IMS-III and SYNTHESIS Expansion Trials of Endovascular Therapy in Acute Ischemic Stroke
How Can We Improve?

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The recent results of the Intervventional Management of Stroke III (IMS-III)\(^1\) and SYNTHESIS Expansion\(^2\) trials have brought forth a wave of skepticism on the use of endovascular therapy in acute ischemic stroke reinforcing more than ever the nihilistic behavior that has afflicted this field since its inception.\(^3\)

As research results are only generalizable to a similar cohort to the target study population, it is imperative to acknowledge the existence of 3 distinct populations of patients with large vessel occlusion stroke (LVOS): (1) intravenous tissue-type plasminogen activator (tPA) eligible (0–3–4.5 hours), further categorized in intravenous tPA responders and intravenous tPA refractory patients; (2) early presenting intravenous tPA ineligible patients (0–6 hours); and (3) late presenting and unknown time of onset patients (6–24 hours including wake-up). IMS-III and SYNTHESIS have only focused on intravenous tPA eligible patients, and therefore their results cannot be applied to intravenous tPA ineligible patients. This is an important notion because only \(\leq 40\%\) to \(50\%\) of the patients who currently undergo thrombectomy receive prior intravenous tPA.\(^4\)\(^5\) Notably, there is currently level 1B evidence to support intra-arterial thrombolysis in early presenting LVOS (0–6 hours),\(^6\) and the results of IMS-III and SYNTHESIS do not apply to most of these patients.

Just as important is the fact that, in our opinion, IMS-III and SYNTHESIS did not target the optimal population for endovascular therapy. Three essential requirements should be met to demonstrate the benefit from intra-arterial stroke intervention (Figure): (1) presence of a target vascular occlusion; (2) presence of target salvageable tissue; and (3) fast and effective reperfusion. Vascular imaging (computed tomography [CT] angiography/magnetic resonance angiography) was performed in only 46.6\% (n=306/656) of the IMS-III patients. Out of these, 7.8\% had no occlusion at all (n=24/306), 3.3\% had distal occlusions (anterior cerebral artery, posterior cerebral artery, middle cerebral artery [MCA]-M3/4), 16.7\% had MCA-M2 occlusion (n=51/306), and 2.6\% had proximal internal carotid artery (ICA) occlusions with patent intracranial vessels (n=8/306; Demchuk AM, personal communication, International Stroke Conference, 2013). As such, approximately one third of the patients who had vascular imaging had lesions with no or low chances of benefiting from endovascular therapy. Evidently, these are the same lesions that benefit the most from intravenous thrombolysis. As a reflection of lack of proximal arterial occlusions, 23\% (100/434) of the IMS-III patients randomized to endovascular therapy did not receive any endovascular treatment. The vascular imaging data in SYNTHESIS have yet to be presented, but only 30\% (109/362) of the randomized patients underwent CT angiography. Moreover, it is likely that a significant proportion of the SYNTHESIS patients lacked a proximal arterial occlusion because 7\% of patients had small vessel disease and the median National Institutes of Health Stroke Scale (NIHSS) in SYNTHESIS was only 13. As a comparison, the median NIHSS in most of the previous endovascular trials ranged between 17 and 20.\(^7\) The importance of proximal arterial occlusion and high clinical severity has been recently highlighted by a retrospective study of 203 patients with LVOS demonstrating significantly smaller final infarct volumes in patients receiving mechanical thrombectomy as opposed to either intravenous tPA or no reperfusion therapy (42 versus 109 versus 110 mL; \(P=0.001\)). Mechanical thrombectomy had a greater effect in terms of both lower infarct volumes and better functional outcomes at hospital discharge in patients with ICA or MCA-M1 (versus MCA-M2) occlusions and those with NIHSS \(\geq 14\) (versus 8–13).\(^8\)

Although there is no standardization or consensus on how to estimate precisely the amount of target salvageable tissue (penumbra), it is widely accepted that its magnitude is directly related to the severity of the neurological deficits (eg, baseline NIHSS) and inversely related to the amount of visualized infarct core on the baseline imaging study.\(^9\) Patients with low NIHSS have a higher chance of good outcome with intravenous tPA or even without any reperfusion treatment. The Prolyse in Acute Cerebral Thromboembolism
Fast and effective reperfusion is of paramount importance in face of critical ischemia, yet little importance was paid to times to endovascular reperfusion in IMS-III with a mean time from start of intravenous tPA to groin puncture of 81±27 minutes and a mean time from groin puncture to the start of the intra-arterial treatment of 42±21 minutes. The IMS-III investigators have concluded that every 30-minute delay in reperfusion is associated with a 10% relative reduction in probability of good clinical outcome (mRS≤2), making this average delay of 2 hours a major target for improvement in future trials (Khatri P, personal communication, International Stroke Conference, 2013). In contrast, there was only a 60-minute difference between the median time from stroke onset to treatment initiation among the intravenous and intra-arterial groups in SYNTHESIS (2:45 [interquartile range, 2:20–3:20] versus 3:45 [3:14–4:20]; P<0.001) proving the feasibility of a faster approach. The importance of time to reperfusion has been highlighted by the recent stent retriever trials. 

The SWIFT and TREVO-2 RCTs had longer times to treatment (median time from stroke onset to procedure, 4.6 and 4.7 hours, respectively) in relation to their European single-arm counterparts, TREVO-EU and Solitaire flow restoration Thrombectomy for Acute Revascularization (STAR) (3.2 and 3.4 hours, respectively). Shorter delays translated in better outcomes (90-day mRS≤2: 36.4% and 40% versus 55% and 57.9%, respectively).4,5,11,12

Speed is crucial but so is quantitative and qualitative effective reperfusion. The technology used in the IMS-III and SYNTHESIS trials is now obsolete, which significantly limits the applicability of their results. Almost half (47.9%; 160/334) of the IMS-III patients receiving endovascular treatment were treated only with intra-arterial tPA. The Merci device was the second most commonly used modality (28.4%; 95/334) with substantially less patients treated with Penumbra thromboaspiration (16.2%; 54/334) and only a minimal fraction with the Solitaire device (1.5%; 5/334; Tomsick TA, personal communication, International Stroke Conference, 2013). In SYNTHESIS, about two thirds (109/165) of the patients were solely treated by loco-regional infusion of intra-arterial tPA and fragmentation of the thrombus with a microguide wire.5 The aforementioned treatments do not reflect the current state of the art. The SWIFT and TREVO-2 trials have provided level 1a evidence that the stent retriever technology is superior to the Merci device and, along with the non-controlled STAR and TREVO-EU trials, have shown good outcome rates ranging from 36.4% to 57.9% in patients with angiographically documented LVOS and significantly higher stroke severity than in IMS-III and SYNTHESIS (baseline NIHSS, 17–19 versus 13–16).4,5,11,12

It has been defined recently that a modified Thrombolysis in Cerebral Infarction (m-TICI) score ≥2b best correlates with good functional outcomes.13 In IMS-III, the m-TICI ≥2b rate was only 23% for multiple MCA-M2, 38% for ICA, and 44% for MCA-M1 or single MCA-M2 occlusions, yet favorable outcomes were highly dependent on qualitative reperfusion: m-TICI1=12.7% (n=55), m-TICI1=27.6% (n=29), m-TICI2a=34.3% (n=108), m-TICI2b=47.9% (n=119), and m-TICI3=71.4% (n=7; P<0.001; Tomsick TA, personal communication, International Stroke Conference, 2013). In
contrast, m-TICI ≥2b reperfusion rates of 84.2% and faster times from guiding catheter placement to revascularization have been seen in the stent retriever trials.12

Another crucial limitation is that a substantial number of eligible patients were presumably treated outside of the trials. Indeed, SYNTHESIS had a pragmatic design and eligible patients were those with uncertainty of the most appropriate choice. Accordingly, 91 eligible patients were not randomized because investigators considered there was a lack of equipoise.2 Future trials must implement mechanisms to minimize selection bias and increase external validity. A further point of interest is that endovascular treatment likely leads to a proportional improvement in the wide spectrum of the functional capacity, so the shift analysis of the distribution of mRS might better reflect the treatment effect. Indeed, shift analysis of the more meaningful IMS-III patient subgroups such as those with documented vascular occlusions on pretreatment CT angiography (Demchuk AM, personal communication, International Stroke Conference, 2013) and those with severe strokes (eg, NIHSS≥20) suggests a benefit of endovascular treatment (P=0.011 and P=0.065, respectively). Forthcoming trials may also need to include patients ineligible for tPA because their natural history is known to be very poor. According to the SYNTHESIS results, the benefit and safety of endovascular therapy seem to be comparable with that of intravenous tPA treatment, which suggests that ineligible tPA patients may benefit from endovascular therapy. Therefore, SYNTHESIS brings additional ethical challenges to the randomization of tPA ineligible patients.

In conclusion, we applaud the IMS-III and SYNTHESIS investigators for executing these trials in such a challenging environment. However, it is vital to acknowledge that this is just the dawning era of evidence-based stroke intervention. There were many shortcomings to the recent trials including the fact that many patients did not have the disease process in question (eg, LVOS with sufficient salvageable brain tissue) and either did not receive the study intervention at all or were treated with technologies that no longer reflect the contemporary standards and at treatment times that were substantially delayed. Despite these limitations, none of the recent trials have raised any concerns about the safety of endovascular therapy. The current clinical practice is far different than what was studied, which limits the applicability of the results. Therefore, endovascular revascularization remains justified in properly selected patients. However, patients must be captured in randomized controlled trials with novel designs according to advanced technologies in vascular and tissue diagnosis and evolving endovascular modalities as actual evidence-based medicine is still lacking. The recent trials have been a big step forward as they have provided us knowledge about the target areas for improvement in terms of both design and execution that will be critical for the planning of future trials.

Disclosures

Dr Nogueira is funded by Stryker Neurovascular; PI of Trevo-2 and DAWN Trials; he is a Consultant/Scientific Advisory Board. Covidien: Steering Committee of SWIFT and SWIFT Prime Trials; Angiography Core Laboratory of Solitaire flow restoration Thrombectomy for Acute Revascularization (STAR) Trial; Consultant/Scientific Advisory Board. Penumbra: Executive Committee of the 3D Separator Trial. Rapid Medical: Data Safety Monitoring Board of Rapid Stroke Trial; Consultant/Scientific Advisory Board (all moderate). Dr Gupta is a Consultant/Scientific Advisory Board: Stryker Neurovascular, Covidiens, Rapid Medical. Steering Committee: THERAPY trial Penumbra. Associate Editor Journal of Neuroimaging. Associate Editor Interventional Neurology. Royalties from UpToDate. Dr Dávalos is funded by Covidien: unrestricted grant for REVASCAT trial (significant); Consultant/Scientific Advisory Board (moderate); Steering Committee of STAR trial (moderate).

References


Key Words: clinical trials  ■  stroke  ■  tissue-type plasminogen activator  ■  thrombectomy
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Stroke. 2013;44:3272-3274; originally published online October 10, 2013; doi: 10.1161/STROKEAHA.113.002380

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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