

ALTERNATIVE VIEWPOINTS

Statin Therapy and Intracerebral Hemorrhage

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We read with great interest the review by Drs. Weant and Cook on the potential roles for statins in critically ill patients.¹ However, we are surprised that the authors did not mention the relationship between serum cholesterol and intracerebral hemorrhage.

Epidemiologic data² have clearly shown a relationship between low cholesterol levels and subsequent hemorrhagic stroke, and recent evidence suggests that low-density lipoprotein (LDL) cholesterol concentration is inversely related to incident intracerebral hemorrhage.³

Furthermore, lower baseline LDL-cholesterol levels have been associated with a greater risk of symptomatic intracerebral hemorrhage following thrombolysis for ischemic stroke.⁴ Not surprisingly, the Stroke Prevention with Aggressive Reduction in Cholesterol (SPARCL) study⁵ has shown that as compared with placebo, the use of high-dose atorvastatin in patients who had a stroke or TIA was associated with a 66% increase in the relative risk of hemorrhagic stroke.

There is intense pressure to use higher doses of statins in order to achieve very low LDL-cholesterol levels.⁶ In doing so, we may be increasing the subsequent risk of intracerebral hemorrhage, particularly in the setting of thrombolysis, an accepted and increasingly used therapy for stroke.

References

1. Weant KA, Cook AM. Potential roles for statins in critically ill patients. *Pharmacotherapy* 2007;27(9):1279–96.
2. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989;320:904–910.
3. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke* 2007;38:2718–25.
4. Bang OY, Saver JL, Leibeskind DS, et al. Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. *Neurology* 2007;68:737–42.
5. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al., for the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549–59.
6. O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. *J Am Coll Cardiol* 2004;43:2142–6.

Authors' Reply

We appreciate the thoughtful consideration of our review of the potential for the role of statins in various types of critical illness by Drs. Mascitelli, Pezzetta, and Goldstein. They raise a good point in discussing the possible relationship of statins and low cholesterol values with intracerebral hemorrhage (ICH). Statins stabilize nitric oxide concentrations in the endothelium and inhibit the thrombin platelet-associated receptor (PAR-1), both of which may affect platelet function. We concede that several studies have suggested that this relationship is present, particularly in the setting of ischemic stroke. However, this assertion is not definitive. There are also a number of studies and meta-analyses which suggest no relationship between statin use and the occurrence of ICH.^{1–3} An incontrovertible relationship between statins and ICH has yet to be demonstrated.

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As a result of the increase in ICH in patients randomized to atorvastatin in the SPARCL study, a secondary analysis was performed to examine the contribution of a number of factors, including atorvastatin, related to the occurrence of ICH.⁴ Atorvastatin randomization continued to be identified as a statistically significant factor related to the development of ICH in a multivariate Cox regression model (HR 1.68, 95% CI 1.09–2.59). However, only approximately 1% of the occurrence of ICH was due to measured factors (r^2 for the model = 0.009). In addition, only 14% of the clinical factor-association with ICH occurrence was related to atorvastatin randomization. Thus, in this study, the association of atorvastatin use and ICH likely represents a finding of minimal clinical relevance. In addition, the extent of lipid-lowering did not appear to impact the risk of ICH.⁵

If statins are ultimately to be used to prevent or attenuate sepsis, cerebral vasospasm, or ARDS, it is likely that the therapy will have a finite duration. Defining the length of therapy may be a significant factor when considering the risks of therapy, particularly ICH. Specifically for patients with stroke or transient ischemic attack, the incidence of ICH in SPARCL patients randomized to atorvastatin seems to diverge approximately three years after enrollment (long after statin therapy would likely be needed for an acute non-cardiovascular event).⁴ This appears to indicate that the risk of ICH with statin use is no more than the natural history of the disease during the first several years.

Due to the conflicting data regarding the relationship of statins and ICH, it is prudent to be mindful of this potential association, particularly in ischemic stroke patients or those that have already had an ICH. As mentioned in our review, many of the indications discussed are supported by preliminary data only and require further study to establish safety and efficacy. Applying these therapies is not without risk, so confirmation of benefit is obviously desirable. The development of myopathy or hepatic dysfunction from statins may also be increased in the critically ill, as these patients often acquire these conditions during critical illness independent of statin use. All of these risks need to be thoroughly assessed through prospective evaluations.

Much more insight regarding statin use in the critically ill is needed. High-dose statins work

quickly to lower cholesterol and it is already known that critically ill patients often exhibit acute hypocholesterolemia (with hypertriglyceridemia).^{6, 7} The pharmacodynamics of statins (both pleiotropism and cholesterol-lowering activity) in various forms of critical illness are not well described at this point and merit further study. When using statins for acute scenarios such as cerebral vasospasm or sepsis, where the endothelial perturbations are time-limited, is there a need to wean therapy once initiated to avoid rebound complications or is there value in long-term continuation? If statins are associated with ICH, is it due to antiplatelet activity or alterations in high-density or low-density lipoprotein concentrations? We believe that the potential role for statins in various acute conditions causing critical illness is great. The application of this therapy to critically ill patients should be based on quality clinical evidence and be individualized considering each patient's likelihood to benefit or be harmed by the therapy.

References

1. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366(9493):1267–78.
2. Waters DD, LaRosa JC, Barter P, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (Treating to New Targets) study. *J Am Coll Cardiol* 2006;48(9):1793–9.
3. Byington RP, Davis BR, Plehn JF, et al. Reduction of stroke events with pravastatin: The Prospective Pravastatin Pooling (PPP) project. *Circulation* 2001;103:387–92.
4. Goldstein LB, Amarenco P, Szarek M, et al. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. In: *Neurology*; 2007;01.wnl.0000296277.63350.77.
5. Amarenco P, Goldstein LB, Szarek M, et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2007;38(12):3198–204.
6. Amarenco P, Bogousslavsky J, Callahan III A, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355(6):549–59.
7. Marik PE. Dyslipidemia in the critically ill. *Crit Care Clin* 2006;22:151–9.

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