Continued Statin Treatment After Acute Intracranial Hemorrhage
Fighting Fire With Fire

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Statin therapy has clearly demonstrated a beneficial effect in reducing the risk of first ever and recurrent ischemic stroke in patients with coronary artery and cerebrovascular diseases. However, the overall benefit of statins in patients with previous stroke appears to be partially offset by an increased risk of intracranial hemorrhage (ICH). Post hoc analyses of 2 large randomized trials, Heart Protection Society and Stroke Prevention by Aggressive Reduction in Cholesterol Levels, suggest that patients with previous stroke may be at increased risk of hemorrhagic stroke independently of cholesterol levels.1 Like dynamite, statins help fighting fires (ischemic strokes), but with an added risk of potential collateral damages (ICH). Thus, avoidance of statin initiation or continuation after ICH has been recommended by several experts. In contrast, recent observational cohort studies and 1 meta-analysis found no evidence of increased risk of ICH in patients treated with statins after an ischemic stroke. Therefore, it is a matter of controversy whether continuation or initiation of statins in acute ICH patients with history of ischemic stroke is beneficial or harmful in terms of ICH growth, stroke (ischemic and hemorrhagic) recurrence and clinical outcome.

Dr Goldstein, as a senior and experienced fireman, defends a conservative evidence-based position. He considers that statins should not be started or continued during the initial hospitalization in patients with ICH because there is no evidence of benefit when given early after ICH and at least reasonable concern for collateral damages. In contrast, the brave young firefighters, Drs Bustamante and Montaner, strongly believe in the countless beneficial pleiotropic effects of statins and consider that statin therapy not only is a wet gunpowder with regard to ICH risk but also might even improve ICH outcome. They argue that statin therapy should not be discontinued after ICH, given its neuroprotective properties and potential deleterious effects of statin withdrawal.

Decision on starting/continuation or avoidance/discontinuation of statins in patients with ICH depends, among other factors, on the strength of the evidence available. Although arguments supporting statin discontinuation after ICH are based on few randomized controlled trials, those against statin withholding are mainly based on observational, cohort, and retrospective studies. Although encouraging and hypothesis-generating, observational and retrospective studies are subject to a variety of bias and confounders. On the contrary, however, translation of Heart Protection Society and Stroke Prevention by Aggressive Reduction in Cholesterol Level data into clinical practice is challenging because, as Dr Goldstein points out, available analyses of the impact of statins in patients with ICH are based on small numbers of patients, and almost entirely on post hoc exploratory and secondary analyses.

The mechanism by which statins might amplify ICH risk remains unclear. In addition to their well-known lipid-lowering effects, statins may have antithrombotic properties by inhibiting platelet aggregation and enhancing fibrinolysis. Secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Level trial showed an additive effect of statins on ICH risk, especially in older patients, with prior stroke and ICH as qualifying event. Unfortunately, because of small numbers, this study did not evaluate the impact of location of ICH index on the recurrence rate. Location of ICH may represent a marker of underlying pathophysiology with different recurrent risk. Lobar ICH in older patients suggests cerebral amyloid angiopathy, whereas hypertensive vascular disease is primarily responsible for deep ICH. The risk of recurrent deep ICH can be reduced by appropriate anti-hypertensive therapy, whereas cerebral amyloid angiopathy currently lacks an established preventative treatment, leading to an increased risk of ICH recurrence. A mathematical decision analysis2 showed that for lobar ICH in particular, statin therapy is predicted to raise the baseline annual probability of recurrence up to 22%, offsetting the cardiovascular benefits for both primary and secondary cardiovascular prevention. A recent retrospective study found that statin use in patients with ICH was independently associated with microbleeds on gradient echo T2*-weighted MRI, particularly of cortico-subcortical distribution, suggesting that cortico-subcortical...
distribution, frequently seen in patients with cerebral amyloid angiopathy, may represent a surrogate marker of vascular fragility and may help to identify patients at greater risk of ICH recurrence.

The scenario is even more complex when considering statin continuation during hospitalization in the acute ICH setting. The Stroke Prevention by Aggressive Reduction in Cholesterol Level trial did not enroll patients during the first week of stroke. Although 1 randomized trial demonstrated that statin withdrawal was associated with increased risk of death or dependency at 90 days after ischemic stroke, data on the impact of statin treatment on hematoma growth, clinical course, and long-term outcome after acute ICH are scarce. One study showed that pretreatment with statins affects the volume of spontaneous ICH and contributes to the progression of ICH volume between baseline and follow-up computed tomography scans. However, the impact of active statin treatment on acute ICH growth is unknown. Therefore, our biased preference is to avoid statin therapy during the first few days of the acute phase of ICH, particularly in patients at high risk for ICH recurrence, (ie, older patients, previous stroke, lobar ICH, and cortico-subcortical distribution on MRI). Resuming treatment in patients who were taking statins before ICH onset may be considered at discharge. This decision should be made on a case-by-case basis after taking into consideration the patient’s overall risk factors for vascular disease and recurrent ICH. There is clearly a need for randomized trials of statin use in patients with acute ICH and vascular risk factors, including various agents and different statin doses to guide the management of patients.

Disclosures
None.

References

Key Words: intracranial hemorrhage • statins • stroke recurrence
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Stroke. 2013;44:2062-2063; originally published online June 13, 2013;
doi: 10.1161/STROKEAHA.113.001671
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

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/44/7/2062

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