Statin Therapy for Stroke Prevention

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Background and Purpose—Statins are widely used to reduce the risk of stroke in patients with coronary artery disease (CAD), but less so in patients without CAD. We reviewed recent trials for new evidence for the reduction in risk of stroke.

Summary of Review—In patients with CAD, moderate-intensity statin treatment has been associated with reductions in risk of stroke, with no increase in hemorrhagic stroke. Additionally, in the TNT trial, intensive lipid lowering provided further stroke risk reduction compared with moderate lipid lowering in patients with stable CAD. Evidence is now available that statin therapy also reduces stroke risk in patients without CAD but at high cardiovascular risk, or with diabetes mellitus. The SPARCL trial showed that intensive statin therapy started within 6 months after a cerebrovascular event significantly reduced stroke risk and stroke severity. Low cholesterol levels have been associated with increased risk of hemorrhagic stroke, but although an increased risk of hemorrhagic stroke was observed in patients with prior hemorrhagic stroke in SPARCL, this was not related to low-density lipoprotein cholesterol levels. Clinical trials have recruited few patients with both coronary and cerebrovascular disease, but these patients are also expected to experience significant cardiovascular benefit with statin therapy.

Conclusions—Trial data show that statins reduce the risk of stroke, in addition to providing cardiovascular benefits. Consequently, physicians should consider statin therapy in all patients at high risk of stroke. (Stroke. 2008;39:1042-1048.)

Key Words: cerebrovascular accident • coronary artery disease • statins • cholesterol

Statins reduce the incidence of coronary events in patients with and without prior coronary artery disease (CAD), and have become a cornerstone of CAD prevention therapy.1

Many clinical trials primarily designed to examine the coronary benefits of statins also demonstrated reductions in risk of stroke,2 leading to speculation that statins could be a useful addition to the physician’s armamentarium for stroke prevention. Although, intuitively, linking ischemic stroke and atherosclerosis may seem reasonable, observational studies from 10 to 20 years ago looking at the relationship between elevated cholesterol and cerebrovascular disease reported conflicting results.3 Because hemorrhagic and ischemic strokes are pathologically distinct, it has been suggested that analyzing the two together might mask any relationship between ischemic stroke and cholesterol, but this relationship has remained inconsistent even in observational studies of ischemic stroke alone.4,5 However, the recent Women’s Health Study, a prospective cohort study of 27 937 apparently healthy women, reported a strong association between the risk of ischemic stroke and both total cholesterol (P<0.001) and low-density lipoprotein cholesterol (LDL-C) levels (P<0.003).6

Although evidence from epidemiological studies examining a relationship between cholesterol level and stroke is less than definitive, there is compelling evidence from clinical therapy trials in CAD patients that statin treatment reduces stroke incidence. In a meta-analysis of more than 90 000 patients in 26 randomized statin trials conducted predominantly in patients with overt CAD, statins reduced the risk of first clinical stroke by 21% versus placebo (OR, 0.79; 95% CI, 0.73 to 0.85).2 This reduction in risk of stroke with statins could be largely accounted for by LDL-C changes, with each 10% reduction in LDL-C estimated to decrease the risk of stroke by 15.6% (95% CI, 6.7% to 23.6%).2

Nevertheless, evidence of the benefits of statins in stroke prevention was lacking for patients without CAD, and for patients with prior stroke.2 In the past few years, further trials have clarified these relationships between statin therapy and stroke risk reduction.

Patients With CAD but Without Cerebrovascular Disease–First Stroke Prevention

Numerous trials in patients with CAD have demonstrated that statins reduce the risk of stroke compared with placebo.2 The Heart Protection Study (HPS) randomized 20 536 patients with or at risk of CAD, of whom most (84%) had no history of cerebrovascular disease, to simvastatin 40 mg or placebo.7 During the 4.8-year follow-up, simvastatin reduced risk of first stroke in the overall population by 25% versus placebo.
chiefly because of a 28% reduction in ischemic stroke (95% CI, 19% to 37%; \( P < 0.0001 \)). There was no apparent difference between the groups in the incidence of hemorrhagic stroke (HR, 0.95; 95% CI, 0.65 to 1.40; \( P = 0.8 \)). Of the 20,536 patients randomized, 13,386 (65%) had diagnosed CAD, and when only these patients were analyzed there was a 25% proportional reduction in the rate of stroke (95% CI, 12% to 36%; \( P = 0.0005 \); Figures 1 and 2). This reduction was associated with an absolute difference in LDL-C of 1 mmol/L (39 mg/dL) between the treatment groups.

In the Scandinavian Simvastatin Survival Study (4S), 4444 patients with prior CAD and no history of stroke were randomized to simvastatin 20 to 40 mg or placebo.8 Over the 5.4-year follow-up, mean LDL-C was reduced by 35% from baseline in the simvastatin group (from 4.9 mmol/L [188 mg/dL] to 3.2 mmol/L [123 mg/dL]) and increased by 1% from baseline in the placebo group. In a posthoc analysis, simvastatin was associated with a 30% reduction in the risk of fatal and nonfatal cerebrovascular events (95% CI, 4% to 48%, \( P = 0.024 \); Figures 1 and 2). There were too few hemorrhagic or other types of strokes to detect differences between groups.

The significant stroke risk reduction seen in 4S was confirmed by the Cholesterol and Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trials. Both trials compared pravastatin 40 mg with placebo in patients with CAD, and a combined analysis showed a 22% relative risk reduction in the risk of stroke with treatment (95% CI, 7% to 35%, \( P = 0.01 \)).9

As with other trials in patients with CAD, the Treating to New Targets (TNT) study was primarily designed to determine the effect of statins on coronary events.10 When the study was designed, statins were the treatment of choice for
lipid lowering in patients with CAD, but intensive lipid lowering to what were viewed as low LDL-C targets was controversial. TNT therefore examined whether reducing LDL-C levels to below the then recommended target of 2.6 mmol/L (100 mg/dL) was beneficial in patients with documented CAD. The study randomized 10,001 patients to standard lipid lowering with atorvastatin 10 mg or to intensive lipid lowering with atorvastatin 80 mg, with a median follow-up of 4.9 yr. Compared with atorvastatin 10 mg, patients receiving atorvastatin 80 mg experienced a 23% reduction in the risk of a cerebrovascular event (95% CI, 7% to 36%; P=0.007) and a 25% reduction in the risk of fatal or nonfatal stroke (HR, 0.75; 95% CI, 4% to 41%; P=0.021; Figures 1 and 2). Among patients with no history of stroke (95% of randomized patients), there were fewer cerebrovascular events in the atorvastatin 80 mg group than in the 10 mg group (HR, 0.80; 95% CI, 0.66 to 0.98; P=0.032), and also a trend toward fewer second strokes, although this latter did not reach statistical significance (HR, 0.7; 95% CI, 0.61 to 1.02; P=0.070).

A further analysis appeared to confirm the association between intensive lipid lowering and reduced risk of stroke. When patients were grouped by 3-month LDL-C levels, stepwise reduction was seen from the highest to the lowest LDL-C quintile for cerebrovascular events (P=0.002) and stroke (P=0.041). Each 0.03 mmol/L (1 mg/dL) change in on-treatment LDL-C was associated with a 0.6% change in the risk of a cerebrovascular event and a 0.5% change in the risk of stroke. The number of hemorrhagic strokes in each quintile, from lowest to highest, was 6, 5, 6, 9, and 7 (P=NS), suggesting that reducing cholesterol to very low levels with atorvastatin was not associated with increased risk of hemorrhagic stroke, although numbers were too small for robust statistical analysis.

One exception to the favorable effects of statins on stroke risk in patients with CAD is a posthoc analysis of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial. PROSPER randomized 5,804 older patients (70 to 82 yr) with established cardiovascular disease (44% had a history of cardiovascular disease and 11% had a history of stroke) or at high cardiovascular risk (62% had hypertension, 11% diabetes, and 28% were present smokers) to pravastatin 40 mg or placebo. Pravastatin treatment reduced LDL-C by 34% from a baseline mean of 3.8 mmol/L (147 mg/dL) to 2.5 mmol/L (95 mg/dL) but did not significantly reduce the risk of stroke versus placebo (HR, 1.03; 95% CI, 0.81 to 1.31; P=0.81; Figures 1 and 2). One possible explanation for this differing results may be that, in contrast to the trials mentioned above, PROSPER included patients with prior stroke.

Therefore, overall evidence from prospective analyses indicates that, in patients with CAD, statin therapy reduces the risk of first stroke by 25% to 35% versus placebo and, moreover, intensive statin therapy to LDL-C targets below 2.6 mmol/L (100 mg/dL) appears to reduce the risk further.

Patients With CAD and Cerebrovascular Disease–Recurrent Stroke Prevention

Clinical trials have tended to recruit only a few patients with a history of both coronary and cerebrovascular disease and, therefore, have had little power to detect effects of statins on stroke in patients with CAD and prior stroke. This is further hampered by recruitment of middle-aged patients, who are at higher risk of CAD but lower risk of stroke; for example, the placebo group in the LIPID trial had a stroke rate of 4.5% during the 6.1-year follow-up, but the rate of CAD death or nonfatal MI was 15.9%. In HPS, 1460 (7%) of the 20,536 patients had a history of both coronary and cerebrovascular disease, but recurrent stroke was not analyzed separately for patients with and without CAD.7 Similarly, in PROSPER, recurrent stroke was not analyzed separately.11 In addition, the combined analysis of CARE and LIPID did not show a significant reduction in the risk of recurrent stroke.9 Therefore, little evidence is available to determine whether or not statins will reduce risk of recurrent stroke in patients with CAD.

Patients Without CAD or Cerebrovascular Disease–First Stroke Prevention

Initial results for stroke risk reduction with statins in patients with neither coronary nor cerebrovascular disease were not promising: two large primary CAD prevention trials, the West of Scotland Coronary Prevention Study (WOSCOPS)13 and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),14 showed no decrease in stroke events with statin therapy versus placebo, despite LDL-C reductions of approximately 25% and significant reductions in coronary events (Figure 3). A posthoc analysis of stroke of patients without prior cardiovascular disease in PROSPER...
did not reach significance (Figures 1 and 3).\textsuperscript{11} However, the stroke rate (4.5%) was about half that predicted, reducing power to detect a significant difference, and the number of strokes in WOSCOPS and AFCAPS/TexCAPS may also have been too small to detect reductions in stroke risk.

The first statin trial to show a significant decrease in stroke incidence in patients without prior CAD was the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)–Lipid Lowering Arm (LLA).\textsuperscript{15} In ASCOT-LLA, 10,305 hypertensive patients with no prior CAD, but with at least 3 CAD risk factors in addition to hypertension, were randomized to atorvastatin 10 mg or placebo. Ninety percent of patients had no history of cerebrovascular disease. Atorvastatin 10 mg lowered LDL-C by 29% versus placebo (from 3.4 mmol/L [131 mg/dL] to 2.3 mmol/L [89 mg/dL]) and was associated with a 27% reduction in fatal or nonfatal stroke (95% CI, 4% to 44%; \(P = 0.024\); Figures 1 and 3).\textsuperscript{15}

It is well established that diabetes is a potent risk factor for stroke. Recently, the Collaborative Atorvastatin Diabetes Study (CARDs) randomized patients with diabetes and at least one other cardiovasculare risk factor but no history of cardiovascular disease or stroke to atorvastatin 10 mg or placebo.\textsuperscript{16} Among 2,838 patients randomized, fatal or nonfatal stroke occurred in 21 atorvastatin patients versus 39 placebo patients, representing a 48% reduction in the relative risk of stroke (95% CI, 11% to 69%; \(P = 0.016\); Figures 1 and 3).\textsuperscript{16} There was a 1.2 mmol/L (46 mg/dL) average difference in LDL-C between groups, which would be predicted to give a stroke reduction in the region of 25%, based on previous trial results.\textsuperscript{3} However, the effect in CARDs was almost double this, although the 95% confidence interval included a 25% effect. Because of the unequivocal benefit for patients with diabetes, the American Heart Association and American Stroke Association Council recommended in 2006 that, to reduce risk of stroke, adults with diabetes, especially those with other cardiovascular risk factors, be treated with a statin in addition to tight control of hypertension.\textsuperscript{17}

Patients With Cerebrovascular Disease but Without CAD–Recurrent Stroke Prevention

As recently as 2004 it was uncertain whether statins reduced the risk of recurrent stroke in patients without coronary disease.\textsuperscript{2} The number of patients for analysis at that time was small, with no apparent reduction in the risk of stroke in these patients.\textsuperscript{9,11}

HPS provided the first reasonably-sized group to allow analysis of recurrent stroke in patients with no history of CAD. Of 20,536 patients enrolled, 3,280 had a history of cerebrovascular disease (hemorrhagic stroke was excluded), and 55% (11,820) of these patients had no history of clinical CAD. In the group with prior cerebrovascular disease, simvastatin 40 mg was associated with a 39% reduction in LDL-C, from 3.4 mmol/L (131 mg/dL) to 2.4 mmol/L (93 mg/dL). However, simvastatin did not show a significant effect on stroke recurrence (169 simvastatin patients and 170 placebo patients had a stroke during follow-up; HR, 0.98; 95% CI, 0.79 to 1.22; Figures 1 and 4).\textsuperscript{7} No significant difference was observed between either treatment group for ischemic stroke (6.1% with simvastatin versus 7.5% with placebo) or hemorrhagic stroke (1.3% with simvastatin versus 0.7% with placebo). The HPS investigators suggested that, based on the number of incident strokes, the lack of significance likely reflected the play of chance.

Unlike HPS and other statin trials, which were undertaken to assess the effects of statins on the incidence of symptomatic CAD and examined stroke as a secondary end point, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was primarily designed to evaluate whether intensive statin therapy reduced the risk of recurrent stroke. SPARCL enrolled patients with recent stroke or TIA (1 to 6 months before study entry), but with no history of CAD or atrial fibrillation. A total of 4,731 patients were randomized to atorvastatin 80 mg or placebo. Unlike in HPS, patients with cerebral hemorrhage were not excluded and comprised 2% of SPARCL patients, whereas ischemic stroke accounted for 67% of patients and TIA 31% of patients.\textsuperscript{18}
After 1 month, LDL-C was reduced by 53% in the atorvastatin group, from 3.4 mmol/L (133 mg/dL) to 1.6 mmol/L (61 mg/dL) compared with no change in the placebo group. During the median follow-up of 4.9 years, 265 patients in the atorvastatin 80 mg group and 311 patients in the placebo group had a fatal or nonfatal stroke, representing a 16% risk reduction with atorvastatin after adjustment for baseline factors (HR, 0.84; 95% CI, 0.71 to 0.99; P=0.03; Figures 1 and 4). Atorvastatin was also associated with a significant 23% reduction in the secondary end point of stroke or TIA (HR, 0.77; 95% CI, 0.67 to 0.88; P<0.001). This effect is likely to be robust, because it was seen despite the increase in open-label use of statins during the trial (25% of placebo patients and 11% of atorvastatin patients), with the net difference in statin use between the groups, including those stopping randomized drug therapy, being 78%. Given the lower than expected differential in statin use between the groups, the reductions in recurrent stroke obtained with intensive statin therapy versus placebo are likely comparable to the 23% reduction in risk of recurrent stroke observed with antiplatelet therapies20 and the 24% reduction observed with antihypertensive medications.21

In SPARCL, risk of hemorrhagic stroke was increased in the atorvastatin 80 mg group versus placebo (HR, 1.66; 95% CI, 1.08 to 2.55), although the number of hemorrhagic strokes was low (88 in total). The incidence of fatal hemorrhagic stroke did not differ between the groups (17 fatal hemorrhagic strokes in the atorvastatin group and 18 in the placebo group). The contrast between the statistically and clinically significant reduction in recurrent stroke observed in SPARCL and the lack of reduction in HPS could be attributable to the shorter time between the index event and enrollment in SPARCL, because the risk of stroke recurrence is higher during the first year. In SPARCL, the mean time between the index event and enrollment was approximately 3 months whereas in HPS it was 4.3 years. Alternatively, the differing results could be attributable to greater LDL-C reductions with atorvastatin 80 mg over simvastatin 40 mg or other, currently unknown, factors. Preliminary analyses of SPARCL data appear to suggest that the reduced stroke risk was at least partly related to LDL-C and atherosclerosis. LDL-C level after 1 month on treatment was associated with stroke risk reduction, with each 10% reduction in LDL-C during the first month of treatment associated with a 4% reduction in stroke risk (P=0.005),21 whereas analysis of 1007 patients with known carotid stenosis at baseline revealed a significant reduction in the risk of stroke with atorvastatin (HR, 0.67; 95% CI, 0.47 to 0.94; P=0.023).22

These data support the hypothesis that statin therapy early after stroke may help stabilize atherosclerotic plaques, whether contributing to the incident stroke or at other sites. This concept is consistent with findings from many trials of statins in patients with unstable coronary events, in which plaque rupture in the culprit artery as well as in other arteries was stabilized by early statin therapy.

In SPARCL, atorvastatin was also associated with a reduction in coronary events (any coronary event: HR, 0.58; 95% CI, 0.46 to 0.73; P<0.001), even though patients in SPARCL had no prior CAD and were not selected for high cardiovascular risk. This supports the NCEP ATP III recommendation that patients with ischemic stroke should be considered at equivalent risk of cardiovascular events to those with CAD.1 The finding is not surprising in view of the concept that unstable atherosclerotic plaques represent a systemic inflammatory process and that statin therapy may exert benefits on unstable inflamed atherosclerotic plaques throughout the arterial system. Unstable plaques account for a proportion of strokes, and the improvement in endothelial function that is seen with statin therapy has been postulated to provide further protective effects.

Statins may improve stroke outcomes through neuroprotective actions or effects on the recovery process,23 and a post hoc analysis of SPARCL provides preliminary clinical data in this area. The Modified Rankin Index was used to assess the severity of the index stroke, and was also assessed 90 days after any recurrent stroke. Patients in the atorvastatin group experienced fewer ischemic strokes across all severity categories than patients randomized to placebo (P=0.001). This was related to compliance with statin treatment: stroke severity was significantly reduced only in patients who received a treatment dose within 1 month before a postrandomization ischemic stroke.24

### Intensive Cholesterol Lowering and Hemorrhagic Stroke

Observational population-based studies have shown associations between low cholesterol levels and hemorrhagic stroke.4 Although this might be an artifact—for example, severe and chronic illness may reduce LDL-C levels3—many physicians are concerned that statin treatment will increase the risk of hemorrhagic stroke, even while lowering the risk of ischemic stroke. Because risk of stroke increases with age, the potential for increased risk of hemorrhagic stroke in older patients is of particular concern. Nevertheless, data from PROSPER indicated that statin therapy did not increase risk of hemorrhagic stroke in the older patient population.11 Moreover, in TNT, patients with the lowest LDL-C levels did not experience any increase in hemorrhagic stroke.10 Although the number of hemorrhagic strokes was low in SPARCL, intensive lipid lowering in this trial was associated with an increased incidence of hemorrhagic stroke.18 Preliminary analysis has shown hemorrhagic stroke risk was greatest in patients with hemorrhagic stroke at baseline (HR, 6.17; 95% CI, 3.09 to 12.29; P<0.001), increased with age (HR, 1.40; 95% CI, 1.15 to 1.72, P=0.001 per 10-year increment), and was higher in men (HR, 1.60; 95% CI, 1.01 to 2.53; P=0.04).25 There were no statistical interactions between any of these baseline factors and atorvastatin 80 mg for risk of hemorrhagic stroke, and no effect of time since entry event, baseline LDL-C or total cholesterol, smoking status, or the use of antiplatelet agents or anticoagulants. Those with stage 2 hypertension before the hemorrhagic stroke were at higher risk (HR, 6.19; 95% CI, 1.47 to 26.11; P=0.01), reinforcing the need for aggressive blood pressure control. When data from SPARCL were added to those from 14 earlier statin trials, there was no significant excess of hemorrhagic stroke in patients random-
ized to statins compared with controls (160/47 419 versus 132/47,368; RR, 1.21; 95% CI, 0.96 to 1.5).26

As with the risk of gastrointestinal bleeding with antplatelet agents,19 the possible risk of hemorrhagic stroke with intensive lipid-lowering must be weighed against the benefit from treatment. The overall stroke risk reduction observed in the SPARCL trial, which included the hemorrhagic stroke data, was significant, demonstrating a net benefit of atorvastatin in stroke prevention. The benefit is even greater when the significant reduction in the risk of coronary and vascular events with intensive statin treatment is considered. In addition, high-dose statins generally have an excellent safety profile, and muscle and liver-related disturbances are infrequent even with intensive statin therapy.27

Future Analysis and Inquiry

Substantial cholesterol lowering is likely to be critical to the mechanism by which statins reduce the risk of stroke. Compelling data show that, in patients with prior stroke but no CAD, modest reductions in LDL-C do not provide protection; instead, benefit is achieved when LDL-C is reduced below 2.6 mmol/L (100 mg/dL). It has been suggested that effects beyond lipid lowering, such as antiinflammatory effects, might also be involved.2 Non–lipid-lowering effects may differ among individual statins, which may explain differing results between statin trials; however, potency in reducing LDL-C also differs between statins and might account for these differences.

Another area of interest is whether established treatment with statins might reduce stroke severity, as preliminary results from SPARCL suggest that patients receiving statin therapy within the 30 days before a stroke experienced reduced stroke severity.24 If the mechanism of benefit in the acute and subacute stages is the same, it would be logical to begin therapy as soon as possible after stroke; however, this area requires further exploration, as the mechanisms—and safety concerns—may be different.

Stroke etiology is heterogeneous, and it will be of interest to determine whether benefits are seen only in patients with cardioembolic stroke. SPARCL enrolled patients with ischamic, hemorrhagic, embolic, lacunar, and cryptogenic strokes, and excluded patients with atrial fibrillation or other sources of cardiac emboli,18 allowing speculation that statins may be beneficial in stroke etiologies other than cardioembolic, but further data are required to answer this question.

Conclusions

Recent trials have demonstrated that statins can reduce risk of stroke in patients with and without coronary disease. Until recently, data on the potential benefit of statins in reducing risk of recurrent stroke were limited and unpromising. However, many of the earlier trials used what would now be considered low-dose statin therapy, and greater benefits might be expected from the more intensive statin therapy available today. SPARCL showed that intensive statin therapy can reduce risk of recurrent stroke in nondiabetic as well as diabetic patients with recent stroke or TIA but no CAD. Although cholesterol-lowering with statins should be kept within the perspective of modifying other stroke risk factors such as hypertension, smoking, and diabetes, it is important to remember that statins will lower not only the patient’s risk of stroke but also their overall cardiovascular risk. As statins have both an excellent safety profile and simple administration, physicians should consider using statins, at dosages shown to have efficacy in clinical trials, in all patients whose cardiovascular risk profile puts them at high risk of stroke.

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