Discontinuation of Statin Treatment in Stroke Patients
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Background and Purpose—Statin treatment may improve stroke outcome and even acute ischemic stroke patients suffer significantly higher morbidity and mortality compared to stable vascular patients.9 Here, we review recent experimental and clinical evidence to suggest that the abrupt discontinuation of statin treatment may have adverse vascular effects and may negatively impact outcome of acute vascular patients.

Conclusions—We propose that in all acute ischemic stroke patients chronically treated with statins before the event, treatment should be continued and the patient should receive medication at the day of the stroke. (Stroke. 2006;37:000-000.)

Summary of Review—It is increasingly recognized that statins (HMG-CoA reductase inhibitors) exert rapid cholesterol-independent (pleiotropic) vasoprotective effects. Here, we review evidence to suggest that the abrupt discontinuation of statin medication exerts negative vascular effects in patients with acute vascular events.

Key Words: acute Rx ■ acute stroke ■ brain ischemia ■ cholesterol ■ lipids ■ statins ■ treatment

Statin treatment may improve stroke outcome and even survival at 1 month.1–7 In addition to their cholesterol-lowering properties, statins exert pleiotropic effects that include improvement of endothelium function, anti-inflammatory, antithrombotic, and immunomodulatory effects.8

Most of the pleiotropic statin actions are mediated by HMG-CoA reductase inhibition and are dose-dependent. In fact, inhibition of the mevalonate pathway by statins prevents the formation of a number of biologically important isoprenoid intermediates such as farnesylpyrophosphate or geranylgeranylporphosphate. Isoprenoids serve as important lipid attachments for the post-translational modification of a number of intracellular proteins, including heterotrimeric G-proteins and small GTP-binding proteins. When isoprenylated, small guanosine-triphosphate hydrolases (GTPases) are anchored to the membrane and display GTPase activity. In their nonisoprenylated state they reside inactively in the cytosol. Geranylgeraniol, for example, serves as a lipid attachment of the small GTPases RhoA and Rac1.

It is increasingly recognized that the onset of these pleiotropic effects is rapid and statins have been proposed for early secondary prevention and even acute treatment of vascular disease.9 Here, we review recent experimental and clinical evidence to suggest that the abrupt discontinuation of statin medication may have adverse vascular effects and may negatively impact outcome of acute vascular patients.

Rebound Effect After Abrupt Discontinuation of Statin Treatment: Experimental Evidence
A rebound effect after cessation of statin therapy was exemplarily shown for the small GTP-binding Rho. In cultured endothelial cells, statins (via inhibition of geranylgeranylation) inhibit Rho membrane translocation and GTPase activity but concomitantly upregulate Rho expression.10,11 Rho expression is regulated by a negative feedback mechanism mediated by the actin cytoskeleton: statins increase Rho gene transcription, as do direct disruptors of the actin cytoskeleton. Thus, during chronic statin treatment nonisoprenylated Rho accumulates at high levels in the cytosol. After sudden discontinuation of statin treatment, however, geranylgeraniol becomes available followed by massive membrane-binding and activation of Rho (Figure).10,11

Rho is a negative regulator of endothelial nitric oxide synthase (mediated by Rho kinase and actin stress fibers), and this overshoot activation after statin termination has significant biological consequences: in mice treated with atorvastatin, discontinuation of treatment causes a 90% decrease of NO production after 2 days.12 NO is essential for endothelium-dependent vasodilation and exerts anti-inflammatory and antithrombotic effects.8 In fact, markers of platelet activation (such as P-selectin) are upregulated in patients with acute coronary syndromes treated with statin medication in acute ischemic stroke patients...
Cytosol            Membrane

A. No treatment
   Rho ⇄ Rho-GGPP

B. Statin treatment
   Rho        ↑
   Rho-GGPP       ✫

C. Statin withdrawal
   Rho                             Rho-GGPP
   GGPP             ✫

Withdrawal of statin treatment leads to overshoot activation of Rho GTPase. A. At baseline (no treatment) Rho is present in its active, geranylergyranpyrophosphate (GGPP)-bound form and in its inactive, nonisoprenylated, cytosolic form. B. After initiation of statin treatment, formation of GGPP is blocked and Rho is mainly present in its inactive, cytosolic form. Via negative feedback regulation, however, statin treatment confers increased Rho gene transcription and accumulation of high levels of nonisoprenylated Rho in the cytosol. C. After discontinuation of statin treatment, GGPP becomes available, and large quantities of activated Rho are shuttled and anchored to the membrane. Activated Rho is a negative regulator of endothelial nitric oxide synthase expression and overshoot activation confers an abrupt decrease of NO bioavailability ("statin rebound").

Biological Effects of Abrupt Discontinuation of Statin Treatment in Humans
Cessation of high-dose atorvastatin (80 mg/d) in young, healthy men impaired endothelium function as measured by volume plethysmography independent of low-density lipoprotein cholesterol (LDL-C) and high-sensitive C-reactive protein (hs-CRP) levels.14 In addition, there is evidence that statin discontinuation triggers a proinflammatory and prothrombotic response.15

Huang and coworkers demonstrated that discontinuation of chronic simvastatin treatment (ie, 20 mg/d for >6 months) led to a significant rebound effect on hsCRP but not matrix metalloproteinase levels in hypercholesterolemic patients.16 Similarly, in 20 patients with hypercholesterolemia, termination of atorvastatin therapy (10 mg/d for 3 months) resulted in a rapid increase of hs-CRP levels but not LDL-C within 2 days.17 Plasma human tissue-type plasminogen activator and soluble vascular intercellular adhesion molecule-1 significantly increased at day 1 and 2, respectively, after discontinuation of a 12-week course of atorvastatin (10 mg/days) in 22 hypercholesterolemic individuals.18 In addition, there is evidence for platelet hyperactivity after statin treatment discontinuation.19

Discontinuation of Statin Medication in Stable Vascular Patients
A >3-fold increase in vascular events was reported in a group of 129 patients with stable coronary heart disease after simvastatin treatment was stopped and continued with relatively lower doses of fluvastatin.20 However, in the Treating to New Target (TNT) Study which compared 2 doses of atorvastatin (10 versus 80 mg daily) in a double-blind parallel-group design which included a dietary lead-in/drug washout period did not corroborate these findings.21 More than 9000 stable cardiac patients with prior statin therapy were analyzed for the occurrence of acute coronary syndromes and vascular death during the 6-week drug washout period. There were 24 primary events during this 6-week period which was not different from the 31 events in the subsequent period in which these patients received 10 mg atorvastatin in an open-label fashion. Therefore, the short-term discontinuation of statin therapy in stable cardiac patients apparently does not lead to a clinically important increased risk of vascular events.21

Discontinuation of Statin Medication in Patients With Acute Vascular Events
A retrospective analysis of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial demonstrated that cessation of statins increases event rate in patients with acute coronary syndromes. The rates of myocardial infarction/death at 7 days were 3.8% among patients who did not receive statins, 2.9% among patients who continued statins, and 8.2% among patients who discontinued statins (P=0.082 among all 3 groups and P=0.031 between the continued and discontinued groups).22,23 The National Registry of Myocardial Infarctions (NRMI) 4 is a prospective, observational database of consecutive patients who were admitted with acute myocardial infarctions to 1230 hospitals throughout the United States.24,25 Of 13 871 patients with non-ST-segment elevation myocardial infarction receiving statins before hospital admission, ≈35% had treatment withdrawn during the first 24 hours of hospitalization. These patients had increased hospital morbidity and mortality rates compared with patients in whom therapy was continued. In fact, in multivariate analysis these patients were at significant risk of in-hospital death compared with those continuing statin therapy.24 In another publication from NRMI-4, data were presented from >300 000 patients with acute myocardial infarctions. New or continued treatment with a statin within the first 24 hours was associated with a decreased risk of mortality compared with no statin use (4.0% mortality for...
Discontinuation of statin treatment, however, was associated with an increased risk of mortality (16.5% for “yes/no”). 25

There is accumulating evidence that statin pretreatment may improve stroke outcome. 1–7 In clinical practice, however, many patients are treated NPO (nothing per os) directly after stroke; therefore, statin rebound is a concern. Recently, the results of a prospective study investigating the consequences of cessation of statin treatment in acute stroke patients were presented at the American Stroke Conference. 26,27 Nombela and colleagues studied 215 patients with acute ischemic stroke out of which 89 were chronically treated with statins before the stroke. These patients were randomized to statin discontinuation (n=46) or continued statin therapy (n=43), whereas the remaining 126 patients served as nonstatin control. 27 Statin discontinuation was associated with significantly increased risk of early neurological deterioration which was defined as an increase in National Institutes of Health Stroke Scale (NIHSS) score of >4 points (odds ratio [OR] 9.93; 95% CI, 3.97 to 24.86) and a higher likelihood of poor outcome which was defined as modified Rankin Scale score >2 (OR 3.57; 95% CI, 1.47 to 8.69). Moreover, statin termination was also associated with higher plasma levels of inflammatory markers (such as interleukin-6, soluble vascular cell adhesion molecule-1). 26 It is important to note, however, that the evidence regarding stroke patients is presently limited to this study which has not been published.

There is also evidence to suggest that statin treatment improves outcome from subarachnoidal hemorrhage. For example, Kirkpatrick and coworkers demonstrated that 14 day treatment with 40 mg lovastatin initiated within 3 days in patients with aneurysmatic subarachnoidal hemorrhage significantly decreased the likelihood of vasospasm and delayed ischemic deficits compared with placebo. 28 Interestingly, however, ischemic events did occur in the treatment group after the 14-day treatment trial had finished. This observation calls for a more prolonged treatment period. In line with this is evidence from a retrospective study analyzing the risk for vasospasm in relation to the use of vasoactive medications in patients with subarachnoidal hemorrhage. Statin use surprisingly increased the risk for vasospasm (OR 2.75 [1.16 to 6.5]) which was likely attributable to abrupt statin discontinuation (OR 2.54 [0.78 to 8.28]). 29

Presently, there is no evidence to suggest that patients with hemorrhagic stroke benefit from statin treatment. In contrast, the Heart Protection Study (HPS) 30 as well as the recently completed Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) 31 study reported an increased risk of hemorrhagic stroke after statin treatment in patients with prior stroke/TIA.

Pharmacological Considerations
Generally, it is expected that negative vascular effects after discontinuation of treatment apply for all statins (class effect). Statins, however, differ in their plasma half-lives. Theoretically, side effects after discontinuation of treatment may occur more rapidly with statins which have short plasma half-lives (t1/2; eg, pravastatin 1.5 to 2 hours; simvastatin 1.9 hours) than with those which have longer half-lives (eg, atorvastatin 14 hour, active metabolites 20 to 30 hours). However, the half-life of statins in the serum may significantly differ from their tissue half-life, both in the liver and in the vascular wall. In addition, specific transport mechanisms may exist for statin drugs in various tissues, eg, the organic anion transporter in the liver. 32 Statins differ in their tissue permeability and metabolism. Furthermore, the affinity of binding to HMG-CoA reductase, which is not related to serum t1/2, differs between statins. 33 Small studies suggest that endothelial function does not show circadian changes between dosages of statin drugs. 14 To our knowledge, potentially differential effects of statins with different t1/2 have not been studied systematically, and there is presently no evidence that longer half-life statins are more protective against “rebound” effects.

Moreover, there is presently no evidence available to assess whether the effects observed after discontinuation after statin treatment are dose-dependent. It is plausible to speculate that these negative “rebound” effects are more pronounced after sudden termination of high-dose statin treatment. It should be noted that the concentrations used in experimental studies exceed those used clinically although several authors have attempted to calculate corresponding doses of drugs applied in humans and rodents. In the absence of specific data we propose that the patient should receive at least the dose of the previously prescribed statin. If the patient’s statin on formulary is not available, the patient should receive an equivalent dose of another statin. Because rebound effects were already evident when the medication was withheld within the first 24 hours after the event, the patient should receive statin treatment on the day of admission (eg, in the emergency department) and treatment continued thereafter. For longer-term secondary prevention of stroke, current treatment guidelines recommend statin agents, and the target goal for cholesterol-lowering for those with coronary heart disease or symptomatic atherosclerotic disease is an LDL-C of <100 mg/dL, and LDL-C <70 mg/dL for very-high-risk persons with multiple risk factors. 34

Conclusions
In view of the above evidence, we propose that in patients with acute ischemic stroke chronically treated with a statin before the event, treatment should be continued to avoid possible negative vascular effects. In view of the evidence that statins have serum half-lives between 2 and 27 hours and that withholding statin medication for only 24 hours was shown to increase in-hospital mortality in patients with acute coronary syndromes, the respective patients should receive the medication at the day of the insult (eg, via nasogastric tube if necessary). It should be noted that apart from the unpublished study by Nombela, the effects of statin cessation have not been tested in prospective trials, and case series and retrospective studies may overestimate the adverse effect of statin discontinuation. Another caveat is the paucity of data on acute stroke: it is not clear whether the data from studies in other vascular diseases, particularly acute coronary syndromes, can be generalized.
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References

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