EDITORIAL

Intravenous Thrombolysis Before Endovascular Thrombectomy for Acute Ischemic Stroke

Jeffrey L. Saver, MD; Opeolu Adeoye, MD, MS

The 2 reperfusion therapies of proven benefit for acute ischemic stroke, mechanical endovascular thrombectomy (EVT) and pharmacologic intravenous thrombolysis (IVT), have complementary advantages. EVT, which involves mechanical debulking, works well for accessible sizeable thrombi that occlude large cerebral vessels and are resistant to rapid thrombolytic dissolution. IVT, which involves chemical dissolution, works well for smaller thrombi that occlude medium and small cerebral vessels inaccessible or poorly accessible to endovascular technology. An open, important question has been whether the modest efficacy of IVT for large vessel occlusions is sufficient to make the strategy of initiating IVT prior to EVT more effective than pursuing EVT alone.

Multimedia

Related articles pages 234 and 244

Administration of IVT first, as a bridging therapy prior to EVT, could have several favorable effects. IVT could potentially resolve the ischemic episode quickly, obviating the need for EVT and shortening brain ischemia time. Even if IVT did not yield thrombus dissolution, it could potentially change clot composition in a manner that made the thrombus more responsive to endovascular removal. In addition, at the end of an EVT procedure, residual or newly embolized thrombi are often still present in distal vessels beyond device reach, and an intravenous thrombolytic agent might dissolve this thrombotic debris in downstream vessels.

But giving IVT first could also exert several unfavorable effects. The time taken to initiate IVT, if not done in parallel with steps required for EVT initiation, might delay the start of the definitive endovascular procedure. IVT might partially dissolve a target thrombus, causing it to move distally and lodge in a distal vessel poorly accessible by endovascular intervention, converting a treatable into an untreatable lesion. IVT increases the risk of symptomatic brain hemorrhage. In addition, adding IVT to EVT increases care costs.

Given these challenging physiologic effects, only randomized trials could determine whether there is net additional benefit of IVT prior to EVT among patients with acute ischemic stroke due to large vessel occlusions (AIS-LVO). Accordingly, the 2 trials published in this issue of *JAMA* are important,[1,2] and contribute to the mounting evidence that EVT alone achieves outcomes that may be noninferior to outcomes achieved with combined IVT plus EVT for patients with AIS-LVO.[3]

These 2 trials have some distinctive aspects of the enrolled study populations and interventions. In the Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation (DEVT) trial, reported by Zi and colleagues,[1] among 234 patients at 33 stroke centers in China with anterior circulation large vessel occlusions, the most commonly used dose of alteplase worldwide, 0.9 mg/kg, was used and a longer time interval, approximately 40 minutes, occurred between lytic drug start and EVT procedure start. In the Direct Mechanical Thrombectomy in Acute LVO Stroke (SKIP) trial, reported by Suzuki and colleagues,[2] among 204 patients at 23 hospital networks in Japan, a lower dose of alteplase often used in Asian populations (who have a greater cerebral bleeding tendency), 0.6 mg/kg, was used and a short time interval, approximately 8 minutes, occurred between lytic drug start and EVT procedure start. With its higher drug dose and longer interlude for drug action, the DEVT trial more strongly probed the ability of IV lytics to improve outcome by quickly dissolving the target occlusion before EVT can be performed. The SKIP trial, in comparison, more fully explored the possibility that lower-dose, shorter interlude IV lytics can improve outcome by dissolving residual small thrombi in the distal vasculature after incomplete endovascular reperfusion while minimizing the risk of hemorrhagic transformation.

In the DEVT trial, the primary end point, the proportion of patients achieving functional independence at 90 days (defined as score 0-2 on the modified Rankin Scale, range from 0 [no symptoms] to 6 [death]), occurred in 63 patients (54.3%) in the EVT alone group vs 55 (46.6%) in the combined IVT plus EVT group (difference, 7.7% [1-sided 97.5% CI, −5.1% to ∞]; $P = .003$ for noninferiority), and met the prespecified noninferiority criteria (margin of −10%). In the SKIP trial, the primary outcome, favorable neurologic outcome, also defined as modified Rankin Scale score of 0 to 2 at 90 days, occurred in 60 patients (59.4%) in the IVT alone group and 59 patients (57.3%) in the combined IVT plus EVT group (odds ratio, 1.09 [1-sided 97.5% CI, 0.63 to ∞]; $P = .18$ for noninferiority) but did not meet the prespecified noninferiority criteria (margin odds ratio of 0.74). Together, the trial findings demonstrate that the treatment strategies of EVT alone and of IVT before EVT (when performed soon after one another at thrombectomy-capable stroke centers) yield numerically similar results for patients with AIS-LVO.

The findings from these studies reinforce and extend the results of another recently published study, the DIRECT-MT trial,[3] which enrolled 656 Chinese patients with AIS-LVO. In that trial, EVT alone was noninferior to EVT plus IVT (alteplase, 0.9 mg/kg) with regard to functional outcome at 90 days based on the between-group difference in the distribution of the modified Rankin Scale scores (adjusted common odds ratio, 1.07 [95% CI, 0.81-1.40]), with noninferiority

defined as the lower bound of the 95% CI of the adjusted odds ratio equal to or larger than 0.8. Importantly, none of these 3 trials sought to demonstrate noninferiority in the strongest sense of formally excluding the minimal clinically important difference (MCID). For such important an outcome as being functionally independent at 3 months after stroke, the MCID is small, at less than 1.5%.[4,5] If 2 treatments actually yield similar outcome rates for a binary outcome with a small MCID, the needed sample sizes to demonstrate true indistinguishability are infeasibly large.[6,7] Instead, these trials explicitly or implicitly selected noninferiority thresholds using the "fixed-margin" method, an approach in which the goal is to demonstrate that EVT alone delivers at least a substantial fraction of the benefit that combined IVT and EVT delivers.[6-8] Nonetheless, taken together, the accumulated results from these studies suggest that the simpler EVT alone strategy is broadly noninferior to combined EVT and IVT and accordingly may be reasonable to consider for patients who present directly to thrombectomy-capable centers. Additional trials are needed to determine whether these findings generalize to non-Asian patients and are under way (MR CLEAN-NO IV, ISRCTN80619088; SWIFT-DIRECT, NCT03192332; DIRECT-SAFE, NCT03494920).

Given the generally congruent results of the completed trials, clinicians must now consider whether and how to apply these findings thoughtfully in routine clinical practice. Several caveats will need to be considered whenever the strategy of not providing the proven therapy of IVT is contemplated. First, because EVT is not an option for patients with small to medium vessel occlusions, those patients should continue to receive IV thrombolytics as a standalone rather than bridging therapy. Second, among patients with AIS-LVO, thrombolytics prior to EVT should be withheld only when clinicians are confident EVT will be delivered quickly and reliably. Patients with AIS-LVO who present to a nonthrombectomy-capable hospital, among whom EVT start will be delayed until after interfacility transfer, should receive IVT at the first hospital site so that reperfusion therapy could be started before the stroke has progressed to near completion.[9] Even among patients with AIS-LVO who present directly to thrombectomy centers, initial IVT should be administered to patients who harbor conditions that slow or preclude endovascular access to intracranial vessel occlusions, including excessive aortocervical arterial tortuosity and chronic cervical occlusions. If rapid EVT access to the intracranial vasculature is not certain, IVT should be initiated so the patient is assured of receiving at least 1 form of reperfusion therapy.

Beyond these major cautions, physiologic reasoning and clinical observations suggest there may be subgroups of patients who will differentially benefit from receiving or avoiding IVT before EVT. Patients harboring thrombi that are particularly susceptible to pharmacologic lysis likely will have net benefit from IVT, including patients with erythrocyte/fibrin-rich thrombi (hyperdense artery signs on computed tomography), greater thrombus perviousness (contrast penetration of clot on computed tomographic angiography), and smaller clot volumes (visible as distal M2 occlusions or short-length thrombi on computed tomographic angiography), and patients treatable on mobile stroke units within the first 60 minutes after onset before thrombus organization has greatly advanced.[10-12] An additional likely differentiating feature is proneness to brain hemorrhagic transformation. Patients with greater cerebral bleeding risk are less likely to benefit from IV lysis, including patients with larger established infarct cores, greater blood-brain barrier permeability, known multiple cerebral microhemorrhages, and more advanced chronic white matter injury.[13] Nuanced precision medicine clinical trials are desirable to definitively confirm or disconfirm the desirability of such individualized patient treatment strategies.

An additional caveat is that the current trials provide information only regarding IV alteplase alone as the IV thrombolytic strategy. Improvements in IV thrombolytic therapy efficiency would shift the balance of advantage back to combined IVT plus EVT for a preponderance of patients. Enhancing thrombolysis, potentially by use of newer-generation fibrinolytic agents or addition of glycoprotein IIb/IIIa inhibitors or direct thrombin inhibitors, continues to be an important avenue for further therapeutic study.[14,15]

While awaiting such potential advances, the current trials that have assessed IV alteplase, including the 2 clinical trials in this issue of *JAMA*, have enriched the current therapeutic options, even if applying these findings to individual patients will sometimes be challenging. For stroke clinicians caring for patients with AIS-LVO, it now will sometimes be reasonable to avoid using 2 therapeutic approaches, pharmacologic and mechanical, and instead proceed with a single strategy of rapid direct endovascular thrombectomy.

ARTICLE INFORMATION

Author Affiliations: Comprehensive Stroke Center, Department of Neurology, University of California, Los Angeles (Saver); Associate Editor, *JAMA* (Saver); Departments of Emergency Medicine and Neurosurgery, University of Cincinnati, Cincinnati, Ohio (Adeoye).

Corresponding Author: Jeffrey L. Saver, MD, Department of Neurology, University of California, Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095 (jsaver@mednet.ucla.edu).

Conflict of Interest Disclosures: Dr Saver reported being an employee of the University of California, which has patent rights in retrieval devices for stroke. The University of California received payments on the basis of clinical trial contracts for the number of participants enrolled in multicenter clinical trials sponsored by Medtronic, Stryker, Cerenovus, BrainsGate, NONO Inc, and Boehringer Ingelheim (prevention only). The University of California receives grant support from the National Institutes of Health (NIH) for Dr Saver's service in leadership roles in the National Institute of Neurological Disorders and Stroke StrokeNet national clinical trial network and from Diffusion Pharma for Dr Saver's leadership role in the PHAST-TSC multicenter trial. Dr Saver reported serving as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr Saver received any payments for this voluntary service. Dr Saver paid for his own travel. Dr Saver reported receiving contracted hourly payments and travel reimbursement for services as a scientific consultant advising on rigorous trial design and conduct to Medtronic, Stryker, Cerenovus, BrainsGate, Boehringer Ingelheim (prevention only), NONO Inc, BrainQ, and Abbott; contracted stock options for services as a scientific consultant advising on rigorous trial design and conduct to Rapid Medical; and personal fees from Johnson & Johnson and Novo Nordisk. Dr Adeoye reported being an employee of the University of Cincinnati. He is cofounder and equity holder for Sense

Diagnostics Inc, which is developing a brain monitoring device for which the University of Cincinnati holds the patent. The University of Cincinnati receives grant support from the NIH for Dr Adeoye's leadership role in the Multi-arm Optimization of Stroke Thrombolysis (MOST) trial and the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN). Dr Adeoye reported receiving hourly payments and travel reimbursement for services as a scientific consultant advising on clinical trial design and conduct to Genentech.

REFERENCES

1. Zi W, Qiu Z, Li F, et al; DEVT Trial Investigators. 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*. Published January 19, 2021. doi:10.1001/jama.2020.23523

2. Suzuki K, Matsumaru Y, Takeuchi M, et al; SKIP Study Investigators. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA*. Published January 19, 2021. doi:10.1001/jama.2020.23522

3. Yang P, Zhang Y, Zhang L, et al; DIRECT-MT Investigators. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med*. 2020;382(21):1981-1993. doi:10.1056/NEJMoa2001123

4. Cranston JS, Kaplan BD, Saver JL. Minimal clinically important difference for safe and simple novel acute ischemic stroke therapies. *Stroke*. 2017;48(11):2946-2951. doi:10.1161/STROKEAHA.117.017496

5. Lin CJ, Saver JL. Noninferiority margins in trials of thrombectomy devices for acute ischemic stroke: Is the bar being set too low? *Stroke*. 2019;50(12):3519-3526. doi:10.1161/STROKEAHA.119.026717

6. Food and Drug Administration. *Non-inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*. Food and Drug Administration; 2016.

7. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. *Trials*. 2011;12:106. doi:10.1186/1745-6215-12-106

8. Rothmann M, Li N, Chen G, Chi GY, Temple R, Tsou HH. Design and analysis of non-inferiority mortality trials in oncology. *Stat Med*. 2003;22(2):239-264. doi:10.1002/sim.1400

9. Sablot D, Dumitrana A, Leibinger F, et al. Futile inter-hospital transfer for mechanical thrombectomy in a semi-rural context: analysis of a 6-year prospective registry. *J Neurointerv Surg*. 2019;11(6):539-544. doi:10.1136/neurintsurg-2018-014206

10. Heo JH, Nam HS, Kim YD, et al. Pathophysiologic and therapeutic perspectives based on thrombus histology in stroke. *J Stroke*. 2020;22(1):64-75. doi:10.5853/jos.2019.03440

11. Menon BK, Al-Ajlan FS, Najm M, et al; INTERRSeCT Study Investigators. Association of clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke. *JAMA*. 2018;320(10):1017-1026. doi:10.1001/jama.2018.12498

12. Ebinger M, Kunz A, Wendt M, et al. Effects of golden hour thrombolysis: a prehospital acute neurological treatment and optimization of medical care in stroke (Phantom-S) substudy. *JAMA Neurol*. 2015;72(1):25-30. doi:10.1001/jamaneurol.2014.3188

13. Elsaid N, Mustafa W, Saied A. Radiological predictors of hemorrhagic transformation after acute ischemic stroke: an evidence-based analysis. *Neuroradiol J*. 2020;33(2):118-133. doi:10.1177/1971400919900275

14. Adeoye O, Sucharew H, Khoury J, et al. Combined approach to lysis utilizing eptifibatide and recombinant tissue-type plasminogen activator in acute ischemic stroke-full dose regimen stroke trial. *Stroke*. 2015;46(9):2529-2533. doi:10.1161/STROKEAHA.115.010260

15. Burgos AM, Saver JL. Evidence that tenecteplase is noninferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. *Stroke*. 2019;50(8):2156-2162. doi:10.1161/STROKEAHA.119.025080