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Lieberkind et al1 aimed to establish serial Alberta Stroke Program Early Computed Tomography Score (ASPECTS) as a novel measure of ischemic evolution and of the potential therapeutic effects of reperfusion. They conclude that the 24-hour ASPECTS is better at prediction of 90-day function than a baseline score and infer that it provides an early surrogate end point for thrombectomy trials. Good prediction could be valuable. It may render research more practical and could be a factor in training interventionalists on patient selection through feedback on outcomes.

Their findings need to be interpreted with caution, however, for reasons of patient selection, potential confounding, statistical issues, exclusion of alternatives, and timing of data collection.

This is a retrospective study on a subset of patients for whom complete data were available. It is unsurprising that the 24-hour scan appearance associates more strongly with outcome than a baseline scan; although their patients had not been explicitly selected to have near-normal imaging, the exclusion of patients with visible large infarcts certainly skewed the sample toward uniformly high ASPECTS at baseline. Clinical measures, such as National Institutes of Health Stroke Scale (NIHSS) score or even modified Rankin Scale itself, are more predictive of final outcome the later they are first measured.2–4

Hospital care can be influenced by clinical examination and investigation findings and by their effect on perceived prognosis. In the SWIFT study, there was a striking difference in NIHSS at 90 days between treatment groups: median 4.5 (interquartile range, 1–12.5) among Solitaire patients and 30.0 (interquartile range, 2–42) among Merci patients.5 Mortality would be a principal factor in this difference, being particularly high among patients without evident reperfusion. These patients had lower 24-hour ASPECTS (ie, larger visible infarcts). Did the presence of extensive infarction on the 24-hour scan influences clinical management over subsequent weeks, perhaps do not resuscitate orders and rehabilitation options, to the detriment of survival and function?

The authors state that ASPECTS at 24 hours was their best predictor of outcomes at 3 months. However, they tested their score only against baseline measures and did not consider alternatives, such as 24-hour or 7-day NIHSS, or 7- or 30-day modified Rankin Scale that have been validated among larger samples.2–4 Why were alternative post-treatment predictors of late outcome discounted? NIHSS scores differed markedly at 90 days; would early clinical examination have revealed as large an advance among patients who had reperfused? Is the 24-hour ASPECTS any better than 24-hour NIHSS or 7-day NIHSS as a predictor of outcome? Patients with missing scan data were excluded; what influence on study power and sample size would the 24-hour (or serial) ASPECTS have, if used in place of 90-day modified Rankin Scale once adjustment to handle the missing data has been factored in?

Associations with reperfusion status have been identified, but can the 24-hour ASPECTS reliably predict therapeutic efficacy: thrombectomy increases reperfusion, and perfusion status correlates with outcome but to date thrombectomy has not reliably been shown to improve outcome.6–9 A useful surrogate needs to be validated against therapeutic effects, preferably versus untreated controls. Although the authors of SWIFT found a difference between treatment groups on clinical outcome,1 they did not present the ASPECTS imaging findings by treatment group in their current article.1

Statistical issues also feature. Serial change in ASPECTS was defined as dramatic infarct progression and represented by deterioration in score of ≥6 points. Outcome on modified Rankin Scale was also dichotomized. With known wide variation in baseline status of patients with stroke and among outcomes, it may be more powerful statistically and more relevant clinically to consider the full range of disability, using ordinal approaches to both measures rather than arbitrary dichotomizations.10–13

The authors were surprised that infarct progression was seen in patients with reperfusion, despite absence of hemorrhagic transformation. Two factors may contribute to this finding. There was a delay of unknown duration, probably 1 to 2 hours, between the baseline scan and the opening of the artery that would allow the ASPECTS to deteriorate before reperfusion. There was a further delay of 16 to 24 hours after the outcome angiogram during which unrecognized reocclusion would be possible.1

Surrogate outcomes have been explored previously and several have been shown to offer potential statistical advantage. Some are simple, clinically relevant, and universally applicable (eg, 24-hour or 7-day NIHSS)2,3 and can be repeated at
will; some require complex equipment and cooperation and would apply to only selected subgroups of patients; some such as angiography are sophisticated and biologically relevant but provide only a snapshot and have to date failed to translate into therapeutic benefit. Serial ASPECTS deserve further investigation but are not yet ready for implementation as a valid outcome measure in stroke reperfusion trials.

Disclosures
Dr Lees is a member of the Virtual International Stroke Trials Archive (VISTA) and VISTA-Imaging subgroup, the Virtual International Cognitive and Cardiovascular Trials Archive (VICCTA). He serves on the steering committee for the Safe Implementation of Treatments in Stroke-OPEN (SITS-OPEN) trial, and on the data monitoring committees for the REVASCAT, PISTE, and ECASS-4 trials. None of these activities represents a conflict with the selection of surrogate end points.

References


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