Intensive Statin Therapy After Stroke or Transient Ischemic Attack
A Sparling Success?

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Anyone aware of the conflicting data regarding the importance of circulating cholesterol in stroke will welcome the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.1 Unlike with coronary heart disease, epidemiological studies often failed to demonstrate an association between elevated cholesterol levels and stroke incidence.2 However, many studies did not take into account the distinct underlying pathophysiological mechanisms of stroke and instead examined conflated end points such as a combination of ischemic and hemorrhagic stroke, or total ischemic stroke without subtyping, and others did not evaluate cholesterol subfractions. In contrast, epidemiological studies that carefully distinguished ischemic and hemorrhagic strokes generally found both a modest association of elevated cholesterol with increased risk of ischemic events and of low cholesterol with an increased risk of intracerebral hemorrhage.3

HMG-CoA reductase inhibitors or “statins,” which inhibit the synthesis of cholesterol that contributes to atheroma development and progression, have been shown to reduce the risk of first stroke in patients with established coronary heart disease, diabetes, or multiple cardiovascular risk factors.4 Indeed, as our cardiology colleagues kept finding the benefit of lower and lower cholesterol targets for reducing the risk of coronary heart disease events,5 the jury remained out as to what role, if any, that statins played in stroke patients without established coronary heart disease.

Subset analyses of prior clinical trials had suggested, but not definitely proved, a benefit of statin therapy in patients with prior strokes. A retrospective subset analysis of 3280 subjects with a remote (mean 4.3 years) history of symptomatic cerebrovascular disease enrolled in the Heart Protection Study (HPS) showed that simvastatin therapy yielded a 20% reduction in major vascular events (0.80, 0.71 to 0.92).6 This benefit was driven by a reduction in myocardial infarction and vascular death end points. For the end point of recurrent strokes, the statin exerted no net benefit (0.98, 0.79 to 1.22), being associated with both a nonsignificant 19% reduction in ischemic stroke and a nonsignificant doubling of hemorrhagic stroke (1.3% simvastatin, 0.7% placebo; relative risk 1.91, 0.92 to 3.96). Because avoiding death and heart attack are outcomes highly desired by stroke patients, the benefit observed in HPS was deemed by most to be clinically worthwhile. In the wake of HPS, the FDA approved simvastatin as indicated for patients with evidence of cerebrovascular disease and the AHA/ASA National practice guidelines recommended statin therapy for patients with ischemic stroke or transient ischemic attack presumed attributable to atherosclerosis.7 Appropriately, for symptomatic cerebrovascular disease patients without coexisting coronary artery disease, the guidelines rated the evidence supporting this recommendation as level B, reflecting an evidence base of post hoc, subgroup analyses that were not definitive.

SPARCL was designed to prospectively examine whether statin treatment prevents secondary stroke among individuals with recent symptomatic cerebrovascular disease.1 In the trial, 4731 individuals with nonseverely disabling (modified Rankin scale score <3) strokes or transient ischemic attacks, LDL cholesterol levels between 100 to 190 mg/dL, and no known history of coronary artery disease, were randomized between 1 to 6 months after the index event to atorvastatin 80 mg daily versus placebo. Approximately 67% of event entry were ischemic strokes, 2% primary hemorhages, and 31% transient ischemic attacks. During the trial, LDL cholesterol levels dropped by 45% in the atorvastatin group (132.7 to 72.9 mg/dL) and only 4% in the placebo group (133.7 to 128.5 mg/dL). During a median follow-up of 4.9 years, the incidence of fatal or nonfatal stroke was lower in the atorvastatin arm than in the placebo group (13.2% versus 13.1%, adjusted hazard ratio 0.84, 0.71 to 0.99; \(P=0.03\), unadjusted \(P=0.05\)). There was also a significant reduction in major coronary events in favor of atorvastatin (3.4% versus

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risk for hemorrhage patients could be identified in whom cerebrovascular disease patients would be improved if high treatment benefit by causal stroke subtypes. Analyses from the SPARCL trialists will clarify the variation in intracerebral hemorrhages. Presumably, forthcoming secondary analyses will elucidate cryptogenic infarcts, and (unaccountably) primary intracerebral hemorrhages. SPARCL enrolled not only patients with large artery atherosclerotic mechanisms would be expected to benefit most from statin therapy. The SPARCL results likely underestimate the magnitude of the true treatment effect in fully compliant patients. Attributable to high rates of discontinuation of assigned therapy in the statin group (15.4%) and crossovers to open label nonstudy therapy effect on mortality (1.00, 0.82 to 1.21). There was a higher incidence of hemorrhagic strokes in the atorvastatin arm compared with the placebo group (2.3% versus 1.4%, hazard ratio 1.66, 1.08 to 2.55). The high-dose statin therapy was well tolerated, with a mildly increased rate of elevated liver enzymes (2.2% versus 0.5%, \( P<0.001 \)), no cases of liver failure, and no excess cases of myopathy.

From a clinical perspective, the benefits of statin therapy demonstrated in SPARCL are modest, but worthwhile. The number-needed-to-treat to prevent a first recurrent stroke over one year is 258 and to prevent one nonfatal MI 288. Among 1000 ischemic stroke and transient ischemic attack patients, high-dose atorvastatin over 1 year will avert 4.8 ischemic strokes and 3.5 nonfatal myocardial infarctions, while causing 1.9 additional hemorrhagic strokes. However, stroke, myocardial infarction, and vascular death are important health events. Taking into account the disability-adjusted life years gained by averting one nonfatal stroke (10.8 disability-adjusted life years), one nonfatal myocardial infarction (5.7) and one vascular death (16.5), the number-needed-to-treat for one year of poststroke statin therapy to yield one additional disability adjusted life year is 12.5. On average, a poststroke/transient ischemic attack individual will gain one more month of high quality life during each year of statin therapy.

The SPARCL results likely underestimate the magnitude of the true treatment effect in fully compliant patients. Attributable to high rates of discontinuation of assigned therapy in the statin group (15.4%) and crossovers to open label nonstudy statin therapy in the placebo group (7.5%), the net difference in actual statin use between the 2 treatment groups was only 78%. An additional factor contributing to the only modest benefits observed in SPARCL is that enrolled patients were aggressively treated with established secondary prevention interventions, including antithrombotic and antihypertensive therapy. The low event rate in the placebo arm, 2.7% recurrent strokes per year, limited the ability to detect benefits of the addition of statin therapy.

It is noteworthy that in SPARCL the benefit of statin therapy accrued only after a delay, with event curves starting to separate substantially only in the third year after start of treatment. Perhaps earlier and more potent treatment effects would have been observed in SPARCL had the trial enrolled patients in the first month after their index cerebrovascular event, when the risk of recurrence is greatest.

The heterogeneity of cerebrovascular disease likely also limited the observed benefit of statins on secondary stroke prevention. Infarcts attributable to atherosclerotic mechanisms would be expected to benefit most from statin therapy. SPARCL enrolled not only patients with large artery atherosclerotic infarcts but also patients with lacunar infarcts, cryptogenic infarcts, and (unaccountably) primary intracerebral hemorrhages. Presumably, forthcoming secondary analyses from the SPARCL trialists will clarify the variation in treatment benefit by causal stroke subtypes.

The benefit-risk ratio of statin therapy in symptomatic cerebrovascular disease patients would be improved if high risk for hemorrhage patients could be identified in whom treatment should be avoided or pursued at lower doses. In the SPARCL population as a whole, for every 2.5 ischemic strokes averted, 1 intracerebral hemorrhage was caused. A combination of age, hypertension, excess alcohol use, intracerebral hemorrhage as entry event, lacunar infarct as entry event, leukoaraiosis, cerebral microbleeds on MRI, and additional clinical features may identify a subset of patients with greater hemorrhagic propensity in whom statins should be used judiciously, if at all.

Other questions linger. How generalizable are the SPARCL results? The very elderly were not studied (average age in SPARCL was 63 years): cardioembolic strokes, disabling strokes, and those with uncontrolled hypertension were similarly excluded from SPARCL. Is intensive LDL-lowering better than moderate LDL-lowering? Combined patient level analyses of SPARCL and HPS correlating achieved LDL levels with events avoided will provide some insight, but the available dataset is likely not large enough to resolve this pressing issue.

The publication of SPARCL is an important achievement that should reinforce current prevention approaches in everyday practice. Virtually all athereosclerotic stroke patients should receive the “tripill” strategy of stroke secondary prevention–antiplatelet, antihypertensive, and statin agents, in addition to lifestyle counseling regarding regular physical activity, appropriate diet, tobacco cessation, and the stroke warning signs. Hitherto, underuse of statins in appropriate stroke patients was unfortunately rampant. Although SPARCL studied delayed initiation of treatment, increasing evidence suggests that early start of statins during the initial acute stroke hospitalization promotes patient medication adherence in the longer term. Structured programs like Get With the Guidelines-Stroke and PROTECT that take advantage of hospital systems to ensure initiation of proven therapies in acute stroke patients before discharge should be more widely adopted.

Cost is always a potential barrier to optimal implementation of evidence-based therapies. Based on SPARCL data and the current cost of atorvastatin 80 mg ($1400 per year), SPARCL-based therapy costs $203 000 to prevent one stroke in 5 years. However, considering all major vascular events, SPARCL-based therapy costs $17 920 to yield one additional disability-adjusted life year, a highly cost-effective benefit.

SPARCL has provided convincing evidence that statins are beneficial in patients with ischemic stroke and transient ischemic attack. Treatment guidelines, clinical practice, and quality improvement indicators should now be updated to ensure the widespread implementation of this important therapeutic advance.

Disclosures

B.O. has served as a scientific consultant to Bristol-Myers Squibb, is on a Speaker’s Bureau for Bristol-Myers Squibb, is an investigator in NIH-funded trials of stroke secondary prevention, is Director of a Stroke Prevention Program, and practices Vascular Neurology. J.L.S. has served as a scientific consultant to AstraZeneca, Bristol-Myers Squibb and Pfizer, is on a Speaker’s Bureau for Bristol-Myers Squibb, is an investigator in NIH-funded trials of stroke secondary prevention, is Director of a Stroke Center, and practices vascular neurology.
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