Reduction of Stroke Events With Pravastatin

The Prospective Pravastatin Pooling (PPP) Project

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Background—Stroke is a leading cause of death and disability. Although clinical trials of the early lipid-lowering therapies did not demonstrate a reduction in the rates of stroke, data from recently completed statin trials strongly suggest benefit.

Methods and Results—The effect of pravastatin 40 mg/d on stroke events was investigated in a prospectively defined pooled analysis of 3 large, placebo-controlled, randomized trials that included 19,768 patients with 102,559 person-years of follow-up. In all, 598 participants had a stroke during ≈5 years of follow-up. The 2 secondary prevention trials (CARE [Cholesterol And Recurrent Events] and LIPID [Long-term Intervention with Pravastatin in Ischemic Disease]) individually demonstrated reductions in nonfatal and total stroke rates. When the 13,173 patients from CARE and LIPID were combined, there was a 22% reduction in total strokes (95% CI 7% to 35%; P=0.01) and a 25% reduction in nonfatal stroke (95% CI 10% to 38%). The beneficial effect of pravastatin on total stroke was observed across a wide range of patient characteristics. WOSCOPS (West of Scotland Coronary Prevention Study, a primary prevention trial in hypercholesterolemic men) exhibited a similar, although smaller, trend for a reduction in total stroke. Among the CARE/LIPID participants, pravastatin was associated with a 23% reduction in nonhemorrhagic strokes (95% CI 6% to 37%), but there was no statistical treatment group difference in hemorrhagic or unknown type.

Conclusions—Pravastatin reduced the risk of stroke over a wide range of lipid values among patients with documented coronary disease. This effect was due to a reduction in nonfatal nonhemorrhagic strokes. (Circulation. 2001;103:387-392.)

Key Words: lipids ■ prevention ■ stroke ■ trials

Cerebrovascular disease is the second leading cause of death in the Americas and Europe, accounting for 10% and 14% of all deaths in these regions, and is the leading cause of death among the Western Pacific countries, accounting for 14% of all deaths. In the United States, strokes killed almost 160,000 persons in 1997 and ranked third as cause of death after heart disease and cancer. Approximately 600,000 persons have a stroke each year in the United States. It is a leading cause of disability and increased healthcare costs.

Numerous studies have demonstrated that the risk of coronary heart disease events is reduced by lipid-lowering therapy. The effect of lipid lowering on stroke events is less well established: meta-analyses of the early clinical trials with older lipid-lowering agents have suggested that modest reductions in cholesterol did not reduce stroke. However, the introduction of the HMG-CoA reductase inhibitors (or “statins”) raised the expectation that these agents might demonstrate a beneficial effect on stroke.

This report presents the results of a pooled analysis of stroke data from 3 recently completed event trials that used a specific statin, pravastatin. The Prospective Pravastatin Pooling (PPP) Project included data from WOSCOPS (West Of Scotland Coronary Prevention Study), the CARE (Cholesterol And Recurrent Events) trial, and the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) trial. Individual patient data from the 3 trials were pooled into a single database to provide increased power overall and for subgroup analyses. The larger sample size also permits analyses by stroke subtype.

Methods

The PPP Project was initiated in 1992 before completion of any of the constituent trials. The design and rationale for the project have been previously described, as have been the primary results of the 3 constituent trials. Each of the 3 studies was a randomized, double-masked, placebo-controlled trial of 40 mg/d pravastatin. WOSCOPS, conducted in Scotland, was a primary prevention trial.
that evaluated the effectiveness of pravastatin in the prevention of fatal and nonfatal coronary events in 6595 men aged 45 to 64 years with hyperlipidemia and no history of myocardial infarction (MI).\textsuperscript{6} WOSCOPS patients were followed for a mean of 4.8 years. CARE, conducted in the United States and Canada, was a secondary prevention trial that evaluated the effectiveness of pravastatin in the prevention of fatal and nonfatal coronary events in 4159 men and women aged 21 to 75 years with average lipid levels and an MI 3 to 20 months before randomization.\textsuperscript{7} CARE patients were followed for a mean of 4.8 years. LIPID, conducted in Australia and New Zealand, was also a secondary prevention trial. It evaluated the effectiveness of pravastatin in the prevention of coronary deaths in 9014 men and women aged 31 to 75 years with a history of MI or unstable angina and a wider lipid range than CARE.\textsuperscript{8} LIPID patients were followed for a mean of 6.1 years.

Strokes in WOSCOPS were monitored with national computerized record linking, reviewed by an adverse events committee, and defined as episodes of motor paralysis, sensory or speech dysfunction, diplopia, or visual disturbance lasting $\geq$ 1 hour. CARE and LIPID used an end points committee to predefine and blindly classify strokes. Stroke was defined as a new acute disturbance of focal neurological or monocular function that resulted in either death or signs and/or symptoms of presumed vascular origin.\textsuperscript{14,15} Strokes for CARE and LIPID were categorized in the pooled database as hemorrhagic, nonhemorrhagic, and unknown.

Following the PPP protocol, the specific objectives for the analyses presented here were to determine the effect of pravastatin on the rate of total stroke both for the 3 trials combined and for the combination of CARE and LIPID. Analyses of time to first event were performed using log-rank statistics and proportional hazards models.\textsuperscript{16} In the pooled analyses, tests were stratified by trial. The absolute event rates presented in the tables used the mean follow-up as the unit of time. Interactions between treatment and baseline characteristics were explored in stratified analyses and proportional hazard models. Simple tests of proportions and means were conducted to evaluate treatment group differences in baseline characteristics. All analyses followed the intention-to-treat principle. Hazard ratios and 95% CIs are presented as indications of relative effect sizes.

### Results

The baseline descriptions of the 3 trials and the treatment group comparisons are presented in Table 1. Collectively, there were 19 768 patients in the PPP database with 102 559 patient-years of follow-up.

#### Table 1. Baseline Descriptions

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>WOSCOPS (n=6595)</th>
<th>CARE (n=4159)</th>
<th>LIPID (n=9014)</th>
<th>Pool of 3 Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>54.7</td>
<td>58.6</td>
<td>60.8</td>
<td>58.3</td>
</tr>
<tr>
<td>Female, %</td>
<td>0.0</td>
<td>13.9</td>
<td>16.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Qualifying event/condition, %</td>
<td>100.0</td>
<td>63.8</td>
<td>33.4</td>
<td>50.1</td>
</tr>
<tr>
<td>MI (CARE + LIPID)</td>
<td>...</td>
<td>100.0</td>
<td>...</td>
<td>50.1</td>
</tr>
<tr>
<td>Unstable angina (LIPID)</td>
<td>...</td>
<td>36.2</td>
<td>...</td>
<td>16.5</td>
</tr>
<tr>
<td>Hyperlipidemia (WOSCOPS)</td>
<td>100.0</td>
<td>...</td>
<td>...</td>
<td>33.4</td>
</tr>
<tr>
<td>Cigarette smoking status, %</td>
<td>Current</td>
<td>35.2</td>
<td>16.1</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>39.2</td>
<td>61.5</td>
<td>63.7</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>25.6</td>
<td>22.4</td>
<td>26.7</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg</td>
<td>83.9</td>
<td>78.6</td>
<td>80.5</td>
<td>81.2</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg</td>
<td>135.5</td>
<td>128.9</td>
<td>134.1</td>
<td>133.3</td>
</tr>
<tr>
<td>Mean heart rate, bpm</td>
<td>72.8</td>
<td>67.2</td>
<td>68.9</td>
<td>69.7</td>
</tr>
<tr>
<td>Mean cholesterol level, mg/dL (mmol/L)</td>
<td>271.8 (7.0)</td>
<td>208.5 (5.4)</td>
<td>218.7 (5.7)</td>
<td>234.3 (6.1)</td>
</tr>
<tr>
<td>Mean LDL-C level, mg/dL (mmol/L)</td>
<td>191.9 (5.0)</td>
<td>138.6 (3.6)</td>
<td>150.0 (3.9)</td>
<td>161.4 (4.2)</td>
</tr>
<tr>
<td>Mean HDL-C level, mg/dL (mmol/L)</td>
<td>44.1 (1.1)</td>
<td>37.9 (1.0)</td>
<td>35.9 (0.9)</td>
<td>39.3 (1.0)</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>4.5</td>
<td>3.7</td>
<td>4.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Mean triglyceride level, mg/dL (mmol/L)</td>
<td>163 (1.8)</td>
<td>156 (1.8)</td>
<td>160 (1.8)</td>
<td>161 (1.8)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²</td>
<td>26.0</td>
<td>27.6</td>
<td>26.8</td>
<td>26.7</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>1.0</td>
<td>2.9</td>
<td>4.1</td>
<td>2.7</td>
</tr>
<tr>
<td>History of angina, %</td>
<td>5.1</td>
<td>20.7</td>
<td>99.9</td>
<td>51.7</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>1.2</td>
<td>14.1</td>
<td>8.7</td>
<td>7.3</td>
</tr>
<tr>
<td>On insulin, %</td>
<td>0.1</td>
<td>4.6</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>15.7</td>
<td>42.6</td>
<td>41.7</td>
<td>33.1</td>
</tr>
<tr>
<td>Taking a medication that reduces BP,* %</td>
<td>15.8</td>
<td>81.2</td>
<td>75.7</td>
<td>56.7</td>
</tr>
<tr>
<td>Taking aspirin, %</td>
<td>2.9</td>
<td>83.6</td>
<td>62.4</td>
<td>56.4</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; NA, not available.

*Includes $\beta$-blockers, calcium channel blockers, ACE inhibitors, and diuretics.
The effects of pravastatin on all stroke events occurring during the entire follow-up period are presented in Table 2. Overall, 598 of the participants had a fatal or nonfatal stroke during follow-up. More than half of these were from LIPID, although LIPID and CARE had similar placebo group event rates (8.0 and 7.6 strokes per 1000 patients per year, respectively). WOSCOPS had the fewest strokes and the lowest rate of strokes. Each trial individually demonstrated a reduction in total stroke, although the CI for the WOSCOPS hazard ratio was large and crossed 1.00 (Table 2, top). CARE had a 32% reduction (4% to 52% reduction) and LIPID had an 18% reduction (0% to 33% reduction). Combining all 3 trials resulted in a 20% reduction in total stroke with pravastatin (7% to 32% reduction, \( P < 0.01 \)). This difference in total strokes was maintained if WOSCOPS was removed from the calculations: CARE and LIPID combined had a 22% reduction (7% to 35% reduction, \( P = 0.01 \)). This difference in total strokes was maintained if WOSCOPS was removed from the calculations: CARE and LIPID combined had a 22% reduction (7% to 35% reduction, \( P = 0.01 \)). In the combined CARE/LIPID database, it was estimated that 588 patients would have to be treated per year to avert 1 stroke event; in WOSCOPS, 3333 patients would have to be treated.

About 90% of the strokes were nonfatal (Table 2, middle), and there was an overall 24% reduction in nonfatal stroke attributable to pravastatin. This treatment benefit on nonfatal strokes was maintained when only the 2 secondary prevention trials are combined. Less than 10% of the strokes reported in the trials were fatal (Table 2, bottom).

Figure 1 presents the cumulative fatal/nonfatal stroke curves. There was no statistical evidence that the proportional hazards assumption was violated. Event rates in the primary prevention trial (WOSCOPS) were consistently lower, with no clear overall benefit attributable to pravastatin. Among the 2 secondary prevention trials (CARE and LIPID), the stroke rates were generally consistent, both in terms of the long-term absolute risks of stroke and the benefit attributable to pravastatin. Figure 2 presents the cumulative treatment-specific stroke curves for the combined CARE and LIPID population, in which it is noted that the curves diverge after 1 year of treatment.

The effect of pravastatin on total stroke was examined in various baseline subgroups in the combined CARE/LIPID group. The beneficial effect of pravastatin in reducing strokes was evident and consistent across subgroups (Figure 3). There was no evidence of a statistical interaction (at \( P < 0.05 \))
between any baseline characteristic and treatment group assignment. The rates of hemorrhagic and nonhemorrhagic stroke from CARE/LIPID are presented in Table 3. Seventy percent of all stroke events were nonfatal nonhemorrhagic strokes. Pravastatin was associated with a 23% reduction in total nonhemorrhagic stroke (6% to 37% reduction), primarily a function of its effect on nonfatal nonhemorrhagic strokes (24% reduction). There is no evidence that pravastatin had an effect on hemorrhagic strokes.

### Discussion

For decades, there had been considerable doubt regarding the value of lipid lowering in stroke prevention. This was because total stroke incidence (in which hemorrhagic and nonhemorrhagic strokes were combined together) had only been weakly associated, if at all, with increased cholesterol levels in observational studies and because of the observed lack of benefit of lipid lowering on stroke incidence in the early cholesterol-lowering trials. Even as late as 1995, a meta-analysis of cholesterol-lowering trials (none of which used a statin) reported that patients assigned to cholesterol lowering experienced no reduction in total stroke. In that report, summarizing the stroke results from 11 randomized trials of lipid lowering, the relative risk for total fatal/nonfatal stroke in participants assigned to treatment compared with controls was 1.0 (95% CI 0.8 to 1.2).

However, this doubt began to evaporate with the publication of the results of the secondary prevention statin trials. For example, the Scandinavian Simvastatin Survival Study reported in 1995 the post hoc finding that there was a 30% reduction in any cerebrovascular event attributable to simvastatin. In another post hoc analysis that same year, a pooled analysis of 4 regression trials conducted primarily in coronary patients reported a 62% lower rate of total stroke attributable to pravastatin. Subsequently, and with stroke as a prespecified outcome, CARE and LIPID individually reported fewer strokes among patients assigned to pravastatin therapy compared with placebo. CARE and LIPID remain the only trials to publish the results of prospectively defined stroke end points. Supporting these findings were the results from the B-mode ultrasound regression trials that documented the effectiveness of pravastatin in slowing and/or reversing carotid atherosclerosis.

The analyses presented here clearly demonstrate that pravastatin is more effective than the older, nonstatin lipid-lowering therapies in reducing stroke rates. The consistent reductions across the trials and subgroups are striking. Attention is drawn to the beneficial effect of pravastatin among patients on aspirin and on or not on blood pressure-lowering medications. It is also noted that the 22% reduction in relative risk and the 1.7$^{\pm}$1000 patients$^{-1}$·y$^{-1}$ reduction in absolute risk in CARE/LIPID are comparable to those reported for stroke with antiplatelet therapies given to post-MI patients.

In observational studies, higher lipid levels have been associated with higher rates of nonhemorrhagic stroke and lower lipid levels associated with higher rates of hemorrhagic stroke. Therefore, analyses should be stratified by type of stroke. Moreover, an overall benefit is more likely to be observed in populations in which nonhemorrhagic strokes greatly outnumber hemorrhagic strokes. It has also been estimated from observational studies that hemorrhagic stroke rates may increase if the LDL cholesterol levels are $<$70 mg/dL ($<$1.8 mmol/L), a level not usually attained with a 40 mg/d dosage of pravastatin. Therefore, the observed PPP...
results would be expected: the primary effect of pravastatin were to reduce nonhemorrhagic strokes.

The PPP analyses demonstrate that the long-term use of pravastatin is associated with a reduction in total stroke incidence in the setting of secondary prevention and across a wide range of patient characteristics. This benefit is seen as a reduction in nonfatal nonhemorrhagic strokes. There is a suggestion in these data that this benefit occurs after ~1 year of therapy.

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Appendix

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