The Case:
A 72-year-old man with history of hypertension, lacunar stroke, and mild cognitive impairment presents with a spontaneous cerebellar hemorrhage. He takes a statin.

The Questions:
1. Should statin therapy be discontinued in this patient and why?
2. Are there tests to help with this decision making?

The Controversy:
STATIN THERAPY IN PATIENTS WITH INTRACEREBRAL HEMORRHAGE

Statin Therapy Should be Discontinued in Patients With Intracerebral Hemorrhage

Larry B. Goldstein, MD

Statins are of unequivocal benefit in reducing the risk of a first stroke in patients with coronary heart disease and other high-risk conditions.1 A secondary analysis of the Heart Protection Study (HPS) further found that a statin reduced the risk of major vascular events in patients with established cerebrovascular disease, although there was no reduction in recurrent stroke, possibly because the subjects were randomized a mean of 4.3 years after the qualifying event.2 The Stroke Prevention with Aggressive Reductions in Cholesterol Levels (SPARCL) trial randomized patients with noncardioembolic stroke or transient ischemic attack and no known coronary heart disease to a statin or placebo between 1 and 6 months after the index event, found a reduction in recurrent strokes with statin treatment, and remains the only trial to date specifically designed to test this effect.2 The statin benefit remains whether all trials with even a subgroup of patients with prior cerebrovascular disease are considered (relative risk, 0.82; 95% confidence interval, 0.77–0.87).1 Based largely on SPARCL, American Heart Association secondary stroke prevention guidelines recommend “statin therapy with intensive lipid-lowering effects to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or transient ischemic attack who have evidence of atherosclerosis and a low-density lipoprotein-cholesterol level >100 mg/dL.” It should be noted, however, that even in SPARCL, the statin was not started in the acute setting.

Despite the lack of data from prospective randomized trials showing that beginning a statin immediately after ischemic stroke is of value, discharge on a statin in select patients is one Joint Commission/American Heart Association Primary Stroke Center quality metric. One rationale for initiating statin therapy during the ischemic stroke hospitalization is that doing so may improve patient compliance. The potential benefit of early statin administration is also supported by observational studies suggesting lower mortality and better outcomes associated with their use.

Although the benefit of statins is applicable to those with ischemic stroke or transient ischemic attack, that benefit comes at a potential cost. Exploratory analysis of HPS data showed statistical heterogeneity in the impact of statins on the risks of ischemic versus hemorrhagic stroke among those with a prior cerebrovascular event because of a higher risk of brain hemorrhage among statin-treated subjects. Secondary analysis of SPARCL data found the benefit of the statin in reducing recurrent stroke was partially offset by an increased risk of brain hemorrhage.3 In contrast to data from HPS and SPARCL, a 2011 meta-analysis by Hackam et al reported that, among studies (including SPARCL) exclusively enrolling patients with cerebrovascular disease, there was no evidence that statins selectively increased the risk of intracerebral hemorrhage (ICH), a finding supported by a subsequent retrospective cohort study. Of the studies included in the meta-analysis, however, most were observational and only SPARCL was a prospective randomized trial.

There is a dearth of data related to the impact of statins in patients presenting with an ICH. Approximately 2% of
SPARCL subjects had an ICH as their qualifying event. These subjects could be enrolled in the trial if they were considered by the investigator to be at risk for ischemic stroke or coronary heart disease. The exploratory analysis of SPARCL data found several factors was independently associated with the risk of an outcome brain hemorrhage. These included statin treatment, male sex, increasing age, and having an ICH as the index event. Although statin treatment did not disproportionately increase bleeding risk among those with a prior ICH (ie, there was not a statin×hemorrhage statistical interaction), the effects were additive. Importantly, there was statistical heterogeneity on the basis of type of index event. Those with an ischemic stroke or transient ischemic attack benefited, but there was an overall higher risk of an outcome stroke in those with an index hemorrhage who were randomized to statin treatment (hazard ratio, 2.82; 95% confidence interval, 0.89–9.01). There are no tests to identify those with a hemorrhage who might be helped by early statin treatment. Although a randomized trial by Blanco et al found that withdrawing a statin in patients who were taking one of these medications at the time of ischemic stroke led to poorer outcomes, there are no similar data related to statin withdrawal after ICH.

It needs to be acknowledged that 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 or observational analyses. Nonetheless, because there is no evidence of benefit when given soon (within 1–6 months based on SPARCL) after ICH, no data on statin withdrawal in the acute setting, and at least reasonable concern for harm, statins should not be started or continued during the initial hospitalization in patients with an ICH. This view is supported by a decision analysis that concluded avoiding statins after ICH was favored over a wide range of values for many clinical parameters, particularly in survivors of lobar ICH who are at highest risk of ICH recurrence. Statin use can be reconsidered after the acute/subacute period after ICH on the basis of patient’s general cardiovascular risks.

Disclosures
Dr Goldstein is a member of the SPARCL steering committee and past consultant (Pfizer).

References

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Larry B. Goldstein

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