STATINS FOR PRIMARY AND SECONDARY STROKE PREVENTION

Larry B. Goldstein, MD, FAAN, FANA, FAHA
University of Kentucky
Lexington, KY

Epidemiology
Epidemiological studies show that hyperlipidemia is a stronger risk factor for death due to ischemic heart disease than stroke. The Prospective Studies Collaboration included data from 61 prospective studies with 55,000 vascular deaths. [1] There was increasing risk of coronary death with increasing total cholesterol levels across al age groups from the 4th to the 8th decade. In contrast, there was a similar relationship only in the 40-59 year-old group for stroke. This may, in part, be related to competing risk. For example, in the Asian Cohort Study, there was a 25% increase in ischemic stroke but a 20% decrease in hemorrhage stroke per 4.5 mg/dL increase in total cholesterol. [2] The relationship is even more complex when lipid subclasses are considered. One study found that higher HDL-C is associated with a lower risk of ischemic stroke with no effect of total or LDL-C; in contrast, higher HDL-C is associated with a higher risk of hemorrhagic stroke with higher total and LDL-C associated with a lower risk. [3]

Statins and Primary Stroke Prevention
The use of fibrates, resins or N3-fatty acids to lower lipid levels does not reduce stroke risk. [4] In contrast, meta-analysis of studies including adults >40y with no history of cardiovascular disease or stroke (19 trials(n=71,344 subjects) shows that statins reduce the risk of stroke (RR 0.71, 95% CI, 0.62 to 0.82), all-cause mortality (risk ratio [RR 0.86, 5% CI, 0.80 to 0.93), cardiovascular mortality (RR 0.69, 95% CI, 0.54 to 0.88), myocardial infarction (RR 0.64, 95% CI, 0.57 to 0.71) and composite cardiovascular outcomes (RR 0.70, 95% CI, 0.63 to 0.78). There was no increase in the risk of diabetes (RR 1.05, 95% CI, 0.91 to 1.20) or impaired cognition. [5] Another meta-analysis found no increased risk of brain hemorrhage among patients with no prior stroke. [6]

Statins and Secondary Stroke Prevention
Data for prospective randomized studies evaluating the effect of statins in reducing the risk of stroke after stroke or TIA are limited. The Heart Protection Study, randomizing high-risk subjects to simvastatin 40-mg daily or placebo included 3,280 persons with a history of stroke with 1,820 having stroke, but no known coronary heart disease. [7] There was a 21% reduction in major vascular events regardless of a history of prior stroke, a 25% reduction in stroke in subjects without a prior stroke (i.e., a primary prevention population), but no reduction in stroke in those with a prior stroke. The study, however, lacked statistical power for a stroke endpoint in those with a history of stroke and subjects were randomized an average of 4.3-years after the qualifying event.

The SPARCL trial randomized subjects with non-cardioembolic stroke or TIA within the prior 6-months and an LDL-C$\geq$ 100-mg/dL and $\leq$ 190-mg/dL to double-blind treatment with atorvastatin 80-mg/day or placebo. [8] The primary endpoint was the time to the first occurrence of a fatal or non-fatal stroke. Randomization to treatment was associated with a mean reduction in LDL-C from 129-mg/dL to 73-mg/dL and a 16% reduction in the primary endpoint (adjusted HR 0.84, 95% CI 0.71-0.99). Although the subjects had no known coronary heart disease at the time of enrollment, those randomized to atorvastatin had a 35% reduction in major coronary events (HR 0.65, 95% CI 0.49-0.87), a 20% reduction in major cardiovascular events (HR 0.80, 95% CI 0.69-0.92), a 42% reduction in any coronary heart event (HR 0.58, 95% CI 0.46-0.73) and a 45% reduction in revascularization procedures (HR 0.55, 95% CI 0.43-0.72). There was no heterogeneity of the benefit based on sex, age less than or greater than 65-years, the presence of carotid stenosis, or the presence of diabetes or metabolic syndrome. The benefit was greatest in those with a $\geq$ 50% reduction in LDL-C. [9] When combined in a meta-analysis with other statin trials including subjects with prior stroke, statins were associated with a 12% (95% CI 1-22%) reduction in recurrent stroke. [6] Subsequent observational studies find that statin treatment during the stroke hospitalization is associated with a lower 1-year mortality after adjustment for comorbidities and demographic factors. [10]

A randomized trial assessed whether statin withdrawal during the acute stroke hospitalization was harmful. [11] The odds of death or dependency in those in whom a statin was stopped was increased over 4-fold (OR 4.68, 95% CI 1.46-14.91) and the odds of early neurological deterioration was increased nearly 9-fold ()R 8.67, 95% CI 3.05-

24.63). The harmful effect of statin withdrawal during the acute hospitalization was also supported by an observational study. [10]

Statins and Intracerebral Hemorrhage

As noted above, despite an epidemiological association between low lipid levels and hemorrhagic stroke in some populations, there is no increased risk of ICH with statin treatment in primary prevention populations. In contrast, In SPARCL, the overall benefit of statin treatment for secondary prevention was partially attenuated by an increased risk of brain hemorrhage. [12] In particular, those having a hemorrhagic stroke at the time of randomization tended not to benefit. [12] In addition to statin treatment and baseline hemorrhage, the risk of ICH was greater in men, with increasing age, and in those with uncontrolled hypertension. [12] Among those randomized to the statin, the risk was higher in those who had a baseline hemorrhage, in men and with increasing age. There, however, was no relationship with LDL-C among treated subjects. An analysis by outcome stroke subtype was not pre-planned in SPARCL, and subsequent analyses have questioned the relationship between statin treatment and ICH in this setting. [13]

A decision analysis found no improvement based on Quality Adjusted Life Years with statin treatment in those with either lobar or deep ICH. [14] It is unclear whether statins should be continued or stopped during the acute hospitalization in patients with an ICH (SPARCL randomized patients 1 to 6-months after stroke). A observational study found that, compared to non-users, inpatient statin users had a lower 30-day mortality (OR 4.25 for survival, 95% CI 3.46-5.23) were more likely to be discharged to home or an acute rehabilitation (OR 2.57, 95% CI, 2.16-3.06) whereas those whose statin was stopped had a higher 30-day mortality (OR for survival 0.16, 95% C, 0.12-0.21) and were less likely to be discharged to home or to acute rehabilitation (OR 0.26, 95% CI 0.20-0.35). [15]

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