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Six randomized, multicenter trials demonstrated a clinical benefit for patients with low ASPECTS regardless of the amount of the penumbra on advanced perfusion imaging. These findings not only question the utility of neuroimaging and advanced techniques to identify infarcted tissue, but they also profoundly challenge the foundation of our understanding of hypoperfusion and its reversibility. Now more than ever, there is tremendous need for better neuroimaging tools to reliably identify patients with large ischemic strokes who will benefit from endovascular treatment.

Recently, 6 large, multicenter, randomized controlled trials[1-6] have concluded their investigations on the efficacy and safety of endovascular thrombectomy (EVT) for patients presenting with large ischemic strokes seen on initial neuroimaging. Overall, the 6 trials demonstrated consistent clinical benefit for patients with a low ASPECTS of 3–5, with subgroup analyses also showing the benefit of EVT for even lower ASPECTS (0–2) and large infarct volumes seen on perfusion imaging or MR imaging (>200 mL), regardless of the amount of stroke penumbra. These results seem to suggest that re-establishing blood flow to areas of the brain labeled as "ischemic core" (which was previously thought to be infarcted) may yield clinically significant benefit, and they have major implications for the role of neuroimaging during acute stroke triage and management.

Historically, neuroimaging played a critical role in the understanding of ischemic brain diseases. CT revealed the brain as a digital craniotome, and the detailed tissue resolution provided by MR imaging yielded great insight into stroke pathophysiology. When it became clear that patients with strokes have limited time before tissue ischemia progresses to infarct and neuronal death, neuroimaging techniques were used to provide real-time assessment of tissue viability. To this end, the identification of early ischemic changes on noncontrast CT was proposed, and the quasi-quantitative ASPECTS system was developed. Subsequently, quantitative analyses using CT perfusion and MR imaging made possible the identification of already-infarcted tissue (also termed the ischemic core) and symptomatic-but-salvageable ischemic tissue (also termed the "stroke penumbra"), and recent advances in artificial intelligence ushered these advanced imaging tools into routine clinical use. Some hospital systems also devised specialized protocols to allow rapid MR imaging, which provides additional tissue resolution to quantify the approximate age and extent of ischemic lesions during acute stroke triage. These advanced imaging modalities were part of the main inclusion and exclusion criteria for numerous landmark stroke trials, and they laid the foundation for the expanding use of both IV thrombolysis (via the Efficacy and Safety of the MRI-Based Thrombolysis in Wake-Up Stroke [WAKE-UP] and Extending the Time for Thrombolysis in Emergency Neurological Deficits [EXTEND] trials) and EVT (via the Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment for Acute Ischemic Stroke [SWIFT PRIME], Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial [EXTEND-IA], Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo [DAWN], and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 [DEFUSE 3] trials).

The utility of advanced neuroimaging during acute stroke triage was largely predicated on the notion that stroke therapy does not always lead to successful recanalization of occluded vessels, with substantial hemorrhagic and procedural risks. Thus, it was thought that aggressive treatment for larger ischemic cores and smaller penumbras may expose patients to minimal benefit and excessive harm, particularly for EVT. The first endovascular treatment for acute intracranial occlusions can be dated to the 1980s, mostly using intra-arterial thrombus-dissolving medications. For about 25 years, these procedures were mostly unsuccessful until the first mechanical thrombectomy devices were introduced (Merci retriever, Concentric Medical; and Penumbra Separator, Penumbra). Since 2015, technical advancements from stent retrievers to direct aspiration catheters to balloon guide catheters have been concatenating incredibly quickly. Research behind these devices moves so quickly that the US FDA had to establish guidelines specifically regulating preclinical and clinical studies for neurothrombectomy tools, first in 2007,[7] then updated in 2016.[8]

The remarkable advances in neurothrombectomy devices culminated in high rates of successful recanalization and low rates of hemorrhagic transformations in the recently published trials on large-core thrombectomies, and the consistent efficacy signal observed across the 6 trials essentially upends the original value proposition of advanced neuroimaging during acute stroke triage. Thus, we are now entering an era of crisis in which we are witnessing a reverse trend in which the so-called "advanced imaging" techniques are set aside in favor of noncontrast head CT or even direct-to-thrombectomy protocols.

Despite the proved benefit of EVT in multiple trials, not all patients will benefit from reperfusion. The pathophysiologic umbra-penumbra dogma was originally proposed by Astrup et al,[9] in which there is a certain volume of tissue irreversibly damaged defined as "core" and a certain volume of tissue that is oligemic defined as "penumbra." This artificial construct was a valuable model during the development of acute stroke reperfusion treatments. Volumetric analyses of core and penumbra have been reliably associated with patient prognosis following revascularization, suggesting that the umbra-penumbra dogma likely holds true in a general sense. However, this model is likely an oversimplification of true pathophysiology, which likely involves many more nuances in the dynamic macrovascular and microvascular environment during acute ischemic stroke. Thus, while the umbra-penumbra dogma can provide valuable information on neuroprognosis following EVT, it is likely insufficient for predicting the treatment effect

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of EVT on each individual patient and may not be as well-suited for selecting patients for EVT treatment as previously believed. Our foothold at this time is that we know that at a certain point, ischemic brain tissue will fully infarct if blood flow is not restored. Thus, a major challenge for treatment decisions in the future will be to better identify when tissue is truly no longer viable and therefore will not benefit from reperfusion. We must concede that current neuroimaging tools for acute stroke triage (ASPECTS, CT perfusion, and DWI) are inconsistent and largely unable to accurately predict the extent of unsalvageable stroke damage.

The high rates of poor outcomes in the EVT arms of the recently published trials for large strokes (close to 80% death or dependency) suggest that treating all patients with large-vessel occlusion strokes regardless of tissue status is a crude strategy at best, and doing so will inevitably strain the existing neuroendovascular workforce and jeopardize precious health care resources for patients more likely to benefit from treatment. Thus, there remains tremendous foundational research opportunities for better neuroradiologic technologies to further optimize stroke triage, focusing on the need to devise new imaging constructs specifically with the aim of predicting treatment effect and improving patient outcomes. It is, therefore, our belief that the recently published trial results should not be interpreted as a setback for advanced stroke imaging, but instead, they should be viewed as a call for further development and refinement of neuroimaging tools to rapidly assess the viability of ischemic stroke tissue.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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