Statins in Threatened Stroke

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What Is Known: Statins in Stroke Prevention
Both a meta-analysis1 and the large secondary prevention trials of coronary heart disease (CHD) with simvastatin2 and with pravastatin3,4 revealed a reduction of 19% to 32% in ischemic strokes in patients with CHD. The results led to the Food and Drug Administration approval of pravastatin and simvastatin for stroke prevention in patients with CHD. Accordingly, patients with atherosclerotic stroke are candidates for lipid-lowering therapy, although before the Heart Protection Study (HPS), no randomized trials of cholesterol-lowering therapy in patients with transient ischemic attack (TIA) or stroke had verified the benefits of statins in stroke prevention in these high-risk patients without diagnosed CHD.5 The HPS enrolled 1821 patients with TIA or stroke but without CHD and altogether 3280 TIA or stroke patients with or without CHD. The results of the study helped resolve most of the still-remaining uncertainties.5

Study Design
To ensure the compliance, potentially eligible people entered a prerandomization run-in phase, which involved 4 weeks of placebo followed by 4 to 6 weeks of a fixed dose of 40 mg simvastatin daily to allow assessment of responsiveness of each individual. A central telephone randomization system was used to balance the treatment groups with respect to eligibility criteria and other major prognostic factors.

Study Population
Men and women aged 40 to 80 years with nonfasting blood total cholesterol concentrations of at least 135 mg/dL (3.5 mmol/L) were eligible provided that they were considered to be at substantial 5-year risk of death from CHD because of past history of CHD, occlusive disease of noncoronary arteries, ie, nondisabling stroke not thought to be hemorrhagic, TIA, peripheral arterial disease, carotid endarterectomy, other arterial surgery or angioplasty, type 1 or 2 diabetes, or being men aged 65 years or older with treated hypertension. Patients with severely disabling strokes were excluded. A total of 63 603 people attended the initial screening clinic visit, 32 145 were potentially eligible, and 20 536 were randomized (15 454 men and 5082 women). Of these, 5806 were at least 70 years of age. A total of 8510 patients had previous myocardial infarction. Some other history of CHD was reported by 4876, whereas 7150 participants did not have diagnosed CHD. Among those 7150, 1820 had cerebrovascular disease (CVD), 2701 had peripheral arterial disease, and 3982 had diabetes mellitus. Some had more than 1 of these 3 conditions. Among the 13 386 with known CHD, 1460 had CVD, 4047 had diabetes mellitus, and 1981 had peripheral arterial disease. A total of 8457 had treated hypertension, but only 237 were included on the basis of hypertension alone. On admission, participants had mean nonfasting blood cholesterol of 5.9 mmol/L, directly measured LDL cholesterol of 3.4 mmol/L, HDL cholesterol of 1.06 mmol/L, and triglycerides of 2.1 mmol/L. The mean duration of follow-up was 5 years for all randomized participants and 5.3 years for survivors. Mean difference (SE) in blood total cholesterol concentrations (simvastatin minus placebo) was 1.2 (0.02) mmol/L, and that of LDL cholesterol was 1.0 (0.02) mmol/L.

Effects on Mortality
During the treatment period, 1328 (12.9%) of the 10 269 patients allocated 40 mg daily simvastatin died compared with 1507 (14.7%) of the 10 267 allocated matching placebo (P=0.0003). The proportional reduction of 18% in the coronary death rate, 587 (5.7%) versus 707 (6.9%), was highly significant (P=0.0005).

Coronary Events
The proportional reduction in the incidence of nonfatal myocardial infarction was 38% (357 [3.5%] versus 574 [5.6%]; P<0.0001).

Stroke
Allocation to simvastatin produced proportional reduction of 25% in the incidence rate of first stroke after randomization (444 [4.3%] versus 585 [5.7%]; P<0.0001) (Figure). This was mainly attributable to a 30% proportional reduction in the incidence rate of ischemic strokes (290 [2.8%] versus 409 [4.0%]; P<0.0001) with no difference in hemorrhagic strokes (51 [0.5%] versus 53 [0.5%]; P=0.8).

The proportional reduction in the first major vascular event (major coronary event, stroke, or revascularization) was significant in patients with CVD but without CHD (172 of 922 [18.7%] versus 212 of 898 [23.6%]) as well as in CVD patients with or without CHD (406 of 1645 [24.7%] versus 488 of 1635 [29.8%]). The proportional reduction in the incidence rate of first stroke after randomization in the subgroup of patients with CVD but without CHD as the inclusion criteria has not yet been
LDL cholesterol was reductions among the 6793 participants whose pretreatment triglyceride concentrations. There were highly significant risk to be materially influenced by the pretreatment cholesterol or most notably, the proportional reduction in risk did not seem enzyme inhibitors, and acetylsalicylic acid. Furthermore, P[17.6%] versus 756 [22.2%]; evidence of adverse effect on hemorrhagic stroke.

The treatment reduced the risk of ischemic stroke without any statistically significant reduction in carotid endarterectomy or angioplasty (42 [0.4%] versus 82 [0.8%]; P=0.0003) as well.

**Subgroups**
The proportional reduction in the rate of major vascular events with allocation to simvastatin seemed to be about one fourth, irrespective of the sex or age of the participants. It also was largely independent of the blood creatine concentration at entry as well as of cigarette smoking, treatment for hypertension, and use of β-blockers, angiotensin-converting enzyme inhibitors, and acetylsalicylic acid. Furthermore, most notably, the proportional reduction in risk did not seem to be materially influenced by the pretreatment cholesterol or triglyceride concentrations. There were highly significant risk reductions among the 6793 participants whose pretreatment LDL cholesterol was <3.0 mmol/L (116 mg/dL) (589 [17.6%] versus 756 [22.2%]; P<0.0001) and among the 3421 presenting with LDL <2.6 mmol/L (100 mg/dL) (282 [16.4%] versus 358 [21.0%]; P<0.0006).

**What Is New**

**Stroke Prevention**
The HPS clearly verified the effects of 40 mg daily simvastatin in prevention of major vascular events (major coronary events, strokes, and revascularization together) among patients with TIA or stroke with or without CHD.

**Benefits Not Influenced by Pretreatment Level of Cholesterol or Triglyceride Concentrations**
The study revealed that among the high-risk individuals, statin therapy produced substantial benefits that were not much influenced by the initial concentrations of blood lipids. Accordingly, there seems to be no LDL cholesterol threshold. The treatment reduced the risk of ischemic stroke without any evidence of adverse effect on hemorrhagic stroke.

**Benefits Independent of Age, Sex, Smoking, and Treatment of Hypertension**
Before the HPS we did not have data on the efficacy and safety of statins in elderly population and in women. The HPS verified the beneficial effects of statins not only in patients with CHD but also in those with TIA or stroke, peripheral arterial disease, or diabetes, for each of which there had not previously been direct evidence of benefit.

**Benefits Independent of Other Therapies**
Benefits of statin therapy appeared to be largely independent of and hence additional to those of all the other treatments being used by the participants, including antihypertensive therapy, aspirin, and cardioprotective drugs.

**Still Missing Data**
Although indirect evidence strongly suggests that statin therapy prevents additional strokes in patients with TIA or stroke, the verification is still missing. Additional analyses of HPS data or the ongoing Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study may provide such evidence.

**Discussion**

**Evolution**
One of the evolution paradoxes of mankind is the fact that those properties that once helped humans survive, such as the capability to preserve energy and brisk defense against infections, lead in the developed world to metabolic syndrome and chronic inflammation and by doing so facilitate the progress of atherosclerosis and increase the risk of cardiovascular diseases. Statins influence lipid metabolisms beneficially and reduce chronic inflammation. They may help fight cardiovascular diseases including stroke by many other mechanisms than just lowering LDL cholesterol, which may be equally important as the effects of statins on cholesterol metabolisms.

**The Costs**
Hankey and Warlow estimated that it would cost 41 000 Australian dollars to prevent one stroke by providing statins to all those with blood cholesterol level 7.0 mmol/L or higher, and even if all of those individuals were compliant with therapy, it would annually eliminate only 4% of all strokes. The results of HPS suggest a much greater benefit, because most strokes occur in low-risk individuals, but yet ~19 patients with TIA or stroke would need to be treated for 5 years to avoid 1 patient suffering from major coronary events, strokes, and revascularizations. However, the HPS unequivocally revealed that in patients with threatened stroke it is possible to reduce the overall risk of major vascular events, which makes the therapy much more cost-effective. Warlow suggested in his presentation at the Karolinska Stroke Update 2002 in Stockholm on November 11, 2002, that HPS resolved any remaining uncertainties about the effects of statin therapy, and all patients with threatened stroke should be taking them. According to Collins, statin therapy should be considered for all high-risk patients irrespective of their pres-
Prevention of Cognitive Decline

Treatment with simvastatin slowed down the decline of MMSE in Alzheimer patients, whereas no significant differences were observed between the treatment groups of HPS in the percentage of participants classified as having cognitive impairment. The same held true for elderly patients allocated to pravastatin in the Prospective Study Pravastatin in the Elderly at Risk (PROSPER), which included 5804 patients between 70 and 82 years (average, 75 years). Although pravastatin 40 mg daily reduced the combination of coronary heart disease, nonfatal myocardial infarction, and fatal or nonfatal stroke significantly, the stroke risk was unaffected, nor could pravastatin therapy prevent cognitive decline. Taken together, the results of the HPS and PROSPER studies cast doubt on the hypothesis that statins might reduce cognitive decline.

Conclusions

The Heart Protection Study confirmed that simvastatin reduces substantially the rates of major vascular events among a wide range of high-risk individuals. The study also resolved any remaining uncertainties about the effects of simvastatin in prevention of major coronary events, strokes, and revascularizations in patients with TIA or stroke, whether they had CHD or were free of it at the time of randomization. However, the published data either from the HPS or any other statin trial do not verify that statin therapy prevents additional strokes in patients with TIA or stroke. Verification may need a larger population to be studied than was enrolled in the HPS. Future studies of the HPS Collaborative Group will probably answer this question. If not, we must wait for the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. The study will be completed during the first quarter of 2004. That statin therapy is able to slow cognitive decline in elderly individuals is an important but unproven hypothesis.

References


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