Should We Still Care About Core Volume for Stroke Thrombectomy?

Determining the treatment ceiling for endovascular thrombectomy for large core strokes based on ischemic core size, time, and choice of imaging modality.

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Endovascular thrombectomy (EVT) has been revolutionary in the management of acute ischemic stroke patients presenting with large vessel occlusion (LVO). Multiple clinical trials have proven the safety and efficacy of EVT both in early and late time windows up to 24 hours.[1-7] However, most of these trials used restrictive criteria to select patients for EVT, identifying those with a reversible neurologic deficit and no or minimal ischemic changes on baseline imaging and thus a higher likelihood to benefit from treatment. The patients enrolled in the aforementioned randomized controlled trials (RCTs) had uniformly smaller strokes, with a median Alberta Stroke Program Early CT Score (ASPECTS)[8] of 9 and median ischemic core volume of 10 mL on perfusion imaging in a HERMES meta-analysis of pooled patient-level data from the early time window RCTs.[9] Similarly, diffusion-weighted imaging or CT perfusion assessment with clinical mismatch in the DAWN and DEFUSE 3 studies also excluded patients with significant ischemic changes on both noncontrast CT and perfusion imaging.[6,7] Thus, randomized evidence of EVT safety and efficacy in patients with large ischemic changes is essentially unavailable.

The likelihood of achieving a good outcome with EVT is lower in patients with large ischemic cores due to the significant established tissue damage and perceived irreversible neurologic deficits. There is also a higher risk of hemorrhagic transformation with reperfusion therapy in these patients. Thus, the risk-benefit ratio of EVT is not well established in the so-called large core. However, the natural history of the disease in this population portends a very poor outcome, with a high risk of stroke progression, brain herniation, neurologic worsening, hemorrhagic transformation, and, ultimately, death.

To assess the safety and efficacy of EVT in patients with large core strokes, clinical trials such as TESLA,[10] TENSION,[11] IN EXTREMIS,[12] and SELECT 2[13] are ongoing. However, until the results of these trials become available, treating physicians face a dilemma of whether or not to offer EVT in this subpopulation that accounts for 20% to 25% of all anterior circulation LVOs.[14]

Several considerations factor into the decision of whether to proceed with EVT in large ischemic cores and whether the intervention may result in an adjunctive benefit.

ISCHEMIC CORE SIZE: HOW LARGE CAN WE GO?

Although earlier RCTs enrolled patients with limited ischemic changes, 215 patients with low ASPECTS (≤ 5) were also enrolled in these trials, particularly in MR CLEAN,[1] which had the most liberal imaging inclusion criteria. The HERMES meta-analysis of pooled patient-level data of five RCTs suggested EVT may be associated with better functional independence rates in patients with ASPECTS of 3 to 5.[15] However, in patients with ASPECTS of 0 to 2, it failed to demonstrate a significant improvement in the functional independence rates. A similar post hoc analysis from the HERMES data assessing EVT outcomes based on baseline perfusion imaging did not find significant improvement in functional independence rates in patients with an ischemic core > 70 mL.[16] A significant shift in modified Rankin Scale (mRS) score was observed in patients who underwent EVT, but the statistical significance was not sustained after adjusting for

potential confounders. Thus, a case can be made for the potential benefit of EVT in patients with large core strokes on either imaging modality in the early treatment window (0–6 hours). Because both the DAWN and DEFUSE 3 trials excluded patients with an ischemic core > 50 mL and > 70 mL, respectively,[6,7] no randomized evidence of EVT's safety and efficacy is available in patients with large ischemic cores presenting beyond 6 hours.

Although the likelihood of achieving functional independence in patients presenting with a very large ischemic core would be logically lower than those with small core infarcts, EVT may still reduce severe disability and improve functional outcomes across all mRS categories. In the HERMES meta-analysis of perfusion imaging, the functional independence rates were 8% in the EVT arm and 0% in the medical management arm for patients presenting with an ischemic core volume > 70 mL.[16] However, based on the available data, Campbell et al suggested that the number needed to treat remained < 10 for most functional outcomes and < 5 for at least one score improvement in 90-day mRS score up to 125 mL of ischemic core volume.[16] For functional improvement of at least one category, a significant reduction in absolute risk persisted for up to 150 mL of ischemic core volume. Although these data were derived from statistical models using the population enrolled in trials participating in the HERMES meta-analysis, which largely excluded large core patients, it is not unreasonable to argue that EVT may theoretically benefit patients presenting with up to 150 mL of infarct core.

The prespecified analysis of large core patients from the SELECT prospective cohort study suggested that EVT may be associated with potential benefit and a reasonable safety profile.[14] In SELECT patients with ASPECTS ≤ 5, ischemic core ≥ 50 mL, or both, EVT was associated with improved rates of functional independence (31% vs 14%; odds ratio [OR], 3.27; 95% confidence interval [CI], 1.11–9.62; $P = .03$). However, the likelihood of benefit significantly decreased with increased infarct size (42% reduction with every 10 mL; adjusted OR, 0.58; 95% CI, 0.39–0.87; $P = .007$), with no patients with ischemic core > 100 mL achieving functional independence.

An analysis of pooled data from SELECT and TREVO, two large prospective cohort studies, suggested a very low probability of functional independence in patients with ASPECTS of 3 to 5 who presented with an ischemic core > 100 mL.[17,18]

Therefore, although EVT may result in improved outcomes in patients with a large core, at this point, it remains unknown how far the treatment limit would be—whether it is 100 or 150 mL or an ASPECTS of ≤ 3 remains to be determined.

THE TIME EFFECT

"Time is brain"—for every minute blood flow to the brain is restricted, 1.9 million neurons, 14 billion synapses, and 12 km of myelinated fibers are lost.[19] In the HERMES meta-analysis, with each hour delay of reperfusion, the rates of functional improvement were reduced by 16% (crude OR, 0.84; 95% CI, 0.76–0.93; absolute risk difference, -6.7%) and the rates of functional independence were reduced by 14% (OR, 0.81; 95% CI, 0.71–0.92; absolute risk difference, -5.2%) in patients who underwent EVT.[20] Although no significant heterogeneity in EVT treatment effect was observed, DAWN and DEFUSE 3 also reported a reduction in good outcome rates as time progressed.[6,7] In the SELECT study subanalysis of patients with a large ischemic core, the probability of functional independence decreased as time progressed, with a 40% reduction with each passing hour (adjusted OR, 0.60; 95% CI, 0.36–0.99; $P = .045$) and probabilities reaching < 10% beyond 12 hours of stroke onset.[14]

Logically, time is more of the essence in large core patients given the already established large infarcts and the lower likelihood of benefit from treatment, which would be further reduced as time progresses. Whether it is 6 hours, 12 hours, or up to 24 hours, the time window for intervening in patients with large ischemic cores remains to be seen!

THE TALE OF TWO IMAGING MODALITIES: CT VERSUS PERFUSION

Noncontrast CT and perfusion imaging are the two main imaging modalities used in triaging patients for EVT. The two modalities measure different qualities related to ischemic brain changes. CT demonstrates tissue hypodensities, whereas perfusion imaging represents the blood flow rates and volumes in various areas of the brain. Noncontrast CT largely provides qualitative or semiquantitative measurements in the instance of ASPECTS calculation. On the other hand, perfusion imaging can provide quantitative data of brain areas sustaining ischemic changes. The availability of CT is ubiquitous and acquisition is faster than perfusion imaging. Therefore, paradigms involving patient selection using only CT may result in faster delivery of EVT and thus better outcomes. However, randomized evidence in support of such practice is limited, and the practice is primarily governed by the perfusion imaging, especially in the late time window.

The SELECT study explored how these two imaging modalities correlate and how their concordance and discordance impact functional and safety outcomes in patients with acute ischemic stroke presenting with LVO.[21] Although favorable profiles on either CT (ASPECTS ≥ 6) or CT perfusion (relative cerebral blood

flow [rCBF] < 30%; > 70 mL) was associated with similar functional independence rates with EVT, having an unfavorable profile on CT perfusion was associated with higher symptomatic hemorrhage, neurologic worsening, and mortality rates.[21] In the SELECT subanalysis, EVT was associated with higher rates of functional independence both on CT (ASPECTS 3–5) (35% for EVT vs 18% for medical management; *P* = .10) and CT perfusion (rCBF < 30%; > 50 mL) (21% for EVT vs 3% for medical management; *P* = .03), with a signal for shift toward better functional outcome (CT: adjusted OR, 1.76; 95% CI, 0.67–4.62; *P* = .25; CT perfusion: adjusted OR, 1.53; 95% CI, 0.54–4.30; *P* = .42).[14] However, as the volumes increased on CT perfusion, the likelihood of benefit decreased and safety concerns increased. This relationship was not as well established with lower ASPECTS on CT. Thus, the association between outcomes and ASPECTS was not as linear as that seen with ischemic core volume per CT perfusion. This could be due to the low number of patients in each ASPECTS category. The differences in functional outcomes seen with ischemic cores as measured by CT perfusion and ASPECTS also may be related to differences between the two modalities in their ability to detect the volume of early tissue injury.

Most of the upcoming clinical trials use noncontrast CT or MRI for imaging selection and do not include perfusion findings (TESLA,[10] TENSION,[11] and IN EXTREMIS[12]). SELECT 2 is the only trial using perfusion imaging along with noncontrast CT to define large core strokes without an upper limit for ischemic core volume, which will allow for a randomized assessment of the additional value of perfusion imaging findings.[13] It will also provide an assessment of the upper limit of volume that may benefit from EVT with a reasonable safety profile.

SUMMARY

EVT has made huge leaps in the last few years and has become the treatment of choice for selected acute ischemic stroke patients due to LVO in the anterior circulation in both the early and late time windows. The next major question in EVT evolution is where the treatment effect ceiling should be set in terms of stroke size. Randomized evidence of EVT safety and efficacy will be forthcoming in the next few years. Results from these trials will help us understand if there is indeed a ceiling effect for EVT where it becomes futile beyond a certain stroke size. Will the ceiling be set at 100 mL, 150 mL, or beyond? Should patients with an ASPECTS < 6 undergo EVT, and if so, how low should we go? And if EVT offers benefit in large core patients, how late can these patients still be treated? What imaging modality should be used in selecting large core patients for EVT? Is CT enough, or do we need additional MRI and perfusion imaging? We should get these answers within the next 2 to 3 years. ■

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