Bridging Oceans and Thrombolysis

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Editor's Note: *The* Annals of Emergency Medicine *Journal Club monthly provides a succinct review of high-impact articles from this and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments*

ARTICLE IN REVIEW

Zi W, Qiu Z, Li F, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA*. 2021;325:234-243.

What Question Did This Investigation Aim to Answer?

In patients with acute, proximal anterior circulation stroke, is endovascular treatment (EVT) alone noninferior to EVT plus intravenous thrombolysis (IVT)?

What Study Design Did the Authors Choose?

Design: Open-label, randomized interventional trial.

Setting: Thirty-three stroke centers in China.

Population: Two hundred thirty-four adult patients with proximal, anterior circulation, intracranial, occlusion strokes with 4.5 hours of symptom onset and eligible for IVT.

Intervention: EVT versus EVT plus IVT.

Primary and Secondary Outcomes: Functional independence as measured by the modified Rankin Scale score at 90 days. Secondary outcome measures included successful reperfusion, intracranial hemorrhage, and death.

Sponsors: National Natural Science Foundation of China, Chongqing Major Disease Prevention and Control Technology Research Project, Clinical Medical Research Talent Training Program, and Major Clinical Innovation Technology Project of the Second Affiliated Hospital of Army Medical University.

Chinese Clinical Trial Registry: ChiCTR-IOR-17013568.

How Did the Authors Interpret the Results?

Of the 234 patients included in the primary analysis, 54.3% of those treated with EVT alone achieved functional independence compared with 46.6% of those treated with EVT plus IVT (difference 7.7%; 1-sided 97.5% confidence interval –5.1 to ∞). This lower bound for the 1-sided 97.5% confidence interval for noninferiority was greater than the prespecified margin of –10%. Secondary outcomes showed no significant difference between EVT and EVT plus IVT in deaths (17.2% versus 17.8%, respectively), but any intracranial hemorrhage favored EVT alone (21.7% versus 32.5%, respectively). The authors concluded EVT alone is noninferior to EVT plus IVT.

How Might This Study Affect Your Clinical Practice in the Emergency Department?

This small trial found minimal difference between patients treated with EVT alone versus EVT plus IVT. This finding has face validity, particularly considering that the premise of EVT as an intervention is predicated on the lack of effectiveness of alteplase for clot dissolution in large-vessel occlusions. The previously and concurrently published Direct Intra-arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals (DIRECT-MT) and Direct Mechanical Thrombectomy in Acute LVO Stroke trials[1,2] provide similar evidence reflecting a lack of difference in outcomes. Systems of stroke care should consider algorithms in which pre-EVT thrombolysis is deprecated.

DISCUSSION POINTS

1. *This trial was conducted in China, whereas the SKIP trial was conducted in Japan. How should evidence from these and other trials conducted overseas be applied in the United States?*

An increasing evidence base is being generated by well-designed, well-conducted clinical trials outside of the United States and Europe, with a particularly rapid increase

in trial registration in Asia.[3] These developments are a positive step in improving the integrity of clinical trials because prospective registration allows critical review of study design and outcome modifications. These important steps may help address concerns raised from prior findings implicating overseas sites in research misconduct of major, multicenter trials.[4]

Generalizability from these trials remains a challenge because the ethnic and genetic diversity of study populations may introduce important limitations. For example, in the SKIP trial from Japan, 0.6 mg/kg is the typical dose for alteplase compared with 0.9 mg/kg in the United States. Other genetic polymorphisms, particularly human leukocyte antigen differences, may also affect efficacy or adverse event rates.[5]

These are all reasonable considerations when translating research findings from overseas.

2. *The trial was planned to enroll 918 patients, but termination was recommended after interim analysis of the first 194 patients reaching 90-day follow-up. How is this early termination justified?*

There is a risk to the premature stoppage of trials.[6] Early in a trial's enrollment, elevated variations in the effect size may be observed because a small sample magnifies random error. As the cohort approaches its full sample size, these variations most likely diminish, regressing toward the true effect size. Although an interim analysis is just as likely to underestimate as overestimate an intervention's true effect size, it is more likely an overestimate will lead to premature trial termination. These trials stopped early for benefit are observed, on average, to overestimate the effect size of the therapy in question.[7] This risk increases in trials stopped after enrolling very small sample sizes.[8] Therefore, it is important that interim analyses be conducted by an independent data and safety monitoring board at the appropriate predetermined enrollment thresholds. Decisions to halt the trial must be based on specific, clearly defined, a priori stopping criteria published in the clinical trial registration.

In this trial, the first interim analysis at 194 patients met the boundary criteria for efficacy, indicating the trial would reach its primary endpoint regardless of completion of enrollment. We can be confident the intervention is noninferior to the control arm, despite the early stoppage. No conclusion can be drawn regarding superiority, however, owing to the imprecise estimate of the effect size resulting from the reduced sample size.

The termination rule for this trial was clearly defined, but enrollment was not stopped because of the interim analysis, but rather owing to publication of DIRECT-MT. At this point, 234 patients had been recruited, but the 90-day outcomes data on the first 194 enrolled were not yet available. Serendipitously for all, the stopping criteria were, in fact, met.

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REFERENCES

1. Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA*. 2021;325:244.
2. Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med*. 2020;382:1981-1993.
3. Viergever RF, Li K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. *BMJ Open*. 2015;5:e008932.
4. Seife C. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. *JAMA Intern Med*. 2015;175:567.
5. Fan W-L, Shiao M-S, Hui RC-Y, et al. Hla association with drug-induced adverse reactions. *J Immunol Res*. 2017;2017:1-10.
6. Guyatt GH, Briel M, Glasziou P, et al. Problems of stopping trials early. *BMJ*. 2012;344:e3863.
7. Pocock SJ, Hughes MD. Practical problems in interim analyses, with particular regard to estimation. *Control Clin Trials*. 1989;10(suppl 4):209-221S.
8. Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit: a systematic review. *JAMA*. 2005;294:2203-2209.