# Select wisely: the ethical challenge of defining large core with perfusion in the early time window

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The pivotal stroke trials published in 2015 provided indisputable evidence of the benefit of thrombectomy in early window (0–6 hours) patients with anterior circulation emergent large vessel occlusion (ELVO) and small infarcts on non-contrast CT (NCCT), measured by ASPECTS 6–10.[1–5] Since then, endovascular treatment of this population has been standard guideline-based care.[6] Efforts, similar to the late window trials,[7 8] are now directed at further expanding thrombectomy indications. Five trials are underway investigating the role of thrombectomy in patients with ELVO with ASPECTS <6, the 'large core' population for whom formal level I evidence is lacking (TENSION (NCT03094715); IN EXTREMIS-LASTE (NCT03811769); TESLA (NCT03805308); SELECT 2 (NCT03876457); and RESCUE-Japan LIMIT (NCT03702413)). Of these studies, all define large core using ASPECTS alone, except for one (SELECT 2). This study defines large core using ASPECTS *or* CT perfusion (CTP), and in doing so includes patients with poor NCCT ASPECTS (score <6) and also those with NCCT ASPECTS 6–10 with CTP-estimated ischemic core volumes ≥50 mL. Because the pivotal trials show unequivocally that patients with ASPECTS 6–10 and ELVO benefit from endovascular treatment in the 0–6-hour time window, we believe that this subgroup in SELECT 2 withholds proven class I treatment from eligible patients, raising concern for patient harm.

As its name implies, CTP provides a measure of cerebral perfusion or, in the case of stroke, the strength of the collateral circulation.[9] Even if one accepts the proposition that CTP can provide an accurate measure of cerebral blood flow (CBF),[10] basic physiologic experiments and clinical studies have demonstrated that the progression from reversible ischemia to infarction is dependent on both CBF and the duration of ischemia.[11–13] Taken together, the idea that one can accurately identify the region of irreversible injury (the core) from a threshold applied to a single snapshot of CBF is mistaken.

Studies advocating the use of CTP for core determination have pointed to significant correlations with reference standard imaging such as MRI diffusion weighted imaging (DWI). However, correlation is not equivalence. These studies are only reporting the obvious correlation between worse collaterals (as measured by CTP) and the likelihood of greater injury (size of the core). Rather, one must focus on the degree of scatter, or the deviations from the identity line, when comparing two imaging approaches. In a study by Copen *et al*, large differences (both underestimation and overestimation) were frequently observed between CTP-estimated core volumes and concurrent DWI core volumes.[14] When defining CTP core using a relative CBF (rCBF) <30% of the normal hemisphere (the threshold used in recent trials including SELECT 2), there was a mean overestimation of the concurrent DWI volume by 65 mL. Tissue that is designated as 'core' by CTP but not truly dead has also been termed 'ghost infarct core'.[15] In a study from Spain, patients with a large core estimated by CTP who underwent successful thrombectomy were found to have had a mean overestimation of core by CTP of 27 mL. These reports and others[16–18] suggest that often CTP-determined 'large core' patients do not in fact actually have large cores, a finding which is not surprising from the standpoint of stroke pathophysiology and which undermines the validity of CTP to define large core populations.

MRI and NCCT, on the other hand, are more reliable indicators of infarction because they depict the pathophysiologic changes after cell death. NCCT hypoattenuation (which is scored by ASPECTS) depicts vasogenic and ionic edema that accompanies the breakdown of the blood–brain barrier and is a highly specific sign of irreversible tissue injury.[19 20] MRI DWI shows cytotoxic edema that is the consequence of the energy-dependent failure of ion pumps in the neuronal cell membrane and is another highly specific indicator of infarction.[21 22] It is worth noting that NCCT and MRI both have limitations when defining early ischemic core and that neither is perfect, particularly in the context of inter-rater reliability for exact ASPECTS scoring. On the other hand, an ASPECTS-driven approach that dichotomizes patients into large versus small/moderate core (ie, ASPECTS 0–5 vs 6–10) has been demonstrated to be an accurate method to identify patients who benefit from thrombectomy in the early time window.[5 6] Moreover, patients with NCCT (or MRI) ASPECTS 6–10 with CTP-estimated large core on CTP (volume ≥50 mL showing rCBF <30%) are not truly 'large core' patients—they are often patients with small cores and intermediate grade collaterals.[15–18]

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Beyond the physiology and imaging data, randomized clinical trial data confirm the ideas explored in the previous paragraph. From the 2015 trials there is a wealth of level I evidence showing that NCCT ASPECTS 6–10 patients benefit from thrombectomy in the early window and also that the effect size for this group is massive, with a number needed to treat of approximately 3.[23] It is important to underscore that this group includes a substantial number of patients with CTP-estimated core volume ≥50 mL.[24] In subgroup analysis of 175 subjects from MR CLEAN who underwent baseline CTP, these subjects had good NCCT ASPECTS (median 9 (IQR 7–10)), but a surprisingly high number (42%) were deemed unfavorable candidates by CTP based on the EXTEND IA mismatch criteria (mismatch defined as core volume <70 mL and mismatch ≥10 mL and 20% larger than core).[24] Critically, their results showed a strong treatment benefit in both the favorable and unfavorable CTP groups. About half of the patients in the unfavorable CTP group had CTP-estimated core volume ≥70 mL, and these subjects too showed benefit with thrombectomy. These findings were confirmed in a secondary analysis of 591 patients with baseline CTP in the HERMES dataset, which found a significant and constant thrombectomy benefit among patients with CTP-estimated core volume up to 150 mL.[25]

The decision made by SELECT 2 to lower the threshold for CTP-estimated large core from 70 mL to 50 mL is also a concern. This lowered threshold will lead to enrollment of patients with favorable CTP who were shown to benefit in previous small core trials.[8 26] A subgroup analysis of DEFUSE 3 reported a clear treatment benefit in the 33 subjects with CTP-estimated cores larger than allowed by the DAWN criteria, half of whom had estimated core volumes of 45–70 mL.[27]

It is also worth noting that there is a scientific cost to the hybrid imaging approach used in the SELECT 2 trial as currently designed. Given the pathophysiologic and evidentiary differences cited above, combining patients with poor ASPECTS (score <6) with those with good ASPECTS+unfavorable CTP core into a single 'large core' population lacks construct validity and compromises the ability to draw meaningful conclusions from the trial results. It may dilute important differences between the two groups. Consider the hypothetical scenario where the trial is positive owing primarily to benefit derived from the good ASPECTS+unfavorable CTP subgroup (a reasonable expectation based on the existing evidence). Would the stroke community accept the trial results to support treatment in the poor ASPECTS group? The answer will likely be 'no'. Alternatively, how should one interpret a trial result if both subgroups show a signal of benefit, but neither are statistically significant? Because data from one group cannot inform the results of the other, one is left with incomplete answers. The only acceptable proof of benefit for each subgroup would be a significant treatment effect within the individual subgroup based on a priori analysis plans. However, because the calculated sample size and statistical power of the trial is divided among these groups, it is probable that both populations will be underpowered to demonstrate a benefit.

Importantly, the SELECT 2 design may also adversely affect the conduct of the other 'large core' trials. If SELECT 2 is stopped early for efficacy, several issues arise. First, because the stopping rule applies to the combination of patients with poor ASPECTS and good ASPECTS+unfavorable CTP, early termination could arise from multiple scenarios. There could be overt benefit in both groups, one group, or potentially neither (if the benefit is shared evenly). Only the findings from the poor ASPECTS subjects would be relevant to whether the other 'large core' trials should stop, as these trials are enrolling only the ASPECTS <6 population. There is further difficulty if it is discovered that there is a benefit in the poor ASPECTS subgroup but not to a degree that would have stopped enrollment early. It is unclear then how the other trials should proceed as this benefit may have occurred simply by chance. Moreover, if the trials decide to continue, will the knowledge of the potential benefit in SELECT 2 undermine the equipoise of the investigators? These issues can only be avoided by having prespecified stopping rules for each subgroup in SELECT 2 that appropriately control for type I error, again highlighting the importance of a parallel trial design.

If there are investigators with equipoise on the topic of ELVO patients with ASPECTS 6–10 in the early time window who wish to randomize these patients potentially away from treatment using CTP findings, then we suggest this question be studied in a separate trial, which should not qualify as a 'large core' trial. It would be an independent trial, aimed at thrombectomy indication constriction. If, on the other hand, SELECT 2 seeks to enroll 'large core' patients, we recommend an amendment to the current design protocol that halts enrollment of the good NCCT ASPECTS+unfavorable CTP patients in the 0–6-hour window. Based on current data, this would protect these patients' best interests. This request is in keeping with current American Heart Association guidelines which advise against CTP in the early window ASPECTS 6–10 population as it "could lead to the exclusion of patients who would benefit from treatment".[6]

Ultimately, this error in the study design could be corrected with a relatively simple protocol amendment. On the other hand, the fact that it was approved by multiple regulatory bodies including the FDA brings into question the effectiveness of these reviews. Paramount to the conduct of patient-based science is trust in the clinicians and investigators performing the research. Advising a patient with a good ASPECTS score who presents early after an M1 occlusion that we do not know whether they will benefit from thrombectomy, and thus should be randomized potentially away from this treatment, runs counter to best available medical evidence. As scientists hoping to move our field forward and improve the care we can provide, we cannot gamble with the faith our patients place in us.

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