

EDITORIALS



Stroke — An Equal Opportunity for the Initiation of Statin Therapy

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Given the disparity in the numbers of cerebrovascular and cardiovascular clinical trials and the similarities in the interventions tested, it seems that stroke neurologists have had to peer at clinical-trial results over the shoulders of their cardiologist colleagues so often that they are at risk for chronic neck ailments. If only for evening the score a little, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators deserve our gratitude.

In their randomized clinical trial that was specifically designed to test statin therapy for the prevention of stroke recurrence in patients who had had a stroke or transient ischemic attack, reported in this issue of the *Journal*,¹ the five-year rate of recurrence was reduced by about 2 percentage points (relative reduction in risk, about 16 percent) in patients who were randomly assigned to receive high-dose atorvastatin. These results are roughly consistent with the decrease in stroke seen as a “side effect” of statin therapy for the heart in previous trials, in which more than 90,000 patients were enrolled.² Also in the SPARCL trial, the five-year rate of major cardiovascular events (including, but not limited to, stroke) was lowered by 3.5 percentage points (relative reduction in risk, about 20 percent). The SPARCL investigators suggest that these positive results support a change in clinical guidelines, such that stroke and transient ischemic attack should be a “coronary heart disease risk equivalent” in patients considered for the initiation of statin therapy.

However, the similarities in clinical trials notwithstanding, a stroke is not exactly the same as a heart attack in the brain. For starters, although

there is strong, consistent evidence linking increased cholesterol levels to an increased risk of coronary heart disease,³ some large epidemiologic studies have failed to find a similar relation to stroke,⁴ despite the convincing evidence from clinical trials that statins prevent stroke. This so-called stroke paradox can be easily explained, either by the heterogeneous effects of cholesterol on different subtypes of stroke in the epidemiologic studies⁵ or by the pleiotropic (e.g., antithrombotic, antiinflammatory, and plaque-stabilizing) effects of statins in the clinical trials, depending on which term of the paradox one chooses to privilege.

A meta-regression has shown a strong correlation between reduction in cholesterol level and the treatment effect of statins.² This finding has often been cited as evidence of the important role of the reduction of lipid levels in the prevention of stroke (a view endorsed by the SPARCL investigators in their discussion and in the very name of the trial). However, the finding has not settled the controversy, since a strong correlation between the reduction of cholesterol level and stroke prevention would be expected regardless of the mechanism by which statins decrease risk (i.e., regardless of whether the cholesterol level is the actual mediator of the treatment effect or merely a marker of adequate therapy and adherence).⁶

Perhaps underlying the less certain or less consistent role of cholesterol level in the risk of stroke than in heart attack are the facts that strokes are much more heterogeneous and only a minority of strokes are caused by large-vessel atherothrombosis. Qualifying events in the SPARCL trial also

included hemorrhagic, embolic, lacunar, and cryptogenic events. It is important to note that patients with atrial fibrillation and other cardiac sources of emboli were excluded from the trial, presumably since cardioembolic strokes are less likely than other types of ischemic stroke to be responsive to cholesterol-lowering agents. This raises the issue of whether the SPARCL results apply to the roughly one in five ischemic strokes that are cardioembolic in origin. Also, it is not clear to me why hemorrhagic strokes were considered a qualifying event for inclusion (and it may have been unclear to some site investigators as well, since only 93 such patients were enrolled in the trial). Although the meta-analysis of previous trials did not show an increase in the rate of hemorrhagic stroke among patients treated with statins,² the absence of harm hardly provides a strong rationale for the use of the therapy, especially since there is epidemiologic evidence of an association between the increased risk of intracerebral hemorrhage and cholesterol levels^{5,7} and since statins are well known to have antithrombotic effects. Indeed, the results of the trial underscore these a priori concerns: the relative risk of hemorrhagic stroke was increased by 66 percent among patients in the atorvastatin group, an effect that is likely to be of some import among patients presenting with a hemorrhagic stroke.

The heterogeneity of the patients enrolled in the trial, in terms of not only the cause of stroke but also vascular risk, is important to keep in mind in the interpretation of the results, since the rate of fatal or nonfatal stroke was relatively low and the absolute benefit of treatment with atorvastatin was relatively modest. A modest overall benefit across a heterogeneous population often obscures a more dramatic treatment effect in an influential subgroup among others that are highly unlikely to benefit.^{8,9}

With regard to the heterogeneity of the risk of vascular disease progression, in the SPARCL trial the baseline levels of low-density lipoprotein cholesterol ranged from 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter) and averaged 132.7 mg per deciliter (3.4 mmol per liter). Almost 20 percent of the patients had diabetes, and although the Framingham risk scores of the enrollees at baseline were not reported, the rate of coronary heart disease in the placebo group suggested an average 10-year risk of about 10 percent. Thus,

even without any change in guidelines, it is apparent that many of the patients enrolled would already qualify for statin therapy according to the current Adult Treatment Panel (ATP) III guidelines of the National Cholesterol Education Program (which, in fairness, evolved during the trial).¹⁰ Although post hoc subgroup analyses are always problematic, the argument to change these guidelines would be considerably strengthened if it were demonstrated that the subgroup of patients meeting the ATP III criteria for statin therapy did not account for all the benefit in the trial and that patients at lower risk and not meeting the ATP criteria had a degree of benefit consistent with the overall results of the trial.

Nevertheless, despite the above caveats, the SPARCL trial is likely to add to the gathering momentum favoring the promotion of ischemic stroke to a “coronary heart disease risk equivalent,” the adoption of statin therapy into guidelines for treatment of ischemic stroke,¹¹ the enforcement of statin therapy on discharge after a stroke as a “quality indicator,” and the inclusion of statins in preprinted stroke orders to improve adherence by physicians. Those who might object to this collective-treatment approach to such a heterogeneous disease should be reminded of our abysmal performance as individual doctors taking care of individual patients. In one recent study, even among patients who were eligible for statin therapy according to the ATP II guidelines, only one third had discharge medications that included statins.¹² This finding is especially egregious given the evidence that, as with acute myocardial infarction, hospitalization for stroke provides an excellent opportunity to initiate preventive therapy, and leads to rates of adherence higher than those observed when this therapy is initiated during follow-up.¹³ Although we can all agree with the calls for careful science, and although we await the various SPARCL substudies to help clarify some controversies, it does not take recursive subgroup analyses to show that the greatest current risk to patients with ischemic stroke vis-à-vis statins remains gross undertreatment.

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Molecular Signatures Predict Outcomes of Breast Cancer

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Breast cancer is classified and managed largely on the basis of anatomy — in contrast with lymphoma, which has been classified and treated according to grade for more than 20 years. Tumor size and the degree of involvement of the axillary nodes are used to estimate the risk of systemic micrometastases at diagnosis and, accordingly, whether systemic adjuvant therapy, which improves overall survival in largely unselected populations, is needed.¹

A routine question faced by oncologists is, which of the two thirds of patients with hormone-receptor–positive breast cancer require systemic adjuvant chemotherapy to decrease their chance of recurrence? Although there are substantial differences in the prognosis and natural history between histologically defined low-grade and high-grade breast cancers that express hormone receptors, national consensus guidelines currently recommend the consideration of adjuvant chemotherapy for estrogen receptor (ER)-positive, node-negative tumors that are more than 1 cm in diameter.² However, retrospective analyses suggest that adjuvant chemotherapy does not benefit patients with highly ER–positive breast cancer (regardless of nodal status), whereas it does appear to benefit patients with lower levels of ER expression.^{3,4} This finding suggests that biology trumps anatomy in the determination of prognosis and the benefit of chemotherapy.

Accordingly, a sea change is under way with

subtypes of breast cancer increasingly being recognized as separate diseases that require biologically based therapies. One type of breast cancer, HER2-positive disease, was definitively identified as a separate entity when it was found that survival among patients with early-stage breast cancer is substantially improved by trastuzumab, a monoclonal antibody that interrupts HER2 signaling, when combined with standard chemohormonal therapy.^{5,6} The large magnitude of the benefit seen with the addition of trastuzumab heralds the advances to come, as other biologically defined subtypes become the focus of adjuvant-therapy trials.

Gene-expression profiling has contributed to this evolving realization that the biologic heterogeneity of breast cancer has implications for treatment. There are now several predictors based on this method. One such predictor is the intrinsic-subtype classifier, which uses gene-expression profiles to distinguish among breast cancers on the basis of either their cell type of origin — the luminal cell (which is ER-positive) or the basal cell (which lacks expression of ER, the progesterone receptor, and HER2) — or whether the tumor is HER2-positive.⁷

A second microarray-based predictor, specifically based on the levels of expression of 70 genes, discriminates between a good and a poor outcome (risk of recurrence) in patients with early-stage breast cancer. The signature associated