

Statins for Neuroprotection After Acute Ischemic Stroke ASSORTed Results But More Trials Needed

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The pivotal SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) randomized clinical trial demonstrated that atorvastatin 80 mg daily begun at 1 to 6 months after the index event in patients with noncardioembolic transient ischemic attack, and nonsevere ischemic stroke was effective and safe for the prevention of recurrent stroke and major cardiovascular events.¹ But in addition to their benefits for vascular prevention, might statins also enhance neuroprotection or promote stroke recovery in the acute setting?

Experimental studies in animal models have reported that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce infarct volumes and stroke severity.² Potentially beneficial nonlipid lowering (pleiotropic) effects of statins include actions on the vascular wall (induction of angiogenesis, upregulation of endothelial nitric oxide synthase), improved cerebral blood flow, enhanced neural repair, antiplatelet, anti-inflammatory, and antioxidant effects.^{2,3} Observational studies and meta-analyses have reported that statin use either immediately before or shortly after stroke onset is associated with improved functional outcome and lower fatality at early follow-up.⁴ However, no matter how tempting, inferences about therapeutic efficacy cannot be made from observational studies because of selection bias and other limitations. Randomized clinical trials are needed.

In this issue of *Stroke*, Yoshimura et al⁵ describe the results of the ASSORT trial (Administration of Statin on Acute Ischemic Stroke Patient)—a prospective, open-label, blinded, end-point assessed, randomized clinical trial, which compared the efficacy of early (<24 hours) versus later (day 7) initiation of statin therapy to improve functional outcome at 90 days in patients with noncardioembolic stroke and dyslipidemia. Statin therapy included low-dose atorvastatin, rosuvastatin, or pitavastatin, and outcome was measured by shift across the modified Rankin Scale. Among 270 included patients, no differences in modified

Rankin Scale distribution, National Institutes of Health Stroke Scale score, or early major cardiovascular event recurrence were observed between groups. The adjusted common odds ratio for functional outcome for the early statin group was 0.84 (95% confidence interval, 0.53–1.3). This neutral result is consistent with the recently reported neutral finding from the STARS trial (Stroke Treatment With Acute Reperfusion and Simvastatin).⁶

Should these results be interpreted as sufficient to close the case on the question of whether acute statin therapy might improve functional outcome after ischemic stroke? We think that such a conclusion may be premature, at least for now. Although the authors should be commended for conducting the trial, unfortunately some methodological limitations may have contributed to the neutral findings in ASSORT. A major limitation was a highly optimistic estimation of effect size (twice the likelihood of improved modified Rankin Scale in statin-treated patients), which likely led to an underpowered trial. Although the effect size was estimated based on similar effect size observed in observational studies, sufficient account was not given to the problem that observational studies reporting acute statin benefits are highly likely to be affected by prescribing bias, where patients with less-severe stroke, healthier lifestyle, or fewer comorbid illnesses are more likely to receive statin treatment. Other possible contributors to the neutral results include the low doses and various statins used, high number of patients with subcortical strokes (44% were lacunar), milder-than-anticipated stroke severity of included patients, and lack of quantitative outcome measures, such as motor strength and final infarct volume.

An analysis of the SPARCL trial found that among 492 patients with ischemic stroke outcomes at follow-up, a strong statistical trend toward improved modified Rankin Scale at 90 days was evident in the group assigned atorvastatin 80 mg daily compared with patients taking placebo ($P=0.0647$).⁷ Although this analysis was post hoc, and not clearly supported by benefit measured by the National Institutes of Health Stroke Scale and Barthel Index, these data are the largest to date in a randomized trial of treatment with a standardized high-dose statin in the acute phase at stroke onset. This intriguing signal from SPARCL, when combined with supportive experimental and epidemiological data, suggests that more randomized trials of acute statin therapy are needed.

Others have evaluated the appropriate dose of statin therapy in acute neuroprotection. In the Neu-START dose escalation study, a lovastatin dose of 8 mg/kg per day for 3 days was identified as the maximum tolerable dose.⁸ The follow-up Neu-START-2 phase 2b trial randomized 130 patients with lovastatin 680 mg for 3 days starting within 24 hours post-stroke versus placebo (or lovastatin 80 mg for patients already taking statins before stroke). The results of Neu-START-2

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Guest Editor for this article was Seemant Chaturvedi, MD.

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(*Stroke*. 2017;48:2922-2923.)

DOI: 10.1161/STROKEAHA.117.018725.)

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.117.018725

have not yet been published but are expected soon (personal communication from Dr Elkind, Columbia University).

Nevertheless, ASSORT and other trials have provided reassuring data on the safety of acute statin treatment after stroke. The design of new trials investigating this question should be carefully considered. We support the STAIR recommendations (Stroke Therapy Academic Industry Roundtable) for phase 2b trials of neuroprotective agents.⁹ For statin trials, these might incorporate early standardized acute statin treatment at the appropriate dose, with surrogate outcome measures, such as infarct growth on brain imaging, to increase the likelihood of detecting signals of efficacy. If phase 2 trials suggest benefit, further phase 3 trials with adequate sample sizes to assess functional measures should be conducted. Indeed, a properly designed study testing high-dose acute statin therapy in moderate-to-severe nonlacunar patients with stroke may still be warranted.

Disclosures

Dr Kelly is the clinical lead of the Health Research Board Stroke Clinical Trials Network Ireland (SCTNI) based at University College Dublin. The SCTNI has received research grant support from Pfizer and Bristol Myers Squibb. The other authors report no conflicts.

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KEY WORDS: Editorials ■ animals ■ follow-up studies ■ humans ■ stroke

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Stroke. 2017;48:2922-2923; originally published online October 13, 2017;
doi: 10.1161/STROKEAHA.117.018725

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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