Statin therapy in acute ischemic stroke
Time for large randomized trials?

Andreas Charidimou, MD, MSc (Neuro), PhD
Áine Merwick, MB, MSc (Stroke), PhD

 Despite improvements in stroke mortality coupled with therapeutic advances, stroke patients often face the prospect of substantial disability. Novel strategies are clearly needed to further improve stroke outcomes. These might include new indications for previously licensed drugs proven effective and safe in related disease processes, such as statins. Unlike strong evidence supporting statin use in cardiovascular risk reduction and acute myocardial ischemia, their effects on cerebral tissue and potential benefits on stroke outcomes remain poorly understood and understudied. The only current stroke-specific indication for statin use is atorvastatin for secondary stroke prevention. Recent meta-analyses found an association between pretreatment use and good functional outcome (pooled odds ratio [OR]: 1.50; 95% confidence interval [CI]: 1.29–1.75; \( p < 0.001 \)), and lower mortality (pooled OR: 0.42; 95% CI: 0.21–0.82; \( p = 0.0108 \)), even in acute stroke patients treated with IV thrombolysis. However, these estimates derive from relatively small observational cohorts at risk of bias.

In this issue of Neurology, Tsivgoulis et al. report important new data on the topic, adding to the growing evidence for a beneficial effect of statin use in acute ischemic stroke. The study investigated the role of statin pretreatment on short-term outcome measures in 516 consecutive patients with acute ischemic stroke due to large artery atherosclerosis (per TOAST [Trial of Org 10172 in Acute Stroke Treatment] criteria). The authors used a multicenter prospective design and reported that statin use before stroke was independently associated with favorable functional outcome (modified Rankin Scale score 0–1; OR: 2.44; 95% CI: 1.07–5.53), lower risk of 1-month mortality (HR: 0.24; 95% CI: 0.08–0.75), and lower stroke recurrence (HR: 0.11; 95% CI: 0.02–0.46) in a number of adjusted analyses. Other smaller studies of stroke and TIA patients with large vessel disease in the hyperacute phase and before carotid revascularization have not found an association with statin pretreatment and stroke recurrence at 72 hours. Thus, the work by Tsivgoulis et al. provides key data on late and functional outcomes, suggesting a protective effect.

Despite the rigorous design and statistical analytic approach of this study (e.g., including propensity score matching), the results should be interpreted with caution because of potential residual confounding. The testing of a prespecified hypothesis specifically in a stroke population with presumed large artery atherosclerosis is both a strong point and a limitation for the generalizability of these findings. First, the study hypothesis implies that the potential benefit of statin pretreatment might be higher in ischemic stroke due to large artery atherosclerosis vs other stroke subtypes. However, the relative effect sizes were not compared to other ischemic stroke types. In fact, in a meta-analysis of individual TOAST stroke subtypes, the effect of statin use on functional outcome appeared larger for small vessel strokes compared to other subtypes (OR: 1.97; 95% CI: 1.02–3.8; Breslow-Day \( p = 0.008 \)). This might also have implications for the underlying mechanisms. Statins may have pleiotropic effects, including amelioration of cerebral microvascular dysfunction and improvement of poststroke outcomes by preventing progression of salvageable ischemic tissue to irreversible infarction—possibilities elegantly discussed in the current report. Stroke patients with extensive small vessel disease, e.g., as captured by leukoaraiosis severity, a variable not analyzed in the study, might derive an even greater beneficial effect. Moreover, the definition of large artery atherosclerosis might have led to some misclassification, given that more than 20% of the sample had atrial fibrillation, a major source of cardioembolism. Finally, the reported associations and clinical outcome in the current study could reflect the differences in the time since last seen well (e.g., <12 hours or >12 hours), the window of intervention, acute treatment delays, carotid endarterectomy timing, and statin initiation at discharge. Of note, not all patients with carotid stenosis undergo revascularization, and medical treatments used while
awaiting revascularization and postprocedure remain an important issue.

Nevertheless, the report by Tsivgoulis et al.6 provides an important foundation for future research involving statin-based interventions for stroke prevention and therapy, including symptomatic patients with large artery atherosclerosis. The observational design of this study limits the ability to make evidence-based recommendations on statin initiation, stressing the urgent need for a large randomized clinical trial of high-dose statin treatment in the acute stroke setting. Randomized comparisons should explore the effects of selecting a specific drug within the class, dosing, and administration timeline in acute stroke, across stroke subtypes, and on outcome. Whether beneficial effects of statins are mediated through altering cerebral tissue fate, vascular protection, or some other biological pathways (such as inflammation) warrant further investigation.7,10 The incorporation of advanced neuroimaging protocols and clinical outcomes in any such trial could further elucidate potential mechanisms and identify patient subgroups most likely to benefit from the intervention. The effects of statin treatment should also be investigated in the era of endovascular stroke therapies for eligible acute stroke patients with large vessel occlusion (intra-arterial therapy or mechanical thrombectomy), which are quickly becoming standard of care.

Previous studies have shown that statin pretreatment may improve postoperative outcome in symptomatic and asymptomatic patients undergoing carotid endarterectomy and the periprocedural and postprocedural outcomes of patients undergoing carotid artery stenting procedures. The beneficial effect demonstrated in the current study6 occurred in the setting of treatment commenced before stroke onset; still, the data from this study have implications for interpretation of ongoing studies of symptomatic and asymptomatic carotid disease, e.g., The European Carotid Surgery Trial 2 (see http://s489637516.websitehome.co.uk/ECST2/index2.htm) and management of asymptomatic carotid disease.

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**REFERENCES**