From an imaging standpoint, treatment efficiency can be, and has been, evaluated at different levels: (1) restoration of the patency of the primary arterial occlusion; (2) assessment of the patency of the main branches distal to the occlusion, to take into account that the primary clot can break into fragments that can migrate and occlude branches downstream from the primary occlusive lesion (Figure 1A); (3) evaluation of the entry and clearance rate (“wash-in” and “wash-out”) of antegrade flow in distal branches (Figure 1B), to take into account the no-reflow phenomenon; (4) capillary perfusion blood flow, which goes beyond the angiographic assessment of contrast wash-in and wash-out, because it has the ability to quantitatively estimate the hemodynamic specifics of focal ischemia on the brain parenchyma (Figure 1C). The no-reflow phenomenon, first described in 1967 in the context of cerebral ischemia,1 is defined as inadequate perfusion through a vascular segment without evidence of persistent mechanical obstruction. The underlying pathophysiology of this phenomenon is debated, but it is generally accepted that no-reflow is associated with higher complication rates.2,3

The terms recanalization and reperfusion are often used interchangeably in acute stroke literature, although they refer to different concepts, which complicates the comparison of efficiency among studies. Indeed, different scoring systems using different imaging techniques have been used to assess one, or several, of the levels listed above (Table). Adding to the confusion, the same name has been attributed to scoring systems looking at varying end points (Table). For instance, the Thrombolysis in Myocardial Infarction (TIMI) score, created in 1985 using conventional angiography to report the efficacy of myocardial reperfusion therapy,4 evaluates the wash-in and wash-out of contrast from the distal coronary capillary bed; the degree of patency of the primary occlusive lesion is not included in the original TIMI score. Higashida et al proposed the Thrombolysis in Cerebral Infarction (TICI) score,5 and adapted the original TIMI score for the cerebral circulation as assessed on conventional angiography (Figure 1A). In the DIAS and DEDAS trials,6,7 a modified TIMI score was used, exclusively addressing the primary arterial occlusion on static MRA imaging, and defining reperfusion as a 2 points or greater improvement on this grading scheme.6,7 Efficacy end points also included 30% or more reduction of volume of abnormality on PWI mean transit time maps. The DEFUSE study focused solely on capillary perfusion blood flow, requiring 30% or greater and 10 mL or more reduction in PWI lesion volume (using as threshold a 2-second delay on Tmax maps) on the follow-up MR scan done between 3 and 6 hours to characterize reperfusion.8 Subsequently, in EPI-THT trial, a distinction was made between recanalization and reperfusion as end points. The same MRA-based definition that was applied in DIAS and DEDAS trials (but named reperfusion on those trials) was used this time to characterize recanalization, whereas the criteria for reperfusion required 90% or more reduction in the volume of PWI abnormality (Tmax delay of 2 s or more, same as in DEFUSE) between baseline and day 3 MR studies.9

A comprehensive review addressing the inconsistencies in terminology, definition, and application of recanalization/reperfusion scores has been previously provided.10

Which Score Is Clinically Relevant? The MERCI and PENUMBRA devices received FDA 510(k) clearance based on their demonstrated ability to recanalize

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the primary occlusive arterial lesion without considering the status of arterial branches distal to the treated vessel. However, as stated previously, recanalization of the primary occlusive arterial lesion does not necessarily imply capillary reperfusion.

Also, lack of recanalization does not necessarily reflect absence of reperfusion. Among 57 patients who did not achieve recanalization on the DIAS trial, 24.6% achieved favorable clinical outcome after 90 days (defined as 8 or more points improvement on NIHSS [or 0 to 1], mRS [0 to 2], and

Figure 1. A, Recanalization of primary lesion with distal migration of thrombus. Coronal reformatted image from CT angiography obtained at admission shows occlusion of the proximal segment of the right MCA (arrow). Coronal reformatted image from CT angiography performed 8 hours later (image on the right) shows complete recanalization of the previous occluded segment but occlusion of more distal branches of the MCA, presumably by thrombus migration. B, Slow antegrade flow in distal branches. Right internal carotid angiogram, anteroposterior view. At admission (image on the left) there is occlusion of the proximal segment of the right MCA (arrow). Same views acquired 8 hours later (center and right) show partial recanalization with persistent filling defect in the right MCA and slow antegrade flow through distal right MCA branches. C, Absence of reperfusion in the setting of complete recanalization. CT angiography performed at admission (upper row) shows occlusion of the proximal segment of the left MCA (arrow). Perfusion-CT maps shows a posterior region of decreased CBV and CBF corresponding to the infarct core and a larger MTT defect anteriorly corresponding to the penumbra. Perfusion-CT performed 9 hours later shows that, despite complete recanalization of the occlusive lesion (arrow), there is persistence of the perfusion defect consistent with the absence of reperfusion.
BI [75 to 100]), suggesting that reperfusion can occur in the absence of recanalization. One possible explanation is retrograde collateral flow. Adequate collateral circulation may contribute to maintain tissue viability in the absence of complete recanalization. Collateral flow is currently best evaluated on dynamic angiography, though reliable static scoring systems have been proposed to measure collateral flow on CTA.

Next Steps and Conclusion
The hypothesis—restoration of capillary perfusion and adequate collateral flow results in smaller infarct size and better clinical outcome, whereas lack of reperfusion coupled with poor collateral flow results in larger infarct and worse clinical outcome (Figure 2)—remains to be definitively validated. One possible design would be to systematically evaluate the four different levels of vascular compromise listed above, both before and after revascularization treatment, in a prospective series of acute stroke patients. Arterial patency/flow restoration at these levels, as well as the degree of collateral flow, would serve as predictors. This would be correlated with standard clinical and imaging end points, such as final infarct volume. This design would allow determination of the relative importance of recanalization, reperfusion, and collateral flow in evaluating the efficacy of revascularization therapies for acute ischemic stroke.

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Disclosures
None.

References

Table. Imaging Techniques Used and Different Levels Assessed for Revascularization Used in Acute Ischemic Stroke Trials

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<tr>
<th>Trials</th>
<th>Primary Arterial Occlusive Lesion</th>
<th>Main Branches Beyond Occlusion</th>
<th>Antegrade Flow in Distal Branches (wash-in)</th>
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Figure 2. Reperfusion, collateral circulation, and brain tissue outcome. In the setting of acute cerebral ischemia, tissue viability and outcome is dependent on effective reperfusion and collateral circulation. It is hypothesized that restoration of capillary perfusion and adequate collateral flow results in smaller infarct size and better clinical outcome (light gray), whereas lack of reperfusion coupled with poor collateral flow results in larger infarct and worse clinical outcome (dark gray).


