B. C. V. Campbell, P. J. Mitchell, T. J. Kleinig, H. M. Dewey, L. Churilov, N. Yassi, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. The EXTEND-IA Investigators. N Engl J Med. 2015 Feb 11. [Epub ahead of print]

The result of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN) trial,[1] which showed reduced disability among patients with ischaemic stroke who were treated with endovascular thrombectomy, represent an advance in stroke care. Several trials later had neutral findings with respect to the use of endovascular thrombectomy.[2,3] However none of the previous studies raised any safety concerns, with rates of symptomatic haemorrhage of approximately 6% in both the alteplase group and the endovascular-therapy group. More recent advances in device technology have significantly improved the speed and efficacy of recanalisation.[4,5] The computed tomographic (CT) perfusion imaging can indicate the extent of irreversibly injured brain in the ischaemic core and potentially salvageable but hypo-perfused ischemic penumbra.[6-8] In Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) trial, it was hypothesised that the patients with anterior circulation ischemic stroke who are selected with a dual target of vessel occlusion and evidence of salvageable tissue on perfusion imaging within 4.5 hours after the onset of stroke will have improved reperfusion and early neurologic improvement when treated with early endovascular thrombectomy after intravenous administration of alteplase as compared with alteplase alone.

The present trial was an investigator-initiated, multicenter, prospective, randomised, open label, blinded-end-point study involving 100 patients at 14 centres in Australia and New Zealand. They randomly assigned patients with ischemic stroke who were receiving 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy with the Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone. All the patients had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue and ischaemic core of less than 70 ml on CT perfusion imaging. The primary outcomes were reperfusion at 24 hours and early neurologic improvement (≥ 8-point reduction on the National Institutes of Health Stroke Scale, [ranges from 0 (normal) to 42 (death)] or a score of 0 or 1 at day 3). Secondary outcomes were the score on the modified Rankin scale at 90 days [which ranges from 0 (normal) to 6 (death)], death due to any cause, symptomatic intra-cranial haemorrhage and subarachnoid haemorrhage associated with clinical symptoms.

The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). From August 2012 through October 2014, a total of 70 patients underwent randomization (35 to the endovascular-therapy group and 35 to the alteplase-only group) at 10 study centres (9 in Australia and 1 in New Zealand). Around 25% of clinically eligible patients with vessel occlusion were excluded on the basis of perfusion-imaging criteria The percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular-therapy group than in the alteplase only group (median, 100% vs. 37%; $P < 0.001$). Endovascular therapy, initiated at a median of 210 minutes after the onset of stroke, increased early neurologic improvement at 3 days (80% vs. 37%, $P = 0.002$) and improved the functional outcome at 90 days, with more patients achieving functional independence (score of 0–2 on the modified Rankin scale, 71% vs. 40%; $P = 0.01$). There were no significant differences in rates of death or symptomatic intracerebral haemorrhage.

In patients with acute ischemic stroke with major vessel occlusion and salvageable tissue on CT perfusion imaging, early mechanical thrombectomy with the Solitaire FR stent retriever after the intravenous administration of alteplase was associated with faster and more complete reperfusion than the use of alteplase alone. The increase in reperfusion led to a reduction in infarct growth and substantial clinical benefit in early neurologic recovery and functional outcome at 3 months. This reduction in infarct growth is consistent with salvage of ischemic penumbra as the mechanism of underlying clinical benefit.[9]

The magnitude of the clinical benefit of endovascular thrombectomy was larger in this study than that in previous trials. The main differences between this study and the previous trials was inclusion of CT perfusion imaging to select patients with the greatest potential to benefit from endovascular therapy, shorter time to the onset of treatment, and improved rates of angiographic revascularization. However CT perfusion imaging was also performed in about 65% of patients in the MR CLEAN trial. Such imaging was not required according to the protocol for the MR CLEAN trial but may have influenced patient selection. Hence, positive results in the MR CLEAN trial may not be entirely attributable to imaging selection on the basis of vessel occlusion alone. The interval between the initiation of alteplase and randomization was 30 minutes in this study, as compared with 100 minutes in the MR CLEAN trial, because of this approach of identifying patients with the greatest potential to benefit from

reperfusion and then maximizing early reperfusion with the use of combined alteplase and endovascular therapy, rather than waiting to assess clinical response to alteplase. As a result, the time from stroke onset to the initiation of the endovascular procedure was a median of 50 minutes shorter than the similar interval in the MR CLEAN trial, which may also have contributed to the substantially higher pro-portion of patients with independent functional outcomes observed in this study.

Limitations of this study include the inability to perform subgroup analyses, given the small number of patients. Such analyses will require individual patient meta-analysis of multiple trials. The patients who were excluded from the trial on the basis of a large ischaemic core or absence of significant salvageable ischaemic brain tissue might have benefited from endovascular therapy. Purely volume-based criteria do not account for the location of the core, which is also relevant to the clinical outcome.[10] The early termination of the trial does create potential for overestimation of the effect size. However, the investigators believed that the new information from the MR CLEAN trial ethically mandated review by the independent data and safety monitoring board.

The authors conclude that patients with ischaemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging had improved reperfusion, early neurologic recovery, and functional outcome if endovascular thrombectomy with the Solitaire FR stent retriever was performed without delay after the initiation of intravenous alteplase. Further studies will be needed to clarify remaining uncertainties regarding the benefit in patients with more distal occlusions, later time windows, and the influence of the type of device that is used and variability in the endovascular technique.

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