrombolytic agents. In addition, the criterion standards for diagnosing PE and recognizing post-treatment outcomes varied. Not surprisingly the results varied from study-to-study as demonstrated by the various Forest plots.
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?	"The currently available evidence is insufficient to show any definite benefit of thrombolytics over heparin in the treatment of acute pulmonary embolism". (p 9)
2.	Were all patient important outcomes considered?	No assessment of QOL or healthcare costs.
3.	Are the benefits worth the costs and potential risks?	No. Currently evidence is insufficient to recommend thrombolytic therapy for acute PE.

Limitations

1) **No subgroup analysis of massive vs. submassive vs. sub-sub-massive PE patients.**

2) **No assessment of publication bias.**

Bottom Line

Currently available evidence does not support using thrombolytics in acute PE patients since mortality is not reduced and hemodynamic improvements (which vary by thrombolytic agent) have not been correlated with other patient – important outcomes (symptomatic resolution, hospital LOS, healthcare costs, QOL, etc.).