

Rapid Effects of Statins From Prophylaxis to Therapy for Ischemic Stroke

Ulrich Laufs, James K. Liao

Ischemic stroke is a leading cause of death and disability worldwide and is a major contributor to rising healthcare costs. It has been estimated that in the United States, an individual is afflicted with stroke every 53 seconds with fatality occurring about every 2 minutes. Despite recent advances in the treatment of cardiovascular diseases, the therapeutic options for acute ischemic stroke remain limited. For secondary prevention, antiplatelet therapy with aspirin was the only available treatment. However, recent randomized trials with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins have shown remarkable benefits in terms of reducing the incidence of stroke in patients with risks for cardiovascular disease.¹ It is not clear from these studies, however, how much of the benefits were attributed to the reduction of atherosclerotic coronary artery disease because ischemic heart disease is a risk factor for stroke. Nevertheless, several ongoing trials with statins in patients without coronary artery disease should help clarify the extent of stroke protection.

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Earlier this year, two randomized trials have added important clinical information. The Heart Protection Study (HPS) demonstrated reduction of stroke in a large number of patients irrespective of baseline cholesterol levels and in whom total cholesterol levels were as low as 135 mg/dL.² Furthermore, the analysis of stroke as a predefined secondary endpoint of the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) trial showed that early treatment of high-risk patients with acute coronary syndromes halved the incidence of stroke within 4 months.³ These trials demonstrate not only the rapidity of statin's cardiovascular protective effects, but also its indiscriminate benefits with respect to cholesterol levels. Thus, the relevance of cholesterol as a protective mechanism of statin therapy in ischemic stroke has remained controversial.⁴ Indeed, intervention trials with nonstatin lipid-lowering drugs have failed to demonstrate a reduction in stroke incidence. Thus, we are currently left with several unanswered questions. If cholesterol lowering does not explain the beneficial effects of statins on stroke, then what could be the potential mechanisms? Further-

more, if cholesterol is not the mechanism, is there a role for statins in the treatment of acute ischemic stroke?

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Sironi et al⁵ attempted to address some of these issues using a well-controlled rat stroke model of permanent middle cerebral artery occlusion (MCAO). In contrast to previous studies, they followed the development of cerebral infarction over time using MRI technique. In their vehicle-treated animals, the cerebral infarct volumes increased by 38.5% and 89% after 24 and 48 hours, respectively, compared with the damage detected at 2 hours after MCAO. Treatment with simvastatin (20 mg/kg) at 3 hours after MCAO prevented the increase in brain infarct volume occurring at 24 hours and reduced cerebral infarct size by 46.6% at 48 hours. This effect was similar to that observed when simvastatin was administered before the induction of focal ischemia and occurred without significant changes in baseline cholesterol levels. Thus, the two most surprising findings of this study are that the reduction of infarct volume by statin treatment is even greater at later time points, and that initiation of statin therapy *after* cerebral infarction resulted in reduction of stroke size similar to that observed with prophylactic treatment. These findings, if confirmed clinically, could herald a new therapeutic strategy with the use of statins for both prophylaxis and acute treatment for ischemic stroke.

Previous studies have shown that endothelial NO synthase (eNOS) is an important regulator of cerebral blood flow, especially during cerebral ischemia, where it has been shown to improve perfusion and limit infarct size.⁶ In agreement with previous studies,^{7,8} the neuroprotective effects in the study by Sironi et al⁵ were paralleled by an increase in eNOS immunoreactivity, detectable in the brain of simvastatin-treated rats. However, it is interesting to speculate that additional cholesterol-independent effects of statins may also contribute to the stroke protection (Table).⁹ Thrombosis superimposed on atherosclerosis plays an important role during brain infarctions. In animal experiments, statins have been shown to reduce platelet activation and thrombus formation, which in part, are influenced by eNOS activity.¹⁰ Furthermore, statins have been shown to regulate the fibrinolytic balance via inhibition of plasminogen activator inhibitor-1 (PAI-1) and upregulation of tissue plasminogen activator (tPA) in vascular cells.¹¹ Other potential mechanisms include the anti-inflammatory actions of statins, which are likely to attenuate the inflammatory cytokine responses that accompany cerebral ischemia. Inhibition of free radical release in the presence of statins is likely to contribute to both their antithrombotic and anti-inflammatory actions.^{12,13} Recent experimental and clinical data suggest that statin therapy can increase the number and function of circulating bone marrow-derived endothelial progenitor cells (EPC), which have been shown to facilitate endothelial repair.^{14,15} It is tempting to speculate that

From the Vascular Medicine Research Unit (U.L., J.K.L.), Cardiovascular Division, Brigham & Women's Hospital and Harvard Medical School, Boston, Mass; and Medical Clinic III (U.L.), University of Saarland, Homburg, Germany.

Correspondence to James K. Liao, MD, Vascular Medicine Research, 65 Landsdowne St, Room 275, Cambridge, MA 02139. E-mail jliao@rics.bwh.harvard.edu

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Effects of Statins Potentially Contributing to Protection and Treatment of Ischemic Stroke

Cholesterol lowering
Plaque stabilization
Increase of endothelial NO
Reduction of oxidative stress
Anti-inflammatory effects
Inhibition of platelet activation and enhancement of fibrinolysis
Increase of circulating endothelial progenitor cells

increased numbers of EPC may somehow improve the outcome of cerebral infarction over longer periods.

Many beneficial effects of statins appear to be independent of serum cholesterol levels. For example, upregulation of endothelial NO is, in part, mediated by inhibition of geranylgeranylation of RhoA GTPase, which acts as a negative regulator of eNOS mRNA stability. Indeed, direct inhibition of RhoA in mice with a bacterial toxin, which has no effect on cholesterol biosynthesis, reduced stroke size similarly to that of statin treatment.⁸ Similarly, the upregulation of tPA and downregulation of PAI-1 expression are also mediated by inhibition of RhoA.¹¹ In addition, inhibition of isoprenylation of other small G proteins such as Rac1 could contribute to the statin-induced reduction of NAD(P)H oxidase activity and superoxide production.^{12,13} Another cholesterol-independent effect of statins is the activation of phosphatidylinositol 3-kinase/protein kinase Akt pathway, which activates eNOS and stimulates the release of EPC.^{16,17} Clinically, the importance of these mechanisms may not only relate to the time course of events after initiation, but also after termination of statin treatment, where abrupt cessation of statin therapy is associated with increased adverse events.¹⁸ In agreement with these mechanisms, Sironi et al⁵ reported that the rapid improvement in cerebral infarction occurring only 24 and 48 hours after MCAO was not accompanied by lowering of serum cholesterol.

In contrast to the clinical trials, which have focused on the effects of statin therapy on the incidence of stroke, the experimental set-up of Sironi et al⁵ allowed the investigator to monitor the development of stroke size, which may be at least as important as a reduction of stroke incidence. Their data support the hypothesis that the decreased number of cerebrovascular events observed in clinical trials may in part be due to a reduction of cerebral infarct size to levels that are clinically unappreciated. Recurrent minor cerebral ischemic events may also lead to the development of dementia. Indeed, several reports have suggested a potential beneficial effect of statins on cognitive function and dementia.^{19,20}

These impressive results, however, should be viewed with some caution. The rat model used in the present study is not a model for atherosclerosis. This allowed the investigators to focus on the cerebral blood flow-dependent effects of statins while excluding potential effects of statins on atherosclerotic plaques. However, in humans, most ischemic strokes are caused by thromboembolic or small-vessel disease. Therefore, in contrast to the rodent models reported in this study, in which the vessels are pristine, systemic plaque stabilization and improvement in vascular function are likely to contribute to the neuroprotective action of statins in clinical studies. Nevertheless, the findings by Sironi et al⁵ are provocative and add to the growing list of statin pleiotropism. Further clinical

trials are warranted to determine whether there is a role for statin therapy in the acute treatment of ischemic stroke.

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