

ASK THE EXPERTS

What Is the Biggest Unanswered Question in Ischemic Stroke Care?

Experts discuss who shouldn't be treated, improving center-to-center communication, triaging patients to the right center for care, and reigning in estimates on large vessel occlusions appropriate for treatment.

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*Disclosures: Consultant to Medtronic,
Stryker, Metactive, 880 Medical,
Penumbra, Inc.; stock options for Viz.ai;
stock holdings for Penumbra, Inc.; own-
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Mechanical thrombectomy (MT) began with the question: who should we treat? Today, its journey has led to what I consider the biggest unanswered question in ischemic stroke care: who *shouldn't* we treat?

The story of establishing MT as the standard of care for emergent large vessel occlusion (ELVO) stroke has been one for the medical history books. Even early adopters were surprised to discover that MT delivers one of the strongest treatment effects in medical history. Prior to multiple randomized controlled trials (RCTs) demonstrating this treatment effect, many questions about MT were constantly raised. People wanted to know if it was safe, whether it worked, and if it was better than the medical standard of care for ELVO. Another early question that was debated was which patients with ELVO should be treated?

Defining patient selection inclusion/exclusion criteria was obviously a necessary component of the trial design for the RCTs analyzing the potential benefit of MT. Our early questioning was turned upside down by what we learned from the meta-analysis of the collective RCT data through the HERMES collaboration as well as data from real-world registries. The incredible treatment effect of MT appears to spill over to essentially all analyzed subgroups. Looking to narrow the gateway for patient inclusion and wrestling with the question of who should be treated with MT has now been flipped 180° to opening the gateway and identifying who shouldn't be treated.

Anyone with a 100% completed infarct does not stand to benefit from MT revascularization. The treatment threshold below 100% core infarct at presentation is currently under debate and a focus of recent trial activity. Trials evaluating low Alberta Stroke Program Early CT Score (ASPECTS) or large core infarcts are being initiated to answer the complex question of where the benefit of reducing the infarct burden through revascularization becomes outweighed by the risk of symptomatic intracranial hemorrhagic conversion or "salvaging" a patient to a high modified Rankin Scale outcome, which represents an unacceptable quality of life. This question of how to manage patients with low ASPECTS was the subject of an Ask the Experts article in last year's neurovascular edition of *Endovascular Today*.¹ It's great to follow up and report that answers from RCTs are on the way. The German-

initiated, predominately European-based, TENSION trial (NCT03094715) will be the first study to evaluate this question, with patient enrollment underway. Several other trials, such as IN EXTREMIS, are in the works and hopefully will be actively enrolling in the near future.

In our day-to-day practices, we factor in multiple variables such as patient age, time from symptom onset, National Institute of Health Stroke Scale (NIHSS) score at presentation, baseline functional status, comorbidities, location of occlusion, imaging data (often including perfusion information), and the patient's (and family's)

expectation of outcome to arrive at a treatment decision for patients with low ASPECTS (< 6). We eagerly await data from the RCTs focused on establishing an evidence-based approach to developing our threshold for MT exclusion. Through these trials, we will gain a better understanding of the impact that these multiple variables have on patient outcomes and how they must be considered when trying to answer the question of who shouldn't be treated with MT.

1. Goyal M, Turk AS, Froehler M, Jovin TG. Ask the experts: how do you manage cases with low ASPECTS? *Endovasc Today*. 2018;17:74-78.



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Reperfusion therapy with endovascular therapy (EVT) and/or intravenous thrombolysis (IVT) for ischemic stroke is among one of the most effective therapies in medicine. Globally, systems of stroke care are harnessing the power of early therapy as they aim to identify patients who can benefit from acute reperfusion therapy and rapidly deliver therapy to reduce disability. Within comprehensive stroke centers, the refinement of parallel processing combined with the execution of high-performing stroke and neurointerventional teams have resulted in reductions in in-hospital reperfusion treatment delays. Despite these advances, there remains a major unanswered question: how do we get the right stroke patient to the right therapy at the right place at the right time?

There is no optimal prehospital stroke assessment tool available that can identify patients who are suitable for reperfusion therapy. The specificity of multiple prehospital stroke scales for detecting LVOs varies from 40% to 94%,¹ with a balance required between feasibility of application, patient delivery to the nearest IVT center, and patient triage to the EVT center. Moreover, IVT centers are often primary stroke centers that do not always have the same level of workflow process, advanced imaging, and/or stroke clinician expertise to deliver IVT as rapidly as EVT centers. In the absence of optimal

door-to-needle and door-in/door-out times, sending selected patients with a high likelihood of requiring EVT directly to an EVT center could yield better population-level outcomes, particularly if IVT and EVT centers are < 60 minutes apart.² In the current model where stroke patients are transported to the nearest stroke center and then patients with LVOs are subsequently transferred to EVT centers, at least 20% of transferred patients become ineligible for EVT due to progressive infarct.³ Significant time is lost with inefficient telephone and paper-based communication and logistics that occur in series rather than in parallel; spending just 10 unnecessary minutes translates to 6 weeks of disability-free life lost for an EVT-eligible patient.⁴

Therefore, we have a significant challenge: how do we improve the systems of care to identify the right patient in the field and triage them to receive the right therapy at the right place at the right time?

- **Improve prehospital triage.** Although there is no optimal clinical triage tool or current stroke equivalent of an electrocardiogram, there are multiple imminent contenders. Emerging handheld or portable technologies such as microwaves, electromagnetic waves, electroencephalography sensors, and other methods could provide real-time rapid assessment to augment initial prehospital clinical assessment.
- **Advance imaging and treatment in the field.** Mobile stroke treatment units (MSTUs) with advanced imaging performed in an ambulance offer the best opportunity for reducing the symptom onset-to-IVT treatment time and open the door to potential future prehospital therapies such as neuroprotection to minimize the progression of infarct. However, MSTUs may not be cost-effective for all communities, particularly regional and rural stroke patients.
- **Streamline communication.** There are multiple handovers in the patient's journey from stroke

onset to reperfusion therapy. Integrated prenotification and in-hospital communication tools that involve all required health care providers offer the ability to bring parallel processing to the prehospital phase of stroke care. Electronic multicast communication can create swift and seamless handover both within a health care network and all spoke transfer centers.

Getting the right patient to the right therapy at the right place at the right time requires cross-organizational collaboration with a focus on revolutionizing the prehospital stage. Our field is best placed to consider optimal clinical practice, but this requires us to continually adapt and improve access to EVT centers

in alignment with the advancement of reperfusion therapies. This can be achieved by working together to optimize stroke care, not just in the hospital setting but by considering local geographic context and local treatment paradigms. Our patients deserve our attention to this unanswered question as we work together to deliver the best outcomes to our communities.



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Disclosures: Consultant to Medtronic, Stryker, MicroVention Terumo, Cerenovus, Mentice, GE Healthcare; unrestricted research grants to University of Calgary, Medtronic, Stryker.

In my opinion, our single biggest challenge moving forward is the organization of stroke care, specifically how to get the correct patient to the correct hospital as quickly as possible. We know that MT is highly efficacious irrespective of age, sex, time from onset, severity of stroke symptoms, affected side, and even severity of changes on the initial imaging.¹ Recent data from HERMES show efficacy even in patients with ASPECTS 3 to 5 and CT perfusion core volume > 70 mL.^{2,3} However, the fact is that “time is brain” is absolutely clear and backed by excellent data from multiple studies.

Therefore, it is imperative that we organize stroke systems of care in a way that every patient with LVO has access to MT as quickly as possible. We can think of the overall flow of time in acute stroke in two periods: (1) onset to imaging decides the likelihood of favorable imaging and (2) imaging to high-quality reperfusion decides the likelihood of a good outcome.⁴ I like to use the phrase *denominator fallacy* to further expand on the concept.⁵ Imagine that the likelihood of a good outcome in patients undergoing MT is 60%. For 100 patients who

present to an EVT center within 30 minutes, all will have favorable imaging and will be candidates for MT, consequently resulting in 60 of them having a good outcome. Conversely, at 8 hours from onset, maybe 10 of 100 patients will have favorable imaging and undergo MT, with 6 of those 10 patients still having a good outcome. But in reality, only 6 out of 100 will have a good outcome. Therefore, if we can organize systems of care in a way that these patients can get to the correct hospital much faster, we can have a much greater impact on the disease. We know from the SWIFT PRIME data that, on average, drip-and-ship patients were 2 hours slower to reperfusion than direct-to-mothership patients.⁶

Of course, in parallel, upcoming technologies may allow for more accurate detection of LVOs in the ambulance. In the meantime, we must be cognizant that the criteria for MT are expanding (eg, most interventionalists would treat patients with an M2 occlusion with a significant neurologic deficit). In addition, scoring systems such as the Los Angeles Motor Score and Rapid Arterial Occlusion Evaluation perform reasonably well in the field. Mathematical modeling using data from the trials gives us a clear indication of how stroke care could be centralized in big cities. The biggest obstacles to reorganization are likely human factors such as politics and history rather than scientific factors.

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*Disclosures: Consulting agreement with
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Wildly ranging estimates of LVO strokes amenable to EVT are the most important issue requiring our attention. It is important because overestimation will lead to an overestimation of resources (both human and logistic) to tackle the disease burden and vice versa. It is not that this question has not been answered but rather that the answer has been derived from diverse methodologies and then extrapolated to the general population, leading to the variation in these estimates. A reasonably accurate assessment of the LVO stroke burden has important implications for systems of care and physician training.

Let's start with the oft-quoted number of almost 800,000 strokes, of which 87% are identified as ischemic.¹ This gives a denominator of about 700,000 acute ischemic strokes (AISs) from which an LVO rate can be derived. However, it is critical to note that the 700,000 AIS denominator is derived from specific AIS discharge codes such as those used in the Greater Cincinnati Northern Kentucky Stroke study² and BASIC Project.³ Any study extrapolating an LVO incidence to this denominator has to use the same methodology (ie, International Classification of Diseases [ICD] codes) in defining the denominator as those used for the larger number (approximately 700,000 AISs). LVO rates extrapolated from a different methodology would

be misleading. For instance, a 30% LVO rate among a selected cohort of patients suspected of having an AIS in a tertiary-level hospital assessed by a neurologist does not equal a 30% LVO rate among all 700,000 AIS patients derived from the ICD discharge codes. An LVO diagnosis on reliable imaging such as CTA is also important, because several studies have used transcranial Doppler, which is less reliable, or even NIHSS score as a surrogate for LVO strokes. Population studies estimate an LVO rate of ≤ 22 to 31 per 100,000 people per year⁴⁻⁶ or about 15% of all AISs based on the same ICD codes used in the 700,000 AISs estimate.

An inaccurately inflated demand may lead to an oversupply of resources. A good example would be an overblown need for neurointerventionalists to tackle the "surging" demand of LVO strokes. The requirement for 24/7 stroke coverage does not correlate with the LVO numbers but rather the need for around-the-clock service. Perhaps a way forward would be to organize multicenter registries to track AIS numbers based on uniform ICD codes and imaging-confirmed LVOs. These could be matched to an institution's geographic area and population. Furthermore, combining these with outcomes data will provide a robust and real-time assessment of the disease burden and the effectiveness of our therapies. ■

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