# Large core stroke thrombectomy: paradigm shift or futile exercise?

Michael Chen [1] Thabele M Leslie-Mazwi,[2] Joshua A Hirsch [3] Felipe C Albuquerque [4]

Predicting treatment effect is a popular topic among recent *Journal of Neurointerventional Surgery* stroke thrombectomy publications.[1–3] The primary outcome measure is often functional independence, that is, a modified Rankin Scale (mRS) score of 0–2, which may lead practitioners to ruminate on the probability of this outcome during stroke triage, instead of treating patients with thrombectomy. The authors of this comment believe that the most current data no longer support that approach.

Patients' families do not wish to hear our estimates of the probability of independent function after treatment. They generally prefer us to attend to providing their loved ones with even a slim chance at neurological improvement. In fact, the recent Stroke treatment Assessments prior to Thrombectomy In Neurointervention (SATIN) study demonstrated that neurointerventionalists were only accurate in predicting outcomes 44% of the time, including being overly pessimistic at times when outcomes were better than expected.[4] It is no wonder that the majority of malpractice lawsuits related to acute stroke treatment allege failure to treat.[5]

From the patient's perspective, the most terrifying, costly and overlooked outcome of ischemic stroke is an mRS of 5. These patients are bedridden, incontinent, and require constant nursing care. Many patients would likely prefer death (mRS 6) to this outcome. A treatment that reduces the rate of mRS 5 outcomes would have a disproportionately positive societal and financial benefit, which is not well captured by the conventional outcome measures used in clinical trials.

Re-examining our outcome measures is of particular importance when managing patients with large infarcts at presentation. While awaiting randomized trial data, there existed a rational fear among those involved in stroke treatment that mechanical thrombectomy (MT) in patients with large infarctions at presentation have a higher risk of hemorrhage into the core and a greater chance of a poor outcome regardless of whether blood flow is restored. To that point, current European and North American guidelines do not recommend MT for patients with large infarcts. Meanwhile, if functional independence is the perceived measure of treatment efficacy, it is not surprising that MT for large infarcts seemed futile. For those patients, with a substantial volume of brain already infarcted, whether or not hemorrhagic conversion occurs, independent function is unlikely. With the status quo, many large core patients currently being triaged for possible thrombectomy are not considered for transfer.

The notion that large core thrombectomy is futile is further supported by the high up-front cost of stroke care delivery.[6] Emergency medical helicopter or fixed-wing transportation costs alone can range from $12 000 to $25 000.[7] Turk *et al* calculated the costs associated with thrombectomy cases, including femoral sheaths, guidewires, and catheters based on advertised manufacturer-suggested retail price, and found the mean cost across all groups, regardless of whether a stent retriever was used, was $11 926.45, with a range from $3296.00 to $60 872.91.[8]

Despite these costs, recent cost-effectiveness analysis has challenged therapeutic cost-based nihilism for patients with pre-existing large infarct cores. While thrombectomy costs can be modeled and calculated, the value related to outcomes is more complicated. A recently published study from a European consortium created a model to study the health-economic impact of MT, including patients with low Alberta Stroke Program Early CT Score (ASPECTS) from eight European countries. The authors found a lifetime incremental cost-effectiveness ratio varying from US$2875 to $11 202/quality-adjusted life year (QALY) depending on the country. The cost-effectiveness acceptability curve showed 100% acceptability of MT at the willingness to pay of US$40 000 for the eight countries.[9] Not surprisingly they found the biggest costs over time were associated with severely disabled patients (ie, mRS 4 and 5).

The first randomized published evidence challenging the therapeutic nihilism of large core MT was the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial (RESCUE Japan LIMIT) involving 45 in-country centers. Among 202 randomized patients (mean age, 76 years; 45% women; median National Institutes of Health Stroke Scale (NIHSS) score 20), using primarily MRI for triage, 90-day mRS 0–2 was twice as high in the MT compared with the medical management (MM) group (14% vs 7.8%, respectively). MRS 0–3 (that is, ambulatory) in the MT group was 31% compared with 12.7% in the MM group.[10] A similar analysis was recently published based on the RESCUE-Japan LIMIT study dataset of low ASPECTS large vessel occlusion patients. Sanmartin *et al* found that MT yielded higher lifetime benefits (2.20 QALYs vs 1.41 QALYs) despite marginally higher lifetime healthcare costs per patient ($285 861 vs $272 954). The difference of 0.79 QALYs equated to 288 additional days of healthy life per patient. Despite the higher up-front cost, the incremental cost effectiveness ratio was $16 239/QALY.[11] While these are impressive data, several study caveats prevented generalizability of RESCUE Japan, limiting the potential impact on clinical practice. Nonetheless, these results forced an early pause and interim analyses of several other contemporaneous large core trials.

The results of two of these trials have now been reported. The recently published Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2) trial, using more generalizable imaging triage methods (mostly CT-based), showed efficacy of MT over MM for patients with anterior circulation large vessel occlusion and large ischemic core defined as ASPECTS 3–5 or CT perfusion volume >50 mL. Terminated early, 31 centers in North America, Europe and Australia randomized 352 patients and found MT was associated with a 90-day mRS 0–2 of 20% versus 7% with MM. Symptomatic intracranial hemorrhage was similar between the groups.[12] The number needed to treat for one additional patient to achieve mRS 0–2 and mRS 0–3 were 7 and 5, respectively. All prespecified patient subgroups, including age, stroke

[1]Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA
[2]Neurology, University of Washington, Seattle, Washington, USA
[3]NeuroEndovascular Program, Massachusetts General Hospital, Boston, Massachusetts, USA
[4]Department of Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona, USA

**Correspondence to** Dr Michael Chen, Neurological Sciences, Rush University Medical Center, Chicago, IL 60612, USA; Michael_Chen@rush.edu



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severity, treatment time window, ischemic core volume, CT ASPECTS, target mismatch profiles, affected hemispheres, clot location and US/non-US sites consistently favored MT. Of note, MT reduced the number of mRS 5 patients by more than half. There was also a slight mortality benefit. The majority of the change was due to increasing the number of patients who achieve a clinical outcome of mRS 1–2.

Published simultaneously, the Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusion Patients with a Large Infarct Core (ANGEL-ASPECT) trial randomized 456 patients from 46 centers in China with large infarct core (including those with ASPECTS 0–2 but also core volume of 70–100 mL) and emergent large vessel anterior circulation occlusion within 24 hours. Terminated early, the trial also found efficacy of MT over MM with 90-day mRS 0–2 of 30% versus 11.6%. In addition, the authors found a shift in distribution of mRS scores towards better outcomes with thrombectomy and an OR of 1.37 (95% CI 1.11 to 1.69, P=0.004). Symptomatic intracranial hemorrhage was higher in the MT group (6.1% vs 2.7%; relative risk 2.07, 95% CI 0.79 to 5.41, P=0.12), but similar to prior trials. Most importantly, MT reduced the number of mRS 5 patients by nearly half.[13]

We believe that with three randomized clinical trials proving that MT is effective even with large infarcts, the fears of safety (intracerebral hemorrhage) have been reasonably addressed. Questions nonetheless remain. In these studies, if only 2–3 out of 10 large core patients with MT are functionally independent, with such a high up-front cost, is widening our selection criteria largely an exercise in futility for the 7–8 other patients? Could we also be subjecting more patients with large infarcts to full-time nursing care instead of death? We think not. These studies have shown that MT halved the number of patients with mRS 5.

Do these studies settle the debate on what infarct volume threshold we should be using? Is subgroup analyses between patients with core volume of 70, 100 and even 150 mL something that ought to be done? It is important to recognize that both ASPECTS and CT perfusion volumes, much like using elapsed time, are imperfect measures of salvageable brain and are susceptible to numerous confounders even when automated interpretation is performed. Infarct topography and ASPECTS regions have unequal influence on disability. ASPECTS interrater variability is high. Prior contrast administration and cardiac function (among others factors) can influence CT perfusion results. Despite active debate,[14 15] the current results suggest a fundamental re-evaluation of the value of advanced imaging in the decision to pursue thrombectomy may be in order.

Besides the question of advanced imaging beyond non-contrast head CT in the triage of stroke, several logistical questions follow. Is there a need to repeat head CT at the hub hospital after transfer to evaluate for 'ASPECTS progression'? Are there more eloquent methods to correlate CT hypodensities with functional outcome rather than using the ASPECTS <4 dichotomization? What is the role of time windows as a surrogate marker for salvageable brain? What are the implications of these findings for thrombectomy expansion in lower resource settings, where advanced imaging is less available? In which remaining patients are we able, if at all, to declare confidently that thrombectomy remains futile and thus deny patients treatment?

Results from additional large core trials including LASTE (NCT03811769), TESLA (NCT03805308), and TENSION (NCT03094715) are pending. The recently published large core thrombectomy results will change how stroke therapy for emergent large vessel occlusions is approached. It suggests that MT patient selection should be more inclusive, perhaps reflecting the goal of avoiding mRS 5 (bedridden) rather than only focusing on predicting mRS 0–2 treatment effect. An mRS 5 dramatically increases the costs of care and burden on family and society. Achieving an mRS other than 5 is a win from many perspectives. These recent large infarct MT publications should lead to more thrombectomy transfers, simpler triage imaging and a cumulative reduction in the degree of stroke disability burden.

**Twitter** Michael Chen @dr_mchen and Joshua A Hirsch @JoshuaAHirsch

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**ORCID iDs**
Michael Chen http://orcid.org/0000-0003-2412-8167
Joshua A Hirsch http://orcid.org/0000-0002-9594-8798
Felipe C Albuquerque http://orcid.org/0000-0003-3251-1086

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