

TAKE-HOME MESSAGE

In patients with ST-segment elevation myocardial infarction (STEMI), when percutaneous coronary intervention is not an option, reperfusion therapy with the fibrinolytic agents tenecteplase, reteplase, or accelerated alteplase (90 minutes of infusion) plus parenteral anticoagulation has better overall safety and efficacy than other regimens.

METHODS**DATA SOURCE**

The authors searched PubMed, EMBASE, the Cochrane Library, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform from inception to February 28, 2017.

STUDY SELECTION

Randomized controlled trials comparing fibrinolytic agents with an approved indication of reperfusion therapy in adults with STEMI, whether administered alone or in combination with adjunctive anticoagulant therapy, were included. Studies assessing primary or facilitated percutaneous intervention versus fibrinolytics were excluded. Primary outcomes included all-cause mortality within 30 to 35 days (efficacy) and major bleeding (safety).

DATA EXTRACTION AND SYNTHESIS

Two authors independently screened studies for inclusion and extracted data, which was cross-checked by 2 independent reviewers. Discrepancies were resolved by consensus. Study bias was assessed with the Cochrane Collaboration's risk-of-bias tool. A conventional meta-analysis was performed by using a random-effects model.

In Patients With ST-Segment Elevation Myocardial Infarction, Which Fibrinolytic Agent Is the Safest and Most Effective?**EBEM Commentators**

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Results

Selected network meta-analysis results for efficacy and safety of fibrinolytic regimens.*

Fibrinolytic Regimen	All-Cause Mortality Within 30 to 35 Days, RR (95% CI)	Major Bleeding, RR (95% CI)
Acc tPA+PAC	1.0 [Reference]	1.0 [Reference]
TNK+PAC	1.01 (0.90–1.13)	0.79 (0.63–1.00)
rPA+PAC	1.04 (0.94–1.15)	0.88 (0.69–1.12)
SK+PAC	1.14 (1.05–1.24)	0.92 (0.70–1.21)
tPA+PAC	1.26 (1.10–1.45)	0.63 (0.44–0.92)

RR, Relative risk; CI, confidence interval; Acc tPA, accelerated alteplase infusion during 90 minutes (guideline recommended); PAC, parenteral anticoagulants; TNK, tenecteplase; rPA, reteplase; SK, streptokinase; tPA, nonaccelerated alteplase infusion during 3 hours.

*RR greater than 1.0 tends toward more deaths and bleeding.

Forty studies met inclusion criteria, involving 128,071 STEMI patients treated with 12 fibrinolytic regimens. Four fibrinolytic agents (streptokinase, reteplase, tenecteplase, and alteplase at 2 separate dosing regimens) were compared as reperfusion

therapy alone or in combination with antithrombotic agents, including parenteral anticoagulants (ie, low-molecular-weight heparin, heparin, anti-Xa inhibitor, and direct thrombin inhibitor) or glycoprotein IIb or IIIa inhibitors (ie, abciximab, tirofiban, or

Heterogeneity was determined with the Cochran Q test and I^2 statistic. A network meta-analysis with consistency model compared intervention data. Evidence quality was assessed with the Grading of Recommendations Assessment, Development and Evaluation.

eptifibatide) (Table). Thirty-six trials specified that aspirin was a part of therapy. Thirty-nine studies assessed all-cause mortality and 32 reported major bleeding. In terms of bias, 27 studies had an unclear risk bias, with 13 having high risk of bias at least 1 category of masking of participants or personnel (6 studies), masking of outcome assessments (1 study), selective outcome reporting (2 studies), and other bias (6 studies).

Commentary

Timely reperfusion therapy is essential for successful management of STEMI.¹ Thrombolysis plays a significant role when access to percutaneous coronary intervention is limited or not available in a timely manner, particularly in rural settings or low- and middle-income countries in which percutaneous coronary intervention is not available.² With risks of bleeding, stroke, and intracranial hemorrhage, use of the most effective and safest fibrinolytic regimen is critical.^{3,4}

This systematic review found that in STEMI patients, tenecteplase, reteplase, and accelerated alteplase (90-minute infusion) plus parenteral anticoagulation were the most effective regimens (ie, lower mortality), with an acceptable safety profile (ie, lower risk of bleeding), compared with

streptokinase or nonaccelerated alteplase with or without parenteral anticoagulation. The network meta-analysis showed that monotherapy fibrinolytics (streptokinase and nonaccelerated alteplase) had increased risk of mortality compared with guideline-recommended accelerated alteplase with parenteral anticoagulation. The addition of glycoprotein IIb or IIIa inhibitors to any fibrinolytic regimen significantly increased the risk of major bleeding and therefore should be avoided.

For clinicians with limited access to percutaneous coronary intervention, tenecteplase or reteplase with parenteral anticoagulation is as safe and effective as accelerated alteplase with parenteral anticoagulation and offers the additional advantage of a longer half-life, making it easier to administer as a single intravenous bolus injection. Alteplase has a short half-life and requires a bolus, followed by an infusion. The single-bolus options may be advantageous when treatment must be initiated before a long transport time to a percutaneous coronary intervention center. With these 3 regimens available, non-accelerated alteplase and streptokinase should be avoided because of associated higher mortality rates. However, because of cost, streptokinase continues to be used extensively as the primary treatment for STEMI in low- and middle-income countries. Although studies in the United States have shown alteplase to be more cost-effective than streptokinase, further cost-effective analyses in low- and middle-income countries may help demonstrate the benefit needed to advocate

availability of more effective, safer fibrinolytic regimens.⁵ As cardiovascular deaths increase globally, implementing guidelines using fibrinolytic regimens that maximize safety and decrease harm is important to improving global emergency care for STEMI.⁶

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshots (SRS) series. The source for this systematic review snapshot is:

Jinatongthai P, Kongwatharapong J, Foo CY, et al. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: a systematic review and network meta-analysis. *Lancet*. 390:747-759.

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Michael Brown, MD, MSc, Justin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.