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EDITORIAL

One Treatment to Heal them all: Thrombectomy also Benefits Stroke with Large Ischemic Core

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Thrombectomy has revolutionized stroke treatment worldwide, improving the outlook for severe stroke with a treatment success previously unheard of in acute stroke treatment. Following the Dutch MR CLEAN trial [1], a series of clinical trials has demonstrated the benefit of endovascular thrombectomy (EVT) for patients with large vessel occlusion. In the pooled HERMES analysis of the "first wave" of stroke thrombectomy trials, the number needed to treat with thrombectomy to reduce disability by at least 1 level on the modified Rankin scale (mRS) at 90 days for 1 patient was as low as 2.6 [2]; however, in most of these trials enrolment excluded patients with large ischemic core, either based on the visual assessment of pre-treatment Alberta Stroke Program Early CT score (ASPECTS) or by quantification of the ischemic core using perfusion CT. Moreover, in the early trials the majority of patients were treated within the first 6 h of known symptom onset. As a result, most international guidelines adopted the recommendation for treatment with thrombectomy for large vessel occlusion within the first 6 h guidelines for patients with no signs of extended infarction, usually operationalized by an ASPECTS of ≥ 6. It took no longer than another 2 years until two further groundbreaking trials of stroke thrombectomy were published that challenged the strict time window: both, DAWN and DEFUSE-3 randomized patients in a late time window up to 16 or 24 h after known onset or those with unknown time of symptom onset to treatment with EVT or usual care, if patients had a perfusion mismatch (DEFUSE-3) [3], or a mismatch between a severe clinical deficit and only a small infarct core (DAWN) [4]. In these highly selected patients, the treatment effect of EVT was even stronger than in previous trials but again, and on purpose, patients with already large ischemic infarcts were excluded from both trials. Therefore, until recently, the main open question regarding thrombectomy for stroke remained whether EVT is effective or useless in patients with already extensive ischemic stroke lesions. This question is answered now.

In early 2022 the RESCUE-Japan LIMIT trial was the first randomized trial of EVT in patients with large core to be published [5]. In this trial, patients with stroke due to large vessel occlusion of the anterior circulation with a low ASPECTS, defined as a score of 3–5 within 6 h of known symptom onset or with unknown time of symptom onset were randomized. Of note, the majority of patients (86%) were enrolled based on magnetic resonance imaging (MRI), so ASPECTS was assessed on diffusion-weighted imaging (DWI), and only in 14% on computed tomography (CT). Patients with unknown time of symptom onset were randomized if there were no early changes visible on fluid-attenuated inversion recovery (FLAIR). The primary outcome was a score of 0–3 on the mRS at 90 days. 203 patients were randomized, and the number of patients achieving the primary outcome was significantly higher in the EVT group (31.0% vs. 12.7%) with an odds ratio of 2.43 (95% confidence interval 1.35–4.37, $p = 0.002$). There was a higher rate of symptomatic intracranial hemorrhage (ICH) (9% vs. 4.9%) in the EVT group.

RESCUE-Japan LIMIT did not change clinical practice. Concerns were raised regarding the generalizability of the results, given the small number of patients, the fact that the trial was exclusively run in Japan, and the use of MRI to assess ASPECTS. Quantification of ASPECTS on DWI is completely different from using CT, as DWI is more sensitive to acute ischemic lesions, especially concerning small ischemic lesions, and it can be expected that ASPECTS values on DWI score are on average at least 1 point lower than on CT [6]. Therefore, the use of MRI might result in enrolling a population with on average smaller infarcts than a population enrolled based on CT. The low mortality observed in RESCU-Japan LIMIT, which was only 18% in

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the EVT group and 23.5% in the control group, might point towards this direction.

In February 2023 the results of 2 further randomized trials of thrombectomy for patients with large ischemic core were presented at the International Stroke Conference (ISC) in Houston and simultaneously published in the New England Journal of Medicine (NEJM). The industry-sponsored ANGEL-ASPECT trial was conducted in China and enrolled patients with anterior circulation stroke with large vessel occlusion within 24 h of known onset or last-seen-well time. To be eligible, patients had to either have an ASPECTS of 3–5, or a core volume of 70–100 mL. The primary endpoint was a shift in the mRS score at 90 days. The trial enrolled 456 patients and was stopped early based on the results of a planned interim analysis. There was a significant shift toward better functional outcome at 90 days with EVT as compared with medical management alone with an odds ratio of 1.37 (95% confidence interval 1.11–1.69, $p = 0.004$). Rates of functional independence (mRS 0–2) were also higher with EVT (30% vs. 11.6). Symptomatic intracranial hemorrhage occurred in 6.1% with EVT and 2.7% with medical management.

The second trial was SELECT2, and industry-sponsored trial conducted in the USA, Canada, Europe, Australia, and New Zealand. SELECT2 randomized patients with large vessel occlusion presenting within 24 h of last-seen-well time to EVT or medial management alone if CT showed an ASPECTS of 3–5, or if CT perfusion or MRI estimated a core volume of ≥ 50 mL. Like in ANGEL-ASPECT, primary outcome was a shift in the mRS at 90 days. Following the publication of the Japanese trial, an interim analysis of SELECT2 was performed which resulted in permanent stopping of the trial. The results showed a significant benefit of thrombectomy over conservative treatment with increased odds of a favorable outcome at 90 days (odds ratio 1.51, 95% confidence interval 1.20–1.89, $p < 0.001$). Functional independence was achieved by 20% of thrombectomy patients compared with 7% in the medical management arm, while mortality and symptomatic intracranial hemorrhage were similar.

Taken together, we now have three positive trials that, despite differences in inclusion criteria and population characteristics, unanimously demonstrate a benefit of EVT in patients with acute stroke from large vessel occlusion who already have extended ischemic lesions. In all individual trials, the benefit was observed across the entire range of outcomes assessed by the mRS, and thrombectomy was associated with an absolute increase in the proportion of patients achieving functional independence (mRS 0–2) ranging from 7 to 18%. In all trials, mortality was similar between treatment groups, and there was no increase of patients surviving with most severe deficit (mRS 5), which may have been the most prominent fear of stroke physicians regarding reperfusion treatment in these severely affected patients.

Based on these results, there is no longer any reason to withhold thrombectomy to patients with large infarct core, no matter whether MRI or CT is used as primary diagnostic tool. EVT has clear and proven benefit in these patients, as it has in patients with only small ischemic core at baseline. It is time now to transfer these results into daily clinical practice. The good news is that life will be even easier for stroke interventionalists because based on the evidence now available advanced imaging with time-consuming and error-prone postprocessing is not required, but thrombectomy can be performed when large vessel occlusion is demonstrated and non-contrast CT does not show complete or near-complete middle cerebral artery (MCA) stroke (as reflected by an ASPECTS of 0–2).

The three published trials are just the first round of large core thrombectomy trials, the results of further trials, such as LASTE (NCT03811769), TESLA (NCT03805308), and TENSION (NCT03094715) [7] are pending. What will the results of these trials add? There are still open questions. The sample sizes in the published trials are rather small, preventing meaningful analysis of subgroups, which may be of interest and likely can be answered, once all trials are published and pooled data analysis can be done. Two of the published trials were run in just one country (Japan and China), and more data from globally more representative patient populations will be helpful to generalize the results. The results of the available studies were also quite heterogeneous in some respects, both in the thrombectomy groups and in the groups treated with drugs alone. For example, mortality in the control group ranged from 20% in the Chinese ANGEL-ASPECT study to 41% in SELECT2, the only study conducted in multiple countries. Results from additional trials will help in getting a better understanding of these differences and of the likely range of outcomes among these patients when treated with thrombectomy and standard of care in different healthcare systems. Moreover, it will be highly interesting to learn whether there are clinical or imaging characteristics that predict treatment response of thrombectomy and good outcome in this population of patients with severe stroke.

Finally, we must remember that even with thrombectomy, the rate of severe disability or death (mRS 4–6) was high in this patient population, ranging from 52 to 69%. When communicating the potential prognosis of individual patients, the treating physicians must be aware of this. The likelihood of permanent neurologic deficits in these severe strokes is high, but thrombectomy can still save a patient from severe disability and becoming bedridden. Thus, the results of the present studies of thrombectomy for stroke with large ischemic lesions are encouraging. They will help to bring the benefits of this effective treatment to an even

larger number of patients, thereby saving costs for long-term rehabilitation and care and avoiding the individual burden of the disabling consequences of stroke.

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