Reperfusion in acute ischaemic stroke by sonothrombolysis

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The treatment of acute ischaemic stroke has rapidly evolved in the past few years. Development of mechanical thrombectomy has led to high rates of reperfusion in patients with proximal occlusion, whereas the efficacy of intravenous thrombolysis was scant in this subset of patients.[1] Yet, the situation is far from ideal: endovascular reperfusion treatments are not available in most stroke centres around the world, delays between imaging and reperfusion by means of endovascular procedures can be extensive, and technical failures are frequent. In this context, there is still a need for more effective medical reperfusion treatments that can be rapidly and widely used in patients with stroke.

In *The Lancet Neurology*, Andrei Alexandrov and the CLOTBUST-ER trial investigators[2] report the results of a double-blind, multicentre, phase 3, randomised controlled trial of sonothrombolysis in patients with acute ischaemic stroke with National Institutes of Health Stroke Scale (NIHSS) scores of 10 or higher who were eligible for intravenous thrombolysis. After receiving standard-of-care treatment, including full-dose intravenous alteplase, participants were randomly assigned to 2 h of 2 MHz pulsed-wave ultrasound or sham treatment using an operator-independent device. Sonothrombolysis assumes that ultrasound exposure enhances alteplase penetration inside the occluding thrombus, thereby enhancing thrombolysis efficacy, accelerating reperfusion, and improving stroke outcome. The primary outcome was improvement in the modified Rankin Scale score at 90 days.

The results of the trial are negative. The trial was stopped early after the second interim analysis because of futility at a time when 335 patients were randomised to the sonothrombolysis group and 341 patients to the control group. The adjusted common odds ratio for an improvement in modified Rankin Scale score at 90 days in the intervention group was 1·05 (95% CI 0·77–1·45). Although there was no evidence to indicate a difference between groups in safety analyses, cerebral oedema, brain herniation, and asymptomatic intracranial haemorrhage seemed more prevalent in the sonothrombolysis group, despite use of 2 MHz ultrasound, which is considered safer—albeit probably less efficient—than lower frequency ultrasound.[3]

Is this negative study the end of sonothrombolysis for management of acute ischaemic stroke? Probably not, because several factors might have affected the outcome of the CLOTBUST-ER trial. First, documentation of proximal intracranial occlusion (the target of sonothrombolysis) was not required in this trial to facilitate patients' recruitment in stroke centres without access to emergent angiography. Instead, the investigators used severe stroke (NIHSS ≥10) as a surrogate for large-vessel occlusion. As a result, some patients did not have a proximal occlusion within the target area of the ultrasound device. Second, the operator-independent ultrasound device might have provided less efficient ultrasound exposure because of its multitransduced headframe design. This possibly could account for why the study did not reproduce the positive findings of previous phase 2 clinical trials that used diagnostic, operator-dependent, transcranial doppler devices.[4,5] Moreover, study findings suggest that the efficacy of sonothrombolysis can be further enhanced using optimised devices and contrast agents.[6]

Future trials of sonothrombolysis will have to consider the new landscape of acute ischaemic stroke diagnosis and treatment. Patients' selection should rely on emergent imaging to identify individuals with large-vessel occlusion. Moreover, the largest benefit of ultrasound-induced reperfusion is expected for patients who need to be transferred from primary care to a thrombectomy-capable comprehensive stroke centre, in which delays between imaging and reperfusion are extensive. Accordingly, a sonothrombolysis trial (TRUST; NCT03519737) has been initiated in which patients with large-vessel occlusions in primary care being transferred to a stroke centre will be randomised to either ultrasound or no ultrasound, using an optimised device, with the primary endpoint being recanalisation before thrombectomy. As supported by the results of a similarly designed trial of tenecteplase versus alteplase,[7] achieving a higher incidence of reperfusion before thrombectomy can translate into better functional outcome. In addition to new thrombolytic, antiplatelet, or anticoagulant agents, sonothrombolysis remains a promising method to achieve this goal.

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I declare no competing interests.

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Periprocedural events dominate outcomes of carotid stenting and endarterectomy

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In the past, the risk of stroke or death from symptomatic carotid stenosis was very high, approximately 10% per year. Historical guidelines have recommended that if surgery or stenting can be performed with a risk of stroke or death of less than 6%, it was indicated. However, since 2005, with much better medical therapy, the risk has declined so much that it has been suggested that for some patients with symptomatic carotid stenosis, intensive medical therapy would be reasonable.[1] The 6% benchmark for risk of intervention in patients with symptomatic carotid stenosis is now obsolete. Similarly, the 3% benchmark for intervention in patients with asymptomatic carotid stenosis is also now obsolete because the annual risk of stroke or death in patients with asymptomatic carotid stenosis with intensive medical therapy is about 0·5%.[2] Since 2005, the risk of surgery has declined substantially, as has the risk of stenting. However, most studies have shown that the periprocedural risk of stenting is about twice that of endarterectomy.

In *The Lancet Neurology*, Thomas Brott and colleagues[3] present within-patient results from a pooled analysis of individual patient data from four major trials of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) for symptomatic carotid stenosis in 4754 patients. The authors report periprocedural outcomes (risk of stroke or death within 120 days) and long-term outcomes (risk of ipsilateral stroke up to 10 years). The median length of follow-up ranged from 2·0 to 6·9 years. As in previous reports,[4,5] long-term outcomes were similar for CEA and CAS but, when periprocedural risks and long-term outcomes were combined, CEA was superior, with treatment differences between CEA and CAS for risk of stroke or death or subsequent ipsilateral stroke ranging between 2·8% (95% CI 1·1–4·4) and 4·1% (2·0–6·3) at various follow-up times up to 10 years.

Brott and colleagues[3] express the hope that improvements in CAS will reduce periprocedural risks, but passing catheters through stiff, tortuous, and craggy arteries that have a high plaque burden is hazardous and probably explains the higher risk of stenting in older patients (>70 years).[6] Microemboli can be detected on transcranial Doppler during the transit of a catheter through the ascending aorta and during placement of a stent in the stenosis (figure). Microemboli during stenting are associated with small infarctions detected on diffusion weighted imaging (DWI) and are common: in one study,[8] DWI lesions were detected in 80% (24/30) of patients after stenting. The median DWI count was four lesions (IQR 7), and two (6·7%) of 30 patients had new or worsening clinical deficits after CAS; the size of the emboli was associated with infarction.[8]

Improvements to approaches that use catheters inserted from a femoral or brachial artery are unlikely to further reduce the risk of periprocedural events. It is possible that self-expanding stents might be safer than stenting combined with angioplasty, though the scarce literature does not support that conclusion.[9] Stenting via the carotid artery with flow reversal to prevent embolisation of atheromatous debris is an approach that is more likely to achieve results similar to CEA.[6,10] Further research is needed in this area.

The key message that clinicians should take from Brott and colleagues' report[3] is that CEA is superior to