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A step closer to statin therapy for stroke?

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Abstract

Accumulating evidence suggests that statin therapy could assist functional recovery following acute ischaemic stroke. A recent study indicates that early administration of statins after intravenous thrombolysis for stroke improves functional outcomes, and reduces mortality and neurological deterioration. Owing to the observational study design, however, these findings should be interpreted cautiously.

Ischaemic stroke is the leading cause of serious disability and a major cause of mortality worldwide.¹ Treatment options for patients presenting with ischaemic stroke are limited, however. Only recombinant tissue plasminogen activator (tPA), administered within 3 h after onset of ischaemic stroke symptoms, is approved by the FDA, and few patients are eligible to receive this treatment. A recent non-randomized observational analysis of patients enrolled in an Italian acute stroke registry, the THRombolysis and Statins (THRaST) study, has provided preliminary evidence that administration of statins within 72 h of thrombolytic treatment is safe and might improve neurological outcomes.²

Chronic treatment with statins, which are hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, was previously shown to reduce the risk of recurrent stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial,³ and interest has been growing in the potential for statins to improve functional outcomes when used after stroke. Expanding experimental and clinical evidence indicates that—by reducing downstream products of the HMG-CoA pathway other than cholesterol, including isoprenoids—statins have beneficial effects on endothelial function, cerebral blood flow, inflammation and haemostasis. In rodent models of acute ischaemic stroke, statins have been shown to reduce neuronal injury and infarct size and improve behavioural recovery.⁴

Potential haemorrhagic risks associated with statins have created controversy over their use for stroke treatment. Chronic atorvastatin use was associated with increased risk of intracerebral haemorrhage in SPARCL,³ and some meta-analyses found evidence that statins increase the risk of haemorrhagic conversion of ischaemic stroke after thrombolysis.⁵

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Competing interests

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Conversely, findings in animal studies indicate that statins might extend the therapeutic window of thrombolytics when co-administered.⁶ The recent THRaST study aimed to address these conflicting findings.²

In THRaST, a multicenter consortium of investigators in Italy collected treatment and outcomes data on 2,072 patients with ischaemic stroke who were treated with intravenous tPA within the 3 h time window. Patients were divided into 'statin' and 'no statin' groups: the statin group ($n = 839$, 40.5%) was defined as those who received statins within 72 h of thrombolysis, and the no statin group ($n = 1,233$, 59.5%) was defined as those who did not receive statins within 72 h, irrespective of whether they had been treated with statins prior to stroke ($n = 63$) or never before ($n = 1,170$). Several short-term (7-day) and long-term (90-day) efficacy and safety end points were evaluated.

After adjustment for several potential confounding factors, the statin group was found to be more likely to have neurological improvement at 7 days (OR 1.68, 95% CI 1.26–2.25), and were less likely to have neurological deterioration (OR 0.31, 95% CI 0.19–0.53) compared with the no statin group. The statin group was also more likely to have a good functional outcome (Modified Rankin Scale score <2) at 90 days (OR 1.63, 95% CI 1.18–2.26). Risk of symptomatic intracerebral haemorrhage was not increased by statin treatment, although these analyses were probably limited by the small number of haemorrhages in both groups (1.2% of patients in the statin group versus 3.8% in the no statin group). Mortality was lower in the statin group (5.8%) versus the no statin group (15.1%). The investigators concluded that statins could benefit both short-term and long-term outcomes after thrombolytic-treated ischaemic stroke.

The results of THRaST are consistent with recent meta-analyses of the effects of prior treatment with statin therapy on functional outcomes and mortality after ischaemic stroke.⁷ In the largest of these meta-analyses, statin treatment at the time of stroke was associated with a 41% increase in the chance of a good functional outcome (Modified Rankin Scale score 0–2). The results are also consistent with animal studies that suggest that statins can be administered safely and lead to improvement in functional outcomes.⁸

Strengths of the THRaST analysis include the large number of patients studied, the multicentre design, and the opportunity to explore multiple statin formulations, doses and time windows for delivery of treatment. Notably, the results at 3 months showed that early initiation of statin therapy, within 24 h of thrombolysis, was associated with 88% increased chance of excellent outcomes, whereas statin treatment after this time had a less marked beneficial effect. This suggestion of an increased benefit with earlier administration of statins is consistent with findings in preclinical studies.⁴

One limitation of THRaST was its inability to fully exclude the possibility of a protective effect of statins against recurrent stroke, which could explain some of the apparent effect on longer-term functional outcomes. The main limitation of the study, however, as readily acknowledged by the investigators, is its nonrandomized, non-blinded design. Statins were not administered to patients with certain characteristics that were also likely to be associated with outcomes: atrial fibrillation and greater stroke severity, for example, were more

common in patients in the no statin group. In effect, patients with larger embolic infarcts might have been least likely to be treated with statins. Although analyses were adjusted for these probably confounding factors, residual confounding by these and other factors associated with the decision to treat with statins might have occurred.

Ultimately, determination of whether statins should be administered acutely after stroke—and the optimal time, route of administration, and dose—will require completion of randomized clinical trials. Some preliminary randomized trials have already provided evidence of benefit of statins on functional outcomes. In one pilot study, for example, investigators randomly assigned 60 patients with acute ischaemic stroke within 12 h of stroke onset to 40 mg simvastatin daily for 7 days followed by 20 mg daily for up to 90 days, versus placebo. Statistically significant improvement in the NIH Stroke Scale score was seen as early as 3 days after treatment initiation, but this improvement did not persist at 90 days.⁹ Recent dose-escalation trials have also found that short-term administration of statins at doses higher than that currently approved is probably safe in patients with stroke, and this strategy is being further investigated in ongoing trials.¹⁰

The findings from THRaST add to the growing literature on the safety and potential benefit of statin treatment in the setting of acute ischaemic stroke. Whether all patients with acute ischaemic stroke who receive thrombolysis should receive statins soon after stroke onset, however, remains a question that can only be answered with a suitably designed randomized clinical trial.

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