Abstract—The occurrence of stroke increases with age, particularly affecting the older elderly, a population also at higher risk for coronary heart disease (CHD). Epidemiological and observational studies have not shown a clear association between cholesterol levels and all causes of stroke. Nonetheless, large, long-term statin trials in patients with established CHD or at high risk for CHD have shown that statins decrease stroke incidence in these populations. Combined data from 9 trials including 70 070 patients indicated relative and absolute risk reductions for stroke of 21% and 0.9%, respectively, with statins. The number of strokes prevented per 1000 patients treated for 5 years in patients with CHD is 9 for statins, compared with 17.3 for antiplatelet agents. Statins have not yet been shown to reduce stroke risk in the typical general population without known CHD, nor have they been shown to prevent recurrent stroke in patients with prior stroke. Potential reasons for the effects of statins on stroke and the non–cholesterol-lowering mechanisms that may be involved are discussed. Treatment strategies based on global cardiovascular risk may be most effective. Additional studies in patients representative of the typical stroke population are needed. (Circulation. 2004;109[suppl III]:III-44–III-49.)

Key Words: cardiovascular risk ■ prevention ■ statins ■ stroke

In the past decade, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or “statins,” have been proven to significantly decrease coronary events in primary and secondary prevention of coronary heart disease (CHD).1–8 In patients with known CHD1–3,6 and high-risk patients (eg, those with hypertension8 or diabetes mellitus9), stroke, a secondary end point, was also reduced by statin treatment. The neutral effect on stroke in older patients in the recent 3-year Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial7 may have related to the relatively short period of follow-up, but has led some experts to again question whether stroke reduction by statins results from reductions in cardiac events and, therefore, systemic thrombomodulism rather than from a direct effect on the cerebral arteries.

Cholesterol as a Risk Factor for Stroke

Whether increased serum cholesterol levels are a risk factor for stroke remains controversial. A meta-analysis of 45 prospective cohorts that included 450 000 subjects (total of 7.3 million patient-years; average follow-up: 16 years) and 13 000 incident strokes found no association between total cholesterol levels and stroke.10 The Multiple Risk Factor Intervention Trial (MRFIT), however, showed that the risk of death from nonhemorrhagic stroke increased with increasing serum cholesterol in 351 000 men aged 35 to 57 years.11 Conversely, in the same study, there was a negative association with hemorrhagic stroke for cholesterol levels <5.2 mmol/L (<201 mg/dL): the lower the total cholesterol level, the higher the risk of hemorrhagic stroke, suggesting a possible U-shaped relationship between cholesterol and stroke. The association between low cholesterol levels and hemorrhagic stroke was notable particularly in men with hypertension. The link between low cholesterol concentration and hemorrhagic stroke also was shown in a meta-analysis of 13 Chinese and Japanese cohorts, including 125 000 subjects and 1800 strokes, in which there was a tendency for increased risk of hemorrhagic stroke and decreased risk of ischemic stroke as cholesterol levels decreased.12 Finally, in the Copenhagen City Heart Study, total cholesterol was positively associated with risk of nonhemorrhagic stroke, but only for levels >8 mmol/L (>309 mg/dL), corresponding to levels in the upper 5% of the study cohort.13

There are several possible explanations for the lack of association between cholesterol levels and stroke in most epidemiological and observational studies. Epidemiological studies did not consider the relation between blood cholesterol and the risk of incident strokes in a high-risk cohort selected on the basis of high global cardiovascular risk (eg, increased carotid intima-media thickness, high Framingham
risk score). Also, because the cohorts were selected primarily to study CHD, they particularly included middle-aged subjects at risk of myocardial infarction (MI), whereas brain infarction typically occurs in much older subjects (>70 years). Moreover, the more likely aggressive risk-factor management in study patients may have accounted for a lower incidence of stroke. Finally, cerebrovascular events were not analyzed according to stroke subtypes in most case-control or prospective studies. Because of the U-shaped relationship observed in MRFIT, counting hemorrhagic strokes together with ischemic strokes could have masked a small, but true relation between cholesterol levels and ischemic stroke. The prevalence of atherothrombotic causes of stroke in middle-aged subjects is low, and the most frequent causes (eg, embolism associated with cardiomyopathy, arterial dissection) are usually unrelated to cholesterol levels.

### Statins for Stroke Prevention

Older trials of lipid-modifying therapy with diet or drugs (eg, fibric acid derivatives) did not show a reduction in the incidence of stroke, nor did early long-term trials of statins for primary prevention of CHD.5,6 Because the mean age of patients in these primary prevention studies was low, the incidence of stroke was also low, so that these trials lacked adequate statistical power to reliably detect any significant effect. However, numerous statin trials in patients with known CHD and recent primary prevention trials including high-risk populations6,8 demonstrated a decrease in stroke incidence.

A compilation of data from 9 major long-term statin trials1–3,6,8,15–18 including 70,070 patients with known CHD or considered at increased risk shows that, on an intention-to-treat basis, an incident stroke occurred in 1501 of 34,739 patients (4.3%) randomized to the control group and 1215 of 35,331 patients (3.4%) randomized to statin therapy, yielding a 21% relative risk reduction in stroke and a modest 0.9% absolute risk reduction (ie, 9 strokes prevented per 1000 patients treated for 5 years; Table). By comparison, meta-analyses have shown that, in similar patients with known CHD, antplatelet agents prevent 17.3 strokes and ramipril prevents 17 strokes per 1000 patients treated for 5 years in patients with prior stroke, antplatelet agents prevent 27 strokes per 1000 patients treated for 3 years, or 45 strokes/1000 projected to 5 years.19

#### Global Cardiovascular Risk

In practice, the results achieved with statins in most major trials cannot be directly applied to all stroke patients. This is because the relatively modest effects on stroke (compared with other stroke prevention strategies) were obtained primarily in patients with established CHD, not in ischemic stroke patients without CHD. The latter constitute the majority of stroke patients.2,3,11,15 In addition, the majority of patients in the statin trials were male, whereas the sexes are approximately equally distributed in typical stroke patients (ie, ≈53% men). Further, subjects in the trials were relatively young and had lower rates of hypertension (≤40%) than usual stroke patients (55% to 60%). Finally, stroke rates (3% to 5% over 5 to 6 years) were quite low compared with rates in patients with previous stroke (risk of recurrent stroke, 4% to 8% per year), resulting in a very small reduction in absolute risk with treatment.20

In the Heart Protection Study (HPS), 65% of patients had established CHD, 16% had stroke before randomization, and, overall, 9% had previous stroke without known CHD.6 In the total cohort of 20,536 patients, simvastatin was associated
with a 24% reduction in relative risk of major vascular events (coronary death, nonfatal MI, fatal or nonfatal stroke, revascularization procedures), and a 25% reduction in relative risk of ischemic stroke. Patients who had a stroke before randomization had a 19% reduction in relative risk of major vascular events, and stroke patients without known CHD showed a 23% risk reduction. However, it is possible that the reduction in the composite end point in the latter subgroup related to reductions in CHD events alone, with no decrease in cerebrovascular events. Unlike other studies\textsuperscript{15,21} that found nonsignificant reductions in ischemic stroke with statin therapy in patients with diabetes, HPS demonstrated a significant reduction of 26% in stroke in this important group.\textsuperscript{9} Thus, HPS indicates that statins undoubtedly prevent stroke, as well as major vascular events, in patients with CHD, and they prevent major vascular events in stroke patients, but currently available HPS data do not demonstrate prevention of recurrent stroke in patients with prior stroke (ie, secondary prevention of stroke).\textsuperscript{6}

Age is the main determinant of the absolute risk of future cardiovascular events. In the PROSPER trial of 5804 men and women (52% women) aged 70 to 82 years with total cholesterol levels of 4.0 to 9.0 mmol/L (155 to 348 mg/dL), half of the patients had a high-risk profile (62% hypertension, 11% diabetes, 28% current smokers), and the other half had established vascular disease (44% cardiovascular disease, 11% stroke before randomization).\textsuperscript{7} The 15% reduction in relative risk of the primary composite end point (coronary death, nonfatal MI, fatal or nonfatal stroke) was significant ($P=0.14$). Pravastatin had no effect on stroke incidence (hazard ratio, 1.03; $P=0.81$) and did not slow the decline in cognitive function in the elderly. However, PROSPER confirmed that statins could be safely used in elderly as in younger patients. Possible explanations for the neutral effect on stroke incidence are a lack of power (the expected stroke rate in the placebo group was 8%, compared with an actual event rate of 4.5%) and the duration of the trial, which lasted only 3 years. In other large-scale pravastatin trials (Cholesterol and Recurrent Events [CARE]\textsuperscript{2} and the Long-term Intervention with Pravastatin in Ischemic Disease [LIPID]\textsuperscript{3}), the Kaplan–Meier curves for the stroke end point started to diverge after 3 years; if the analyses had been undertaken at 3 years, those trials would have yielded results consistent with those in PROSPER.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) randomized 19 342 hypertensive persons who also had $\geq 3$ other cardiovascular risk factors to treatment with either a $\beta$-blocker $\pm$ diuretic or amlodipine $\pm$ angiotensin-converting enzyme inhibitor with follow-up for 5 years.\textsuperscript{8} A total of 10 305 patients who had a total cholesterol $<6.5$ mmol/L ($<251$ mg/dL) were further randomized in a factorial design to atorvastatin 10 mg daily or placebo. On the recommendation of the study’s independent Data Safety Monitoring Board, the lipid-lowering arm was stopped prematurely (mean follow-up, 3.3 years) because of strong efficacy of active treatment on the primary trial end point (nonfatal MI and fatal CHD). Despite early termination of the lipid-lowering arm of the trial, there was a significant (27%) reduction in relative risk of fatal and nonfatal stroke with atorvastatin ($P=0.024$), and the benefits of treatment apparently began early during follow-up.\textsuperscript{8}

Findings from these trials are consistent with the need for a global approach to cardiovascular risk assessment for stroke prevention. Treatment with a statin was very effective in patients with CHD, patients at high risk because of multiple risk factors, and those with normal cholesterol levels but elevated blood pressure.

**Risk of Hemorrhagic Stroke?**

One concern from observational cohort data is the possibility of an increased risk of hemorrhagic stroke with cholesterol-lowering therapy. Possible supporting data\textsuperscript{11,12} have been discussed. However, the diagnosis of stroke subtype in those studies was limited in that imaging was not included. Among 172 patients from Korea who underwent brain MRI using T2*-weighted gradient-echo imaging, which identifies multifocal signal loss lesions believed to represent microhemorrhage, concentrations of total and low-density lipoprotein (LDL) cholesterol were significantly lower in patients with severe imaging defects.\textsuperscript{22} Multivariate analysis showed that imaging abnormalities were significantly associated with the lowest quartile of serum total cholesterol ($<4.27$ mmol/L [$<165$ mg/dL]), the highest quartile of high-density lipoprotein ($>1.47$ mmol/L [$>57$ mg/dL]), hypertension, and white-matter brain lesions (leukoaraiosis). However, an increase in hemorrhagic stroke was not observed in the long-term statin secondary prevention trials that examined hemorrhagic stroke as a secondary end point.\textsuperscript{6,13,23} The incidence of hemorrhagic stroke was $\approx 0.5\%$ in both the placebo and statin-assigned groups. These results, in concert with the PROSPER trial finding of no increase in hemorrhagic stroke in the elderly, are reassuring.

**Statins and Stroke Prevention: Pending Questions**

The observational studies failed to find a clear association between cholesterol levels and stroke. However, as discussed, there should be some reservations concerning these studies. The statin trials and a trial of gemfibrozil in patients after MI\textsuperscript{24} provide strong arguments for an etiological role of lipids in stroke and also possible non–LDL-lowering and/or nonlipid effects of these medications. Results related to stroke prevention with statins must be reproduced in a broad population representative of stroke patients who do not have a history of previous acute coronary syndromes.

By preventing recurrent MI, statins may reduce left ventricular mural thrombosis, which could contribute to a decreased incidence of stroke. In the analysis of stroke subtypes in the LIPID trial, effects appeared to be greater in the cardioembolic subgroup ($-32\%$) and the group with stroke presumably due to lacunar arteriopathy ($-44\%$) than in the atherothrombotic group ($-10\%$).\textsuperscript{15} In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial conducted in patients with unstable angina or non–Q-wave MI immediately after the qualifying event, there was a significant overall risk reduction in the secondary end point of stroke ($51\%$; $P=0.04$).\textsuperscript{25} Of note is that only 9 of the 36 strokes were preceded by a nonfatal MI, and in these cases the stroke occurred from 2 to 86 days after the MI.\textsuperscript{25} Thus,
statins may reduce thromboembolism to the brain by preventing early recurrent MI, but that is not the only mechanism. It has been suggested that statins may reduce stroke simply by reducing blood pressure. A difference in diastolic blood pressure of only 2 mm Hg could account for a 15% reduction in stroke risk, and one study has shown that statins modestly lower systolic and diastolic blood pressure in patients with hypercholesterolemia with untreated hypertension. However, a careful analysis of data from the LIPID trial showed that blood pressure increased during the study, although remaining in the normal to high-normal range. Similarly, the 22% (P=0.01) relative risk reduction in total stroke in the Pravastatin Pooling Project occurred in patients with normal to high-normal blood pressures at baseline.

Failure to adjudicate stroke subtypes and confounding variables could also cloud the interpretation of observational data. There appears to be a strong association between cholesterol levels and documented atherothrombosis. In the Framingham Heart Study, moderate carotid stenosis (≥25%) in men was associated with elevations in systolic blood pressure (≥20 mm Hg) and total-cholesterol level (≥0.26 mmol/L [10 mg/dL]) and a 5 pack-year history of smoking compared with minimal stenosis (<25%). Similar results were observed in women. These results strongly suggest that cumulative effects of important risk factors impact the development of carotid stenosis, and could further argue for a global cardiovascular risk approach to prevent stroke in the context of overall development of atherothrombotic disease events.

Statins may have a direct effect on atherosclerotic plaques in the carotid and vertebrobasilar arteries. Studies have shown that statins reduce the progression of carotid stenosis in patients without previous cardiac or cerebrovascular events and may reduce carotid intima-media thickness in patients with hypercholesterolemia or CHD. More aggressive cholesterol reduction may have a greater effect on carotid atherosclerosis.

A popular explanation for the benefit from statin therapy on stroke is a direct pleiotropic effect on atherosclerotic plaques that promotes plaque stability. Lipid-related mechanisms do not explain the amplitude of clinical benefit with statins, which is greater than the magnitude of atherosclerotic plaque regression. This fact forms the basis for the hypothesis that statins may promote plaque stabilization through direct biological effects on endothelial function, arterial plaques, biological promoters of plaque instability, and even on thrombosis and proteins involved in inflammatory processes. Positive effects of statins on these factors have been demonstrated in vitro and after short-term therapy in humans.

Lipid abnormalities may also play a role in small-vessel disease, and statins appear to improve cerebral vasomotor reactivity. In lacunar arteriopathy, there is an interaction between oxidized LDL cholesterol and endothelial function, which is important for vasoreactivity and may be impaired in small-vessel disease. Arteriolar occlusions are often preceded by transient neurological deficits, sometimes in clusters; based on indirect evidence, these are hypothesized to be of vasospastic origin and may partly reflect disturbances in the nitric oxide pathway. Because of their pleiotropic effects, statins may interact with endothelial function to modify vasoreactivity of small arteries (<300 μm diameter), as has been shown in the coronary circulation of patients with angina pectoris.

Another explanation for the effect of statins on stroke is the mounting evidence that these agents may have a neuroprotective effect in animal models. Statins have been shown to decrease the size of experimental brain infarction and to augment cerebral blood flow by upregulation of endothelial nitric oxide synthase.

Secondary Stroke Prevention

Although the HPS showed that the composite end point of major vascular events, including stroke, was reduced in patients with stroke before randomization, this reduction was due entirely to a lower incidence of CHD events with no decrease in stroke recurrence. Indeed, the rate of recurrent stroke in patients treated with simvastatin was 10.4% versus 10.5% on placebo in the 3280 patients with stroke before randomization. Since these 3280 patients were included a mean of 4.3 years after their stroke/TIA, they were less likely to have a recurrent stroke and more likely to have a coronary event. What is reassuring from HPS, however, is the significant 50% (P=0.0003) reduction in relative risk of carotid endarterectomy or angioplasty with statin treatment, consistent with a clear impact on progression of carotid stenosis and, hence, the potential to reduce stroke recurrence.

The ongoing Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial is addressing the efficacy of statin therapy in preventing recurrent stroke. Recruitment of patients was conducted in stroke units, thereby ensuring a good representation of the entire stroke population as well as a robust diagnosis of transient ischemic attack. In addition, the presence/absence of carotid stenosis was recorded at baseline. The primary study end point is fatal and nonfatal stroke, and the planned follow-up for the 4700 patients with prior stroke or transient ischemic attack randomized to atorvastatin 80 mg/d or placebo is 5 years.

Conclusion

Statins have been shown to have beneficial effects in patients with known CHD as well as in primary prevention of cardiovascular disease in high-risk cohorts. Statins lower stroke incidence in high-risk patients (those with CHD, diabetes mellitus, or hypertension), including patients with normal baseline levels of serum cholesterol. The results of statin trials such as HPS and ASCOT-LLA provide support for treatment strategies based on global cardiovascular risk. Statins decrease the incidence of CHD events in patients with prior stroke, but they have not yet been shown to reduce the incidence of recurrent stroke in typical stroke patients.

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