Are Recanalization Interventions Effective and Safe in the Treatment of Acute Pulmonary Embolism?

TAKE-HOME MESSAGE

None of the studied recanalization interventions (full-dose thrombolysis, reduced-dose thrombolysis, and catheter-directed thrombolysis) improve all-cause mortality for patients with acute pulmonary embolism compared with standard anticoagulation; full-dose thrombolysis demonstrates increased risk of major bleeding compared with reduced-dose thrombolysis.

METHODS

DATA SOURCES

Authors identified randomized controlled trials from the Cochrane Library, PubMed, EMBASE, EBSCO, Web of Science, and Cumulative Index of Nursing and Allied Health from database inception to July 2015, using the following search string: (1) pulmonary embolus; (2) thrombolysis OR thrombolytic therapy OR streptokinase OR urokinase OR tenecteplase OR alteplase OR desmoteplase OR tissue plasminogen activator OR clot-dissolving medication; and (3) search strings 1 AND 2. Authors also searched references of relevant articles, conference abstracts, and ClinicalTrials.gov and contacted experts for additional trials.

STUDY SELECTION

One author performed the search and screening of potential articles for initial consideration. Two authors independently reviewed studies for meta-analysis inclusion. Authors included randomized controlled trials reporting mortality outcomes of adults with acute symptomatic pulmonary embolism

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This review does not reflect the views or opinions of the US government, Department of Defense or its components, US Army, US Air Force, or SAUSHEC EM Residency Program.

Editor'*Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.*

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Jimenez D, Martin-Saborido C, Muriel A, et al. Efficacy and safety outcomes of recanalization procedures in patients with acute symptomatic pulmonary embolism: systematic review and network meta-analysis. *Thorax.* 2018;73:464-471.**

Results

Network meta-analysis outcomes for recanalization interventions.

Direct Head-to-head Comparison	No. of Trials (No. of Patients)	All-Cause Mortality, OR (95% CI)	Major Bleeding, OR (95% CI)
Full- vs reduced-dose thrombolysis	4 (298)	1.28 (0.40–4.12)	2.22 (0.71–6.89)
Full-dose vs catheter-directed thrombolysis	—*	1.93 (0.07–51.33)	2.07 (0.03–126.08)
Full-dose thrombolysis vs anticoagulation alone	16 (2,016)	0.60 (0.36–1.01)	2.00 (1.06–3.78)†
Reduced-dose vs catheter-directed thrombolysis	—*	1.50 (0.05–47.94)	0.93 (0.01–65.65)
Reduced-dose thrombolysis vs anticoagulation alone	1 (121)	0.47 (0.14–1.59)	0.90 (0.25–3.21)
Catheter-directed thrombolysis vs anticoagulation alone	1 (59)	0.31 (0.01–7.96)	0.97 (0.02–56.03)

OR, Odds ratio.

*No head-to-head comparison was conducted based on available studies. These comparisons were indirect.
†Significant associations.

who received diagnoses through conventional imaging modalities and also received anticoagulant therapy. The intervention consisted of recanalization with full-dose thrombolysis, reduced-dose thrombolysis, or catheter-directed thrombolysis, whereas the comparator was either treatment with a different recanalization procedure or no recanalization procedure.

DATA EXTRACTION AND SYNTHESIS

Two authors independently extracted data from included studies and resolved discrepancies by consensus. Primary outcomes included all-cause mortality and major bleeding, whereas secondary outcomes included risk of intracranial hemorrhage and recurrent embolism. Authors abstracted these outcomes according to the intention-to-treat population for the individual trials, calculated pooled odds ratios and 95% confidence intervals (CIs), and assessed outcomes according to the time identified as the primary outcome for the endpoint in each trial. Authors assessed heterogeneity with the estimated between-study variance (τ^2), Cochran χ^2 test, and the I^2 statistic and risk of bias based on the *Cochrane Handbook for Systematic Reviews of Interventions*.[1] Because of the limited number of trials directly comparing recanalization interventions, authors performed a network meta-analysis, including randomized controlled trials comparing different therapies with another common treatment.

Authors included 22 randomized controlled trials comprising 2,494 patients for analysis from 930 citations retrieved from the initial literature search. Sixteen trials compared full-dose thrombolysis with anticoagulation alone (2,016 patients), 1 compared reduced-dose thrombolysis with anticoagulation alone (121 patients), 1 compared ultrasonographically assisted catheter-directed thrombolysis with anticoagulation alone (59 patients), and 4 compared full-dose thrombolysis with reduced-dose thrombolysis (298 patients). Mean age of included patients ranged from 48.7 to 69 years, and sex ranged from 22.4% to 63% men. The time horizons for primary outcome measurements ranged from 1 to 840 days. Eight trials included high-risk pulmonary embolism patients. Network meta-analysis found no reduction in all-cause mortality for full-dose thrombolysis, reduced-dose thrombolysis, and catheter-directed thrombolytics (Table). Full-dose thrombolysis increased major bleeding compared with anticoagulation (odds ratio 2.00; 95% CI 1.06 to 3.78). Sensitivity analysis demonstrated similar outcomes. Most of the included trials were at low risk of bias, except for allocation concealment and blinding. However, several trials did not report details for randomization. No evidence of publication bias was present.

Commentary

Most patients with acute pulmonary embolism tolerate treatment with standard anticoagulation well. Nevertheless, mortality can be significant, reaching 15% in some patient populations.[2,3] Treatment most commonly includes anticoagulation alone for hemodynamically stable patients with no evidence of right-sided heart strain.[3,4] Full-dose thrombolysis may be beneficial in hemodynamically unstable patients with pulmonary embolism, but this therapy increases the risk of major bleeding.[4-6] Reduced-dose thrombolysis and catheter-directed thrombolysis may decrease this risk of bleeding.[4] This network meta-analysis sought to assess the primary outcomes of all-cause mortality and risk of major bleeding and secondary outcomes of intracranial hemorrhage and risk of recurrent embolism when comparing alternative recanalization interventions with one another and anticoagulation in patients with acute pulmonary embolism.[7]

A traditional meta-analysis pools data from multiple studies making direct comparisons between the same 2 interventions. A network meta-analysis differs in that it uses data from studies comparing multiple different interventions. Network meta-analyses then use these data to build networks making both direct comparisons of interventions within trials and indirect comparisons across trials. Indirect evidence compares 2 or more interventions by using data from multiple studies comparing those interventions with a common comparator.[8,9] Network meta-analyses require advanced statistical methodology, which can make transparency for critical appraisal and interpretation challenging for many readers.[8,9] Furthermore, the indirect comparisons by network meta-analysis require the assumption that all included studies are equally applicable to the populations and contexts of the other studies included in the network. Adopting a network meta-analysis framework allowed the authors of this meta-analysis to compare each pair of interventions, even when the number of patients informing

direct comparisons between each pair of interventions was small or nonexistent.[7]

In contrast to this article, several previous pairwise meta-analyses demonstrated decreased mortality with full-dose thrombolysis.[10,11] We believe the difference in findings by the present article is due to multiple factors, including different methodological and statistical techniques including network meta-analysis.[10,11] This network meta-analysis found that full-dose, reduced-dose, and catheter-directed thrombolysis did not decrease all-cause mortality compared with anticoagulation alone,[7] likely because of lack of statistical power and presence of wide CIs. The risk of major bleeding with full-dose thrombolytics was greater in pairwise meta-analysis, likely because of the significant amount of between-study variation found in the indirect comparisons used in the analysis.

Limitations of the data analyzed by this meta-analysis included a paucity of direct head-to-head comparisons of many treatment modalities. In particular, direct comparisons of full-dose versus catheter-directed thrombolysis and reduced-dose versus catheter-directed thrombolysis were not available. Although the use of a network meta-analysis framework helped to circumvent this limitation, this analytic strategy does not obviate the need for further high-quality randomized controlled trials directly comparing alternative recanalization strategies. Indirect comparisons using network meta-analysis methodology carry the risk of imbalance in treatment and control groups.[8,9] Most studies assessed full-dose thrombolysis, with very few assessing reduced-dose or catheter-directed thrombolysis, resulting in small sample sizes and wide CIs for comparisons including these interventions.

Other limitations concern separate components of the meta-analysis. One author performed all initial screening. Only 8 trials included patients with high-risk pulmonary embolism, with no mention of intermediate-risk pulmonary embolism (evidence of right-sided heart strain but hemodynamically stable), making it difficult to conduct subgroup analyses stratified by disease severity. Significant heterogeneity was present in regard to included patients, specific interventions, and trial outcomes (including assessment during variable periods) across the included studies, limiting randomized controlled trial comparability and calling into question the utility of the indirect comparisons performed by network meta-analysis methodology. Several studies did not report details on randomization, increasing the risk of selection bias. Poor reporting in regard to allocation concealment and blinding also increased the risk of performance bias. Authors also did not describe how they resolved discrepancies in assessment of risk of bias. Finally, included studies demonstrated inconsistent estimates of treatment efficacy, which may be due in part to a so-called cohort effect reflecting variations in treatments and study methodologies of older randomized controlled trials.[12]

Results suggest no one recanalization intervention is superior in reducing all-cause mortality, whereas full-dose thrombolytics increase risk of major bleeding. Reduced-dose and catheter-directed thrombolysis may optimize patient outcomes while minimizing the risk of bleeding, although there are few data comparing these interventions with full-dose thrombolysis, and the present meta-analysis did not conclude that these strategies are superior to anticoagulation alone. Further randomized controlled trial data comparing these interventions with anticoagulation alone and full-dose thrombolysis alone are necessary, particularly among patients with intermediate- to high-risk pulmonary embolism.

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