Statins Prevent Stroke Recurrences...But Can They Improve Stroke Outcome?

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See related article, pages 3526–3531.

First, multiple studies firmly established the value of statins in reducing the risk of ischemic stroke among patients with cardiovascular disease. Then the truly seminal Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that high-dose atorvastatin reduced the risk of subsequent stroke in patients without known coronary artery disease who had a recent stroke or transient ischemic attack before enrollment. Now, in this issue of Stroke, the SPARCL investigators present data suggesting that high-dose statin might also reduce the severity of recurrent strokes. Can it be true that statins may not only prevent progression of vascular disease, but also be neuroprotectants or enhance recovery from neurological injury?

There is convincing experimental evidence indicating that statins have various potentially neuroprotective properties, including amelioration of glutamate-mediated excitotoxicity, attenuated production of reactive oxygen species, upregulation of endothelial nitric oxide synthase with favorable effects on the microcirculation, diminished inflammatory reaction by modulation of the cytokine response, and promotion of angiogenesis, which could improve the availability of collateral vessels. Flow in the microcirculation could also be enhanced by statins due to antiplatelet and profibrinolytic effects. Furthermore, statins could positively impact brain regeneration by stimulating neurogenesis and angiogenesis.

However, the promise of neuroprotection and improved neurological recovery from these pleiotropic actions of statin drugs has not been consistently supported by the results of observational studies assessing the effect of previous statin treatment on ischemic stroke outcome. Although some studies suggested that previous statin therapy could improve functional outcome or early mortality after a stroke, others did not show such an effect or found a benefit only in specific subgroups of patients. Still, retrospective studies may have been contaminated by selection biases, which could have affected the results on either direction (eg, patients treated with a statin may have had more severe vascular disease or, conversely, their vascular disease may have been more aggressively treated before the stroke).

The SPARCL population provides a unique opportunity to study the effect of previous statin therapy (in this case high-dose atorvastatin) on subsequent stroke outcome. Yet, the results of the analysis presented by the SPARCL investigators need to be carefully interpreted. The reductions in recurrent ischemic strokes of different severities were actually comparable in patients treated with atorvastatin and those treated with placebo. There was only a trend toward lesser severity of the recurrent ischemic strokes in the atorvastatin groups as measured by the modified Rankin Score, but no differences were noted when stroke severity was evaluated using the Barthel Index (arguably a more sensitive measure of functional outcome) or the National Institutes of Health Stroke Scale. The major difference between the 2 groups was the one we already know: patients on statin have a lower incidence of recurrent brain infarction. It was this reduction in stroke recurrence that led to the finding that patients on statin had a significant benefit in the overall combined end point, which included not only the severity of recurrent strokes, but also stroke-free outcomes.

Hence, it is still unclear if high-dose atorvastatin may reduce the severity of recurrent ischemic strokes. However, the SPARCL trial has shown that high-dose atorvastatin decreases the risk of recurrent ischemic strokes and major cardiovascular events in men and women, with and without carotid stenosis, and regardless of initial stroke mechanism (although patients with identified sources of cardiac embolism were excluded from the trial) or baseline low-density lipoprotein cholesterol levels. Consequently, statins should be prescribed to all patients with ischemic stroke or transient ischemic attack caused by atherosclerosis. The challenge in practice is to optimize the timely prescription of statins and the adherence to therapy, which are currently inadequate. After all, it would be useful to patients if statins reduced the severity of recurrent strokes, but it is even more useful to them that statins can definitely diminish their risk of having recurrent strokes (and coronary events) in the first place. That is the message we need to transmit loudly and clearly to our patients.

Disclosures

None.

References


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