urgent to undertake pragmatic trials of treatment for mild neonatal encephalopathy. Early MR spectroscopy would strengthen such trials.

In conclusion, this demonstration of the extremely high prognostic accuracy for MR spectroscopic measurements of NAA concentration will enable much faster incremental studies of neonatal encephalopathy because it offers robust measurement of outcome within weeks. Moreover, the reference data from the MARBLE study will be made available, allowing MR sequences, and thus individual patient scans, to be done more rapidly within large pragmatic studies. Clinicians in this field can look forward to an era of clinical research in which it is no longer necessary to delay gratification for years!

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Patients with large brain infarcts might also benefit from thrombectomy

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The biological premise of acute stroke therapy rests on time (specifically, the duration of focal cerebral ischaemia) and the presence in these patients of an ischaemic penumbra, an intermediate zone of oligaemia between normal cerebral blood flow and complete ischaemia that surrounds a core region of irreversibly injured tissue. The penumbra, distal to an arterial occlusion and variably supported by collateral blood flow, is potentially salvageable brain tissue that will, in the absence of timely reperfusion, progress at variable rates to become part of the core infarct. Reperfusion of an ischaemic core that has no surrounding penumbra would, by definition, be futile.[1]

The clinical trials that have shown efficacy of endovascular thrombectomy initiated within 6 h of onset of ischaemic symptoms required prerandomisation evidence of acute occlusion of the internal carotid or middle cerebral artery, implying the presence of a penumbra, but they did not require imaging evidence of the ischaemic core or penumbra. These trials found that thrombolysis with endovascular thrombectomy was more effective than standard medical management when they achieved earlier recanalisation and reperfusion.[2,3]

The results of a meta-analysis of these clinical trials by Bruce Campbell and colleagues[4] in *The Lancet Neurology* offer important insights into the question of whether the benefit of recanalisation relates to the volumes of ischaemic core or penumbra. They pooled individual-level data for 1764 patients from the seven randomised controlled trials. Within this pooled sample, 900 patients had prerandomisation CT perfusion (n=591) or MRI diffusion-weighted (n=309) images that were analysed to estimate ischaemic core and penumbral volumes. Because only 33 (11%) of the patients in whom MRI was obtained had perfusion MRI, the MRI patients were only used to estimate ischaemic core volume, defined as the region with an apparent diffusion coefficient threshold of less than 620 m^2/s. From CT perfusion images, the ischaemic core was defined as cerebral blood flow less than 30% of normal brain, critically hypoperfused tissue

(the penumbra and ischaemic core) was tissue with a time to maximum perfusion greater than 6 s, and the mismatch volume (ie, estimated penumbral volume) was critically hypoperfused tissue minus the ischaemic core volume. A penumbra was present in 580 (>99%) of 583 patients in whom CT perfusion was obtained, supporting the implication that a penumbra will be present if a large vessel occlusion is identified within 6 h of onset of stroke.

Pretreatment ischaemic core volume was inversely associated with functional independence (defined as modified Rankin Scale score 0–2), which is a standard outcome assessment of stroke disability. In a multivariable logistic regression model including both endovascular and control patients, a 10 mL increase in ischaemic core volume was associated with reduced functional independence for CT perfusion patients (odds ratio [OR] 0·77 [95% CI 0·69–0·86]) and for MRI patients (OR 0·87 [0·81–0·94]).[4] Although patients with larger ischaemic core volumes were less likely to achieve functional independence, this was true for both endovascular thrombectomy and control groups, and the benefit of thrombectomy was not precluded by larger ischaemic core volumes. The interaction between ischaemic core volume and treatment assignment was not significant—ie, the benefit of thrombectomy was not modified by pretreatment core volume.

Limitations of the study and its interpretation must be noted. The threshold estimates of ischaemic core and penumbral volumes used in this study are imperfectly predictive of functional outcome or therapeutic potential. Another limitation is that different results might have followed from the use of acceptable alternative measures of core volume, such as cerebral blood volume decreases or Alberta Stroke Program Early CT Score.[5,6] This limitation is highlighted by the authors' observation that functional outcomes significantly differed in the subgroup with MRI-derived core volumes (defined by a direct measure of tissue injury, the apparent diffusion coefficient) from those with CT perfusion-derived core volumes (based on reduced cerebral blood flow, an indirect measure that is one step removed from tissue injury).

Another limitation was that only 900 (51%) of the 1764 pooled patients had images for assessment and ischaemic core volumes were mostly small. A 70 mL ischaemic core volume has become a common standard for predicting worse clinical outcome in stroke and worse response to reperfusion therapy,[6] but only a few patients with large ischaemic cores of greater than 70 mL were included in the study. Among the ischaemic cores measured by CT perfusion, the median volume was approximately 10 mL, with only 50 (9%) of 583 patients having an ischaemic core volume greater than 70 mL; among the ischaemic cores measured by diffusion MRI, the median volume was approximately 20 mL, and only 59 (19%) of 309 cases had an ischaemic core volume greater than 70 mL. Although no reduction in therapeutic benefit of thrombectomy at increasing volumes could be shown in this sample, a bigger sample of patients with ischaemic cores of greater than 70 mL will be necessary to establish therapeutic potential, specifically for patients with a large ischaemic core.

Campbell and colleagues'[4] pooled analysis of seven randomised controlled trials of endovascular thrombectomy provides evidence that although large pretreatment ischaemic core volumes were associated with decreased functional independence, ischaemic core volume did not modify the treatment effect of thrombectomy or support a conclusion that treatment of large ischaemic core volumes would be futile. Stroke patients who are otherwise eligible for thrombectomy in the 6-h window should not be denied treatment solely on the basis of estimated ischaemic core volume.

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