ASK THE EXPERTS

Predicting the Next Breakthrough in Ischemic Stroke Therapy

Physicians share their hopes for the future of acute ischemic stroke care.

With Thabele (Bay) Leslie-Mazwi, MD; Ashutosh P. Jadhav, MD, PhD; Justin M. Cappuzzo, MD; Elad I. Levy, MD, MBA; Waleed Brinjikji, MD; and Demi Dawkins, MD

Thabele (Bay) Leslie-Mazwi, MD
Professor and Chair, Department of Neurology
Warren and Jermaine Magnuson Endowed Chair in Medicine for Neurosciences
Co-Director, Neurosciences Institute
UW Medicine
University of Washington
Seattle, Washington
tml01@uw.edu
Disclosures: None.

Prediction of the future is fraught with peril, and there are many frontiers in stroke that have the potential to be the "next big breakthrough." With those two caveats, what does the *near* future look like in endovascular stroke care, and where might this breakthrough lie? In my opinion, this breakthrough should be defined by the number of patients who can be helped.

Our technical ability to recanalize the point of primary occlusion is now consistently approaching 90%. The next big breakthrough will not lie in technologic improvements or new devices, even though achieving complete reperfusion (thrombolysis in cerebral infarction [TICI] 3) is the new goal. The recent publication of the CHOICE trial hinted at the potential for greater reperfusion through the use of thrombolytic augmentation (with alteplase) after thrombectomy.[1] I suspect that, in general, a hybrid mechanical and medical approach to large vessel occlusion (LVO) stroke will prove beneficial. Whether the medical component is an adjunct thrombolytic, a neuroprotectant, stem cells, or another compound remains to be defined and represents an exciting breakthrough.

However, I think that the big breakthrough in the near future will be related to patient candidacy for mechanical thrombectomy (MT). The most important group under consideration is patients with large pretreatment core infarcts. The RESCUE-Japan LIMIT trial recently demonstrated that MT provided benefit to this population.[2] Multiple other trials are actively recruiting and will inform this question in more detail. If this population benefits from MT, it represents a potential expansion of up to 40% of our current MT candidate pool. This major expansion will allow treatment access to a much larger proportion of patients, thus increasing the chance of recovery for these patients. It also simplifies our paradigms for selecting candidates for treatment. I am very excited to see what the next year or two brings in this regard.

1. Renú A, Millán M, San Román L, et al; CHOICE Investigators. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. JAMA. 2022;327:826-835. doi: 10.1001/jama.2022.1645
2. Yoshimura S, Uchida K, Sakai N, et al. Randomized clinical trial of endovascular therapy for acute large vessel occlusion with large ischemic core (RESCUE-Japan LIMIT): rationale and study protocol. Neurol Med Chir (Tokyo). 2022;62:156-164. doi: 10.2176/nmc.rc.2021-0311

Ashutosh P. Jadhav, MD, PhD
Barrow Neurological Institute
Phoenix, Arizona
ashu.jadhav@gmail.com
@ashupjadhav
Disclosures: None.

Endovascular therapy for acute ischemic stroke (AIS) therapy has proven to be superior to medical therapy for a select population of patients. Future breakthroughs in AIS therapy can be divided into three major opportunities: enhancing efficacy of existing treatments, expanding indications for existing treatments, and increasing access of existing treatments. Efficacy, indications, and access are the three domains in which ongoing efforts are currently focused, and each serves to individually improve slightly different aspects of stroke care.

Although recanalization is critical to achieving optimal outcomes after AIS, functional independence is only observed in approximately half of LVO patients undergoing thrombectomy; the remaining patients have permanent dependence or die. Opportunities to improve outcomes include faster symptom onset–to-treatment time via in-field identification of LVO patients and direct-to–angiography suite triage. Rates of complete recanalization (TICI 3) as well as recanalization after one attempt (first-pass effect) both occur in < 50% of patients with existing devices and techniques. Current device development opportunities are focused on faster time-to-clot contact, as well as more efficacious clot extraction. Particularly resilient lesions are enriched in thrombin and platelets (white clot), as well as lesions with intrinsic pathology (intracranial atherosclerotic disease). Real-time understanding of clot composition with imaging and intraprocedural clot feedback represents a potential strategy to guiding a personalized device and technique selection approach to achieving high-quality, rapid recanalization.

Despite recanalization, clinical improvement may not be achieved due to established infarct, hemorrhagic conversion, edema, and limited neurorecovery. To date, no neuroprotectants have improved clinical outcomes; however, a majority of studies were conducted in the preendovascular era, and a major concern was that it was unclear whether the neuroprotectant would reach the target tissue without vessel recanalization. At present, there are numerous neuroprotectant strategies being investigated, specifically in patients during or after endovascular therapy, including nerinetide (ESCAPE-NEXT), glibenclamide (CHARM), stem cells (MASTERS-2), and hypothermia (ReCLAIM-2).

Current class 1A level of evidence is limited to previously functionally independent patients presenting with anterior circulation LVO in the setting of severe symptoms and with a relatively small infarct on presentation. The role of endovascular therapy in patients with preexisting disability (modified Rankin Scale> 2), milder symptoms (National Institutes of Health Stroke Scale [NIHSS] < 6), large core (Alberta Stroke Program Early CT Score < 6), or medium vessel occlusion (MeVO) remains unclear. Although several registries and nonrandomized studies have suggested the benefit of endovascular therapy, these understudied populations are the subject of several ongoing randomized controlled trials (MOSTE and ENDOLOW for low NIHSS patients; DISTALS, DISTAL, and DISCOUNT for MeVO). Notably, the recently completed RESCUE-Japan LIMIT trial demonstrated superior outcomes in patients with large core who were treated with endovascular therapy.[1] Further evidence is awaited from results of ongoing trials studying the large core population (TESLA, TENSION, LASTE). Current estimates suggest a nearly quadruple increase in the number of patients eligible for endovascular therapy if benefit is proven for currently off-label patient populations.

Issues of access exist on varying scales in the developed and developing world. In the developed world, poor outcomes are seen differentially in vulnerable populations, including minorities, women, and socioeconomically disadvantaged populations, and are related to underappreciation of stroke symptoms with delays in seeking time-sensitive treatments, as well as poor access to insurance, medications, and rehabilitation services in the postrecovery period. In contrast, the developing world continues to lag behind in offering endovascular therapies due to lack of trained specialists, infrastructure, and prohibitively expensive devices and equipment. Recognizing these disparities in care is critical to democratizing access and outcomes. This is currently being addressed with improved public outreach, expanding expertise through telemedicine and remote proctoring, and efforts to reduce device costs. Multiple efforts through the global Mission Thrombectomy 2020+ Initiative (missionthrombectomy2020.org) are designed to understand and target treatment inequalities, particularly in low-middle–income countries.

In 1995, intravenous (IV) alteplase was approved as the first treatment to show benefit for AIS. It took nearly 20 years for the next treatment breakthrough to have proven efficacy in the form of endovascular therapy. Despite these critical advances, a large portion of stroke patients continue to have poor outcomes. Multiple ongoing research efforts seek to address current gaps in efficacy, indications, and access at an accelerating pace. The future of AIS therapy in the next 20 years will indeed be exciting to witness.

1. Yoshimura S, Uchida K, Sakai N, et al. Randomized clinical trial of endovascular therapy for acute large vessel occlusion with large ischemic core (RESCUE-Japan LIMIT): rationale and study protocol. Neurol Med Chir (Tokyo). 2022;62:156-164. doi: 10.2176/nmc.rc.2021-0311

Justin M. Cappuzzo, MD
Department of Neurosurgery
University at Buffalo Neurosurgery
Buffalo, New York
jcappuzzo@ubns.com
Disclosures: Consultant, Cerenovus, J&J Medical Device Companies, Integra Lifesciences Corp, MIVI Neuroscience, Inc., Penumbra, Inc., and Stryker.

Elad I. Levy, MD, MBA
L. Nelson Hopkins Chair of Neurological Surgery
Professor and Chair, Department of Neurosurgery
SUNY Distinguished Professor
University at Buffalo Neurosurgery
Director of Stroke Services
Kaleida Health
Buffalo, New York
elevy@ubns.com
Disclosures: Shareholder/ownership interest, NeXtGen Biologics, RAPID Medical, Claret Medical, Cognition Medical, Imperative Care, Rebound Therapeutics, StimMed, Three Rivers Medical; patent, Bone Scalpel; honorarium for training and lectures: Medtronic, Penumbra, MicroVention, Integra; consultant, Clarion, GLG Consulting, Guidepoint Global, Imperative Care, Medtronic, StimMed, Misionix, Mosiac; chief medical officer, Haniva Technology; National Principal Investigator, Medtronic (steering committees for SWIFT Prime and SWIFT Direct trials); site PI study, MicroVention (CONFIDENCE study), Medtronic (STRATIS study-sub 1); advisory board, Stryker (AIS clinical advisory board), NeXtGen Biologics, MEDX, Cognition Medical; Endostream Medical, IRRAS AB; consultant/advisory board, medical legal review, render medical/legal opinions as an expert witness; leadership or fiduciary roles in other board society, committee or advocacy group, paid and unpaid for CNS, ABNS, UBNS.

AIS remains one of the most common causes of morbidity and mortality in the United States and throughout the world.[1] With the advent of IV thrombolysis, we slowly began to treat AIS instead of managing the devastating sequelae that followed. Through the development of stentrievers and aspiration catheters for MT, we have drastically increased the number of patients treated for AIS. The next question we ask ourselves is: Where do we go from here?

Although increasing access to stroke intervention has spared many patients from the devastating results of a completed infarction, it has also revealed that not everyone is suitable to undergo revascularization. Reperfusion hemorrhage and iatrogenic endovascular injury are real phenomenons; therefore, determining who is most likely to benefit from these interventions has been a topic of interest.[2,3] As with most things in medicine, a patient-centric model has been our path toward discovering how to manage this disease. What we have learned is that we are more sophisticated than a stopwatch. We can use patients' own physiology to understand whether they have salvageable brain tissue based on their vascular reserve, regardless of the time of onset.[4-6] This technique using CT perfusion has led us to now carefully select who is most likely to benefit from MT and have reasonable discussions with families about treatment to minimize harm to the patient.

As endovascular devices continue to develop, we are now moving toward treating patients with distal LVOs (DLVOs) as well. Although IV thrombolysis therapy has shown excellent efficacy in treating DLVOs, MT has become another potential option for those patients not eligible for chemolytic therapy. Although the additional MT trials typically treated patients with high NIHSS scores and LVOs, those with either DLVOs or low NIHSS scores may be candidates for MT after weighing the risks and benefits of revascularization in each specific patient. For example, compare a patient with a dominant distal M2/M3 branch affected, resulting in isolated dense aphasia, to a second patient with mild hand clumsiness in their nondominant hand with some paresthesia and drift. Both patients have an identical low NIHSS, but the first patient has symptoms that are much more disabling and much less likely to rehabilitate. Therefore, the patient with the dense aphasia may have a risk-benefit in favor of MT revascularization despite the low NIHSS, whereas the other patient has a much less disabling deficit and has a great deal to lose if there is any complication with MT (eg, hemorrhagic transformation or iatrogenic injury).

As we continue to push the envelope forward in stroke care, we hope to continue further refining not only our endovascular techniques but also our diagnostic strategies so we are better able to advance treating AIS using a patient-centric approach. The future looks bright.

1. Centers for Disease Control and Prevention. Stroke facts. Accessed May 12, 2022. https://www.cdc.gov/stroke/facts.htm
2. Adebayo OD, Culpan G. Diagnostic accuracy of computed tomography perfusion in the prediction of haemorrhagic transformation and patient outcome in acute ischaemic stroke: a systematic review and meta-analysis. Eur Stroke J. 2020;5:4-16. doi: 10.1177/2396987319883461
3. Liu L, Wu B, Zhao J, et al. Computed tomography perfusion Alberta stroke program early computed tomography score is associated with hemorrhagic transformation after acute cardioembolic stroke. Front Neurol. 2017;8:591. doi: 10.3389/fneur.2017.00591
4. Biesbroek JM, Niesten JM, Dankbaar JW, et al. Diagnostic accuracy of CT perfusion imaging for detecting acute ischemic stroke: a systematic review and meta-analysis. Cerebrovasc Dis. 2013;35:493-501. doi: 10.1159/000350200
5. Junejo HU, Yusuf S, Zeb R, et al. Predictive value of CT brain perfusion studies in acute ischemic infarct taking MRI stroke protocol as gold standard. Cureus. 2021;13:e16501. doi: 10.7759/cureus.16501
6. Shen J, Li X, Li Y, Wu B. Comparative accuracy of CT perfusion in diagnosing acute ischemic stroke: a systematic review of 27 trials. PLoS One. 2017;12:e0176622. doi: 10.1371/journal.pone.0176622

Waleed Brinjikji, MD
Professor of Neurosurgery and Interventional Neuroradiology
Mayo Clinic
Rochester, Minnesota
brinjikji.waleed@mayo.edu
Disclosures: Consultant, MIVI, MicroVention, Medtronic, Cerenovus, Stryker, Rapid AI, Balt; research funding, Cerenovus.

I'm going to say something that will come off as unpopular given that I am a neurointerventionalist. The next breakthrough in AIS should be focused on the development of improvement in IV thrombolytics. Currently, the only FDA improved thrombolytic is alteplase. However, many centers are starting to use tenecteplase (TNK) given the improved safety and efficacy profile seen in previous studies. In particular, the EXTEND-IA TNK trial found that in patients with LVO, TNK resulted in a more than twofold increase in revascularization rates when compared to alteplase (22% vs 10%).[1] This shows that even in LVO, there remains potential room for improvement with IV thrombolytics.

The medical community should not be satisfied with these low revascularization rates. Let's step back and ask ourselves why we are still only seeing recanalization rates of 22% in the best-case scenario with newer thrombolytics. Over the past 5 years, our group has worked to create a large multicenter registry of clots collected from AIS patients called the Stroke Thrombectomy Registry of Imaging and Pathology (STRIP). After analysis of > 2,000 MT specimens, we are now starting to uncover the mechanisms of tissue plasminogen activator (tPA) resistance and discover potential new targets for novel thrombolytics aimed at lysing AIS clots. tPA and TNK work to degrade fibrin networks within clots; they are fibrinolytics. So, these drugs are going to work on clots that have a nice, accessible network of fibrin to digest. However, work from our MT registry has found that clots are much more complex than the amalgamation of fibrin and red blood cells than previously thought. Rather, most clots are composed of a complex network of platelets, von Willebrand factor (vWF), and neutrophil extracellular traps (NETs) that are all resistant to fibrinolysis. What's more, the surface of most clots is composed not of fibrin but a dense network of platelets, vWF, and NETs. Therefore, we think tPA and TNK alone will not going to be enough to treat most LVOs.

Without a doubt, mechanical clot retrieval will be part and parcel of the future of stroke management. But, imagine what could be accomplished with novel thrombolytics aimed at things other than fibrin. Even if we can get to 50% of LVOs recanalized with IV thrombolytics, this would significantly broaden the range of patients who could experience good outcomes. Think about patients in rural settings (drip and ship) or patients in resource-poor environments. With the treasure trove of knowledge we are gaining from the analysis of MT specimens, maybe in 10 to 20 years we will be able to treat and cure most stroke patients with just the push of a needle.

1. Campbell BCV, Mitchell PJ, Churilov L, et al; EXTEND-IA TNK Investigators. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med. 2018;378:1573-1582. doi: 10.1056/NEJMoa1716405

Demi Dawkins, MD
Department of Neurosurgery
University of Tennessee Health Sciences Center
Semmes-Murphey Clinic
Memphis, Tennessee
demi.dawkins@gmail.com
Disclosures: None.

I believe the next breakthrough in AIS therapy should be related to targeted therapy based on clot composition. As we have gotten better at thrombectomy and retrieving clots, we have also gotten better at understanding that not all clots are created equal. We know that thrombus composition does influence AIS treatment, including the success or failure of tPA, the number of passes to successful recanalization, and the optimal modality for thrombectomy (ie, direct aspiration vs stentriever).

In the future, I think a thorough understanding of thrombus composition could greatly improve our success in stroke therapy. In my mind, this includes both advancements in imaging modalities and understanding of stroke etiology (ie, cardioembolic or atheroembolic) to help predict clot composition. In turn, our understanding of thrombus and which compositions respond to different techniques may improve our speed and accuracy in stroke therapy. ■