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European Journal of Neurology

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LETTER TO THE EDITOR OPEN ACCESS

Letter to the Editor Regarding "The Added Benefit of Intra-Arterial Thrombolysis After Successful Recanalization by Endovascular Treatment: A Systematic Review and Meta-Analysis of Randomized-Controlled Clinical Trials" Recently Published by Palaiodimou and Colleagues

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Received: 25 August 2025 | **Revised:** 25 August 2025 | **Accepted:** 9 October 2025

Funding: The authors received no specific funding for this work.

Keywords: intraarterial | letter | MEVOs

Dear Editor,

We found the article by Palaiodimou et al. [1] insightful and commend the authors for their rigorous systematic review and meta-analysis of seven randomized controlled trials (RCTs) including 2131 acute ischemic stroke (AIS) patients with anterior or posterior circulation large vessel occlusion (LVO) and successful recanalization following endovascular treatment (EVT). The authors found that adjunct intra-arterial thrombolysis (IAT) was associated with significantly higher odds of excellent functional outcome and greater disability reduction at 90 days, without increasing rates of symptomatic intracranial hemorrhage (sICH), any intracranial hemorrhage, or mortality. The pooled number needed to treat for an excellent outcome was 12, corresponding to a significantly higher likelihood of excellent outcome (RR 1.17, 95% CI 1.03–1.33; $I^2 = 0\%$), a clinically meaningful result given that one-third of patients in the control arm remained functionally dependent despite angiographic success.

Their analysis further suggested that both IA alteplase and tenecteplase were effective, with a reassuring safety profile (pooled sICH 4%, comparable to HERMES EVT data [2]). Benefits were consistent across reperfusion grades and dosing ranges, supporting the hypothesis that IAT enhances microvascular reperfusion and recovery. These results strengthen the rationale for IAT as a targeted, safe, post-recanalization strategy to close the persistent "angiographic–clinical" gap in LVO stroke care. Additionally, and of particular importance, subgroup analysis showed no evidence that intravenous thrombolysis (IVT) pretreatment influenced the effect of adjunctive IAT on achieving excellent functional outcomes [1]. In addition, there is also growing interest in expanding the use of IAT in patients who have not achieved successful recanalization, as emphasized by the authors in their discussion. We may, however, expect time limitations for IAT, which is likely to increase sICH.

These compelling data raise an important question: Can the therapeutic benefits of IAT be extended to patients with medium vessel occlusions (MeVOs), or is it unlikely that the risk–benefit profile of IA thrombolytics after successful recanalization can be favorably altered in this population?

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MeVOs account for about one-third of AIS and, despite higher IVT efficacy in smaller clots, recanalization rates remain below 50%, with one-third of patients not regaining functional independence and 9% dying within 3 months [3]. Although EVT indications for LVO have expanded over the past decade, three recent RCTs failed to show clear benefit in MeVOs [4]. This leaves a substantial therapeutic gap. If thrombectomy remains ineffective in MeVOs, should we pivot towards improved patient selection, next-generation small-caliber thrombectomy devices enabling higher complete reperfusion rates, and subsequent adjunctive IAT—as in LVOs? Or should we explore IAT as a primary, standalone therapy, bypassing mechanical intervention altogether? The challenge is that negative EVT trials limit opportunities for "post-successful-reperfusion" IAT. This highlights two urgent research priorities: (1) advancing novel devices to achieve reliable reperfusion in MeVOs without the drawbacks of using LVO devices in MeVOs, then testing adjunctive IAT, and (2) conducting dedicated trials of IAT alone in MeVOs.

Designing clinical trials that address these challenges is essential to close the therapeutic gap and improve outcomes for patients with MeVO strokes.

Author Contributions

Conceptualization, original draft preparation, review and editing of the manuscript: S.F., A.H.S., R.C. and W.H.Z. Project supervision: W.H.Z., S.F. is a guarantor of the study.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The present research complies with the guidelines for human studies, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflicts of Interest

S.F. received speakers' honoraria from AstraZeneca, Bayer, Boehringer Ingelheim. A.H.S. has financial interest/investor/stock options/ownership in Adona Medical Inc., Amnis Therapeutics (purchased by Boston Scientific, October 2017), Blink TBI Inc., Buffalo Technology Partners Inc., Cerebrotech Medical Systems Inc., Cognition Medical, Endostream Medical Ltd., Imperative Care, International Medical Distribution Partners, Neurovascular Diagnostics Inc., Q'Apel Medical Inc., Rebound Therapeutics Corp. (purchased in 2019 by Integra Lifesciences Corp.), Rist Neurovascular Inc., Sense Diagnostics Inc., Serenity Medical Inc., Silk Road Medical, Spinnaker Medical Inc., StimMed, Synchron, Three Rivers Medical Inc., Vastrax LLC, VICIS Inc., Viseon Inc; serves as a consultant/advisory board member for Amnis Therapeutics, Boston Scientific, Canon Medical Systems USA Inc., Cerebrotech Medical Systems Inc., Cerenovus, Corindus Inc., Endostream Medical Ltd., Imperative Care Inc., Integra LifeSciences Corp., Medtronic, MicroVention, Minnetronix Neuro Inc., Northwest University–DSMB Chair for HEAT Trial, Penumbra, Q'Apel Medical Inc., Rapid Medical, Rebound Therapeutics Corp. (purchased by Integra LifeSciences Corp.), Serenity Medical Inc., Silk Road Medical, StimMed, Stryker, Three Rivers Medical Inc., VasSol, and W.L. Gore & Associates; and is principal investigator/steering committee member for the following trials: Cerenovus NAPA and ARISE II; Medtronic SWIFT PRIME and SWIFT DIRECT; MicroVention FRED & CONFIDENCE; MUSC POSITIVE; and Penumbra 3D Separator, COMPASS, INVEST, TIGER. R.C. received speakers' honoraria from Microvention, Medtronic, Balt, Siemens. W.H.Z. reports speaker fees for Stryker, Medtronic, Cerenovus, Microvention, Nicolab and consultancies for Philips and Bayer.

Data Availability Statement

The authors have nothing to report.

Linked Articles

This article is linked to https://doi.org/10.1111/ene.70399.

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