Acute Ischemic Stroke and Transient Ischemic Attack: An Update on Recent Practically Relevant Clinical Trials

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This short review focuses on recent practically relevant studies in stroke treatment and prevention and discusses their implications on clinical practice and future research, including 3 shortly published randomized controlled trials investigating interventional treatment in acute ischemic stroke (The Interventional Management of Stroke phase III trial [IMS III], Synthesis Expansion: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke, and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE]) and 1 large trial on secondary prevention in high-risk patients with transient ischemic attack (TIA) or minor stroke (Randomized, Double-blind Trial Comparing the Effects of a 3-month Clopidogrel Regimen, Combined With ASA During the First 21 days, Versus ASA Alone for the Acute Treatment of TIA or Minor Stroke [CHANCE trial]).

Endovascular Treatment in Acute Ischemic Stroke

Three larger randomized controlled trials (RCTs) on endovascular treatment in acute ischemic stroke were published in 2013.

The Interventional Management of Stroke phase III trial (IMS III)¹ was initiated in 2006 and planned to include 900 patients with acute ischemic stroke (initially National Institutes of Health Stroke Scale [NIHSS] ≥ 10 , later also including NIHSS 8 or 9 with major vessel occlusion) who were treated with intravenous (iv) tissue plasminogen activator (t-PA) within 3 hours of symptom onset. The patients were randomly assigned to receive either t-PA alone or t-PA with additional endovascular therapy (1:2). After inclusion of 656 patients through April 2012 (434 patients in the endovascular group and 222 controls), the trial was stopped prematurely because the prespecified boundary for futility was crossed. The recently published analysis¹ showed no significant difference between the 2 groups in the proportion of patients with a

modified Rankin scale (mRS) ≤ 2 90 days after stroke although better recanalization rates were achieved in the endovascular group. Secondary end points including mortality at 90 days and safety aspects, especially symptomatic bleeding complications, were also similar between the 2 groups. Subgroup analysis did not show statistically significant differences. Nonsignificant trends toward better outcome in favor of the endovascular group were detected in patients who were treated with iv t-PA within 2 hours after the onset and in patients with severe stroke (NIHSS ≥ 20). The limitations of this trial include a relatively long time to endovascular treatment after start of thrombolysis (2 hours), the predominant use of older generation devices, and the fact that not all patients had a vessel occlusion on vascular imaging.

A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS Expansion) trial² compared systemic versus local thrombolysis in 362 patients with acute ischemic stroke within 4.5 hours from symptom onset. The time until randomization was similar in the 2 groups and the endovascular procedure resulted in a 1 hour longer median time to treatment; however, subgroup analyses did not show a significant effect of time on outcomes. This study also failed to demonstrate a benefit from endovascular treatment, showing no significant difference in the proportion of patients with mRS of 0 to 1 after 3 months. There were also no differences considering secondary outcomes and safety aspects. Similar to IMS III, this trial also mainly used older devices and not all participants had major vessel occlusion.

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The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial³ was designed to investigate whether brain imaging could identify patients who are most likely to benefit from treatments for acute ischemic stroke and whether endovascular treatment improves clinical outcomes in such patients. This study included 118 patients with acute ischemic stroke within 8 hours of symptom onset. Randomization to standard treatment or endovascular management was stratified according to the presence or absence of a favorable penumbral pattern on multimodal computed tomography or magnetic resonance imaging. In this trial, patients with a favorable penumbral pattern (large perfusion deficit and small infarct core) showed slightly better outcomes as compared to patients with nonfavorable penumbral pattern but endovascular treatment did not provide any benefit in either group. The conclusions from this trial, however, may be limited due to the relatively small sample size.

Several aspects deserve to be mentioned when the implications of those trials on clinical practice and future research are being discussed. First, in clinical routine, iv t-PA still remains the only proven treatment for acute ischemic stroke within the 4.5-hour time window, even when vascular imaging shows a major vessel occlusion. In the extended time window beyond 4.5 hours, the MR RESCUE trial failed to provide evidence for the use of endovascular treatment in patients with a favorable penumbral imaging pattern (perfusion/infarct core mismatch). Therefore, the use of endovascular recanalization strategies in acute ischemic stroke should be restricted to clinical trials. This could be facilitated by the decision of Medicare in the United States to place a moratorium on reimbursement for endovascular treatment in ischemic stroke outside of RCTs.⁴ Such trials are urgently needed because in the above-mentioned studies newer generation endovascular devices with better recanalization rates (eg, stent retrievers) were used in a minority of participants. The trends seen in IMS III subgroups may help to identify patients for future trials, who are most likely to benefit from endovascular treatment, for example, patients with severe stroke and major vessel occlusion treated early after symptom onset.

Early Dual Antiplatelet Treatment in Acute Minor Stroke or TIA

A large, double-blind, placebo-controlled RCT conducted in China (Randomized, Double-blind Trial Comparing the Effects of a 3-month Clopidogrel Regimen, Combined With ASA During the First 21 days, Versus ASA Alone for the Acute Treatment of TIA or Minor Stroke [CHANCE] trial)⁵ investigated 2 different regimens of early antiplatelet treatment in 5170 patients with minor stroke (defined as NIHSS

≤3) or TIA within 24 hours from symptom onset. Eligibility criteria included moderate to high risk of stroke recurrence (ABCD2 score ≥ 4). The participants received either a loading dose of 300 mg clopidogrel on day 1 followed by a daily dose of 75 mg until day 90 combined with 75 mg aspirin on days 2 to 21 or aspirin alone (loading dose 75-300 mg, 75 mg daily on days 2-90). The trial showed a benefit in the primary outcome (ischemic or hemorrhagic stroke after 90 days) for the clopidogrel group (8.2% vs 11.7%, hazards ratio 0.68 [0.57-0.81], $P < .001$). No significant differences were found in the rate of moderate or severe hemorrhages.

This trial supports the early use of dual antiplatelets in a selected population with high risk of stroke recurrence and low risk of hemorrhagic complications; however, the generalizability of its results outside of China remains questionable. This issue can possibly be resolved when the results of the still ongoing United States Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial (www.point-trial.org) with a similar design have been published. Both trials end their follow-up at 90 days; therefore, even after POINT it will remain unclear whether the 90-day benefit will translate into a favorable risk-benefit ratio in the long term. Until further trials have been published, the results of the CHANCE trial do not justify changes in stroke prevention guidelines; however, they reemphasize the need for immediate initiation of stroke prevention.

Declaration of Conflicting Interests

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