

Reviewer Comment

Reviewer Comment on Almekhlafi et al. “Adjunctive Intraarterial Thrombolysis after Thrombectomy in Large Vessel Occlusion Stroke: A Meta-Analysis of RCTs”

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Endovascular thrombectomy (EVT) has transformed acute stroke care, yet approximately one-third of patients fail to achieve functional independence despite successful recanalization.¹ This clinical-angiographic mismatch, potentially attributed to micro-vascular dysfunction or ‘no-reflow phenomenon,’ has prompted investigation of adjunctive intra-arterial thrombolysis to enhance tissue-level reperfusion.²

Almekhlafi and Park et al. present a timely meta-analysis of seven randomized controlled trials (2022–2025) evaluating intra-arterial thrombolysis following successful thrombectomy.³ Their rigorous methodology, including their appropriate use of random-effects models for a limited number of trials and comprehensive subgroup analyses, provides valuable insights into this emerging therapeutic approach.

The analysis demonstrates that adjunctive intra-arterial thrombolysis significantly improves excellent functional outcomes (mRS 0–1: OR 1.45, 95% CI 1.19–1.76) and complete recovery (mRS 0: OR 1.34, 95% CI 1.09–1.64). Importantly, this benefit occurs without increased symptomatic hemorrhage risk (5.05% vs 4.49%, $p = 0.53$), addressing primary safety concerns. Even in the subset receiving intravenous thrombolysis before EVT, though limited to two trials, hemorrhagic complications remained comparable, suggesting the feasibility of the adjunctive thrombolytic therapy in selected patients.

The observed absolute risk difference of 9% for excellent functional outcome translates to a number needed to treat of approximately 11, which compares favorably to other adjunctive strategies in stroke, including neuroprotectants (largely negative trials) and mechanical aspiration devices (marginal benefits).^{4–6} However, unlike these interventions, intra-arterial thrombolysis directly addresses a measurable pathophysiological target – persistent hypoperfusion despite epicardial recanalization – providing a stronger mechanistic rationale for selective implementation.

However, important limitations temper enthusiasm. Six of seven trials originated from China, where the prevalence of intracranial

atherosclerosis differs substantially from that of patients from Canada or the USA, potentially limiting generalizability. The heterogeneity in thrombolytic agents and dosing protocols introduces uncertainty about optimal treatment parameters. Additionally, the paradoxical finding of benefit for excellent but not good functional outcomes (mRS 0–2) warrants further investigation.

Several ongoing trials will address these knowledge gaps. BRIDGE-TNK (NCT04733742), BRETIS-TNK II (NCT05657444), TECNO (NCT05499832) and the REACT trial within ACT-GLOBAL (NCT06352632) will provide crucial data on patient selection, optimal dosing and generalizability across diverse populations. These studies will likely establish whether adjunctive intra-arterial thrombolysis becomes standard care for selected patients.

Until definitive evidence emerges, this meta-analysis supports cautious implementation of adjunctive intra-arterial thrombolysis in patients with incomplete reperfusion following thrombectomy. The acceptable safety profile and consistent signal for improved functional outcomes justify continued investigation of this promising approach to bridge the gap between procedural success and optimal clinical outcomes.

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