Additive Benefits of Pravastatin and Aspirin to Decrease Risks of Cardiovascular Disease

Randomized and Observational Comparisons of Secondary Prevention Trials and Their Meta-analyses

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Background: In randomized trials of secondary prevention, pravastatin sodium and aspirin reduce risks of cardiovascular disease. Pravastatin has a predominantly delayed antiatherogenic effect, and aspirin has an immediate antiplatelet effect, raising the possibility of additive clinical benefits.

Methods: In 5 randomized trials of secondary prevention with pravastatin (40 mg/d), comprising 73,900 patient-years of observation, aspirin use was also prescribed in varying frequencies, and data were available on a large number of confounding variables. We tested whether pravastatin and aspirin have additive benefits in the 2 large trials (Long-term Intervention With Pravastatin in Ischaemic Disease trial and the Cholesterol and Recurrent Events trial) that were designed to test clinical benefits. We also performed meta-analyses of these 2 trials and 3 smaller angiographic trials that collected clinical end points. In all analyses, multivariate models were used to adjust for a large number of cardiovascular disease risk factors.

Results: Individual trials and all meta-analyses demonstrated similar additive benefits of pravastatin and aspirin on cardiovascular disease. In meta-analysis, the relative risk reductions for fatal or nonfatal myocardial infarction were 31% for pravastatin plus aspirin vs aspirin alone and 26% for pravastatin plus aspirin vs pravastatin alone. For ischemic stroke, the corresponding relative risk reductions were 29% and 31%. For the composite end point of coronary heart disease death, nonfatal myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or ischemic stroke, the relative risk reductions were 24% and 13%. All relative risk reductions were statistically significant.

Conclusion: More widespread and appropriate combined use of statins and aspirin in secondary prevention of cardiovascular disease will avoid large numbers of premature deaths.

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IN RANDOMIZED TRIALS OF SECONDARY PREVENTION AND THEIR META-ANALYSES, THE 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE INHIBITORS (OR STATINS)1-4 AND ASA5-12 HAVE BEEN DEMONSTRATED TO REDUCE RISKS OF CARDIOVASCULAR DISEASE (CVD). INDEED, REGULATORY AUTHORITIES WORLDWIDE, INCLUDING THE US FOOD AND DRUG ADMINISTRATION, HAVE APPROVED THE USE OF PRAVASTATIN SODIUM,13 ONE OF THE MOST WIDELY TESTED STATINS, AND ASA14 IN THE SECONDARY PREVENTION OF CVD.

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With regard to statins, basic research, as well as clinical investigations and large-scale randomized trials, consistently demonstrate a delayed antiatherogenic effect when the drug is administered before or after recovery from an acute CVD event. In addition, secondary prevention trials of stable patients and their meta-analyses indicate that benefits of statins begin to appear only 1 year or more after initiation of therapy.1-4 In contrast, aspirin has an immediate antiplatelet effect.5-12 Based on these considerations, it has been hypothesized that statins and aspirin will have at least additive effects on the reduction of CVD.13 Indeed, recently published guidelines for use of statins and aspirin indicate favorable risk-benefit ratios for all patients who have survived a prior CVD event.16-18 Nonetheless, there remains underuse and mis-medication with statins19,20 and aspirin.21,22

To test the hypothesis that statins and aspirin have additive benefits, it would be neither feasible nor ethical to conduct randomized, factorial, placebo-controlled trials or to directly compare the combination against each agent individually. Furthermore, the randomized trials of aspirin in
secondary prevention were completed before the advent of statins. For pravastatin, however, the secondary prevention trials were randomized but also included observational data on aspirin use, prescribed in varying frequencies, and information on a large number of confounding variables. Therefore, based on meta-analysis of these trial data, it is possible to test whether pravastatin and aspirin have additive benefits on various clinical CVD end points.

**METHODS**

There are 2 large-scale randomized trials of secondary prevention with pravastatin that had been designed to evaluate clinical CVD end points. These comprise 9014 patients from the Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID) trial1 and 4159 patients from the Cholesterol and Recurrent Events (CARE) trial.2 In addition, clinical end point data are available from 3 smaller randomized angiographic trials of secondary prevention with pravastatin. These include the Regression Growth Evaluation Statin Study (REGRESS) (885 patients)3; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial (408 patients)4; and Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II) trial (151 patients).5 In all these trials, aspirin was prescribed in varying frequencies by the responsible clinicians, and information was available on a large number of confounding variables.

In this study, we analyzed the available data from each trial in which pravastatin use was randomized and aspirin use was observational, individually and in meta-analyses that controlled for a large number of confounding variables. The primary objective was to test the hypothesis, suggested by their differing principal biological mechanisms of action, that pravastatin and aspirin have additive clinical benefits on CVD. We also explored whether the benefits of pravastatin and aspirin were greater than additive by calculating the probability of synergy.

All 5 randomized trials of secondary prevention of CVD with pravastatin (40 mg/d) had at least 2 years’ follow-up. In all the trials, the CVD end points were adjudicated by an independent committee blinded to treatment. Patient follow-up in the LIPID and CARE trials (which comprise 96% of the total patient-years of observation) was virtually 100% complete, as only one patient in the LIPID trial and none in the CARE trial was lost to follow-up. To test whether the benefits of pravastatin and aspirin were additive, first we analyzed the prespecified CVD end point data for the LIPID, CARE, and 3 angiographic trials. Second, we performed meta-analyses. In all analyses, pravastatin comparisons were randomized based on intention to treat, and aspirin comparisons were observational based on use at baseline after controlling for a large number of confounding variables. For the LIPID and CARE trials, 97% of baseline aspirin users were still taking aspirin at the end of the trials. The dosage of aspirin, however, was not recorded, and its use was documented as concomitant medication. The primary end points were coronary heart disease (CHD) death in the LIPID trial and CHD death or nonfatal myocardial infarction (MI) in the CARE trial. Pravastatin and aspirin use had been approved by the US Food and Drug Administration in secondary prevention of CVD for a wide range of indications. Therefore, we also considered CVD end points based on the overlap of the secondary prevention indications as follows: fatal or nonfatal MI, ischemic stroke, and a composite end point that included CHD death, nonfatal MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and ischemic stroke. These end points had also been prespecified in the LIPID and CARE trials.

In the meta-analyses, the larger trials were given proportionately greater weight. We first used a multivariate Cox proportional hazards model in which the trial effect is a fixed covariate.26 To evaluate whether any observed additive benefits of pravastatin and aspirin remain present under different assumptions, we used 2 other multivariate Cox proportional hazards models, one to allow for trial heterogeneity and the other to allow for nonproportionality of treatment hazards. Finally, we used this latter model to calculate the probability of synergy.26

In the 5 individual trials and their meta-analyses, we used Cox proportional hazards models to adjust for confounding by age; sex; previous MI; current cigarette smoking; baseline levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides; and systolic and diastolic blood pressure. In addition, clinical end point data were available from 3 smaller randomized angiographic trials of secondary prevention with pravastatin. These include the Regression Growth Evaluation Statin Study (REGRESS) (885 patients)3; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial (408 patients)4; and Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II) trial (151 patients).5 In all these trials, aspirin was prescribed in varying frequencies by the responsible clinicians, and information was available on a large number of confounding variables.

**RESULTS**

Among 73900 patient-years of observation, the LIPID trial contributed 68%; CARE, 28%; REGRESS, 2%; PLAC I, 1%; and PLAC II, 1%. In the LIPID trial, 9014 patients with previous MI or unstable angina were randomized to pravastatin (40 mg/d) or placebo and treated for a mean of 6.1 years. At baseline, 82.7% of patients assigned at random to pravastatin or placebo were aspirin users. In the LIPID trial, pravastatin reduced the primary prespecified end point of CHD death by 24% (6.4% in the pravastatin group vs 8.3% in the placebo group, P < .001). Among aspirin users randomized to placebo, the RRR in CHD death was 28.3% (P < .001). With respect to the other prespecified end points, aspirin users had statistically significant RRRs of 34.7% in fatal or nonfatal MI (P < .001), 29.7% in ischemic stroke (P = .008), and 23.9% in the composite end point (P < .001). Among patients randomized to pravastatin, aspirin use was associated with a significant RRR of 35.6% in CHD death (P = .002). For the other prespecified end points, aspirin use was associated with a significant RRR of 28.0% in fatal or nonfatal MI (P = .01), a nonsignificant RRR of 25.9% in ischemic stroke (P = .16), and a significant RRR of 14.1% in the composite end point (P = .049) (Table). In the CARE trial, 4159 patients with previous MI were randomized to pravastatin (40 mg/d) or placebo and treated for a mean of 5 years. At baseline, 83.7% of patients assigned at random to pravastatin or placebo were aspirin users. In the CARE trial, pravastatin reduced the primary prespecified end point of CHD death of nonfatal MI by 24% (10.2% in the pravastatin group vs 13.2% in the placebo group, P = .003). Among aspirin users randomized to placebo, the RRR in CHD death or nonfatal MI was 28.2% (P = .001). With respect to the other prespecified end points, aspirin users had a significant 20.6% RRR in fatal or nonfatal MI (P = .02), a possible but nonsignificant 28.9% RRR in ischemic stroke (P = .13), and

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Absolute Cardiovascular Disease Event Rates and Relative Risk Reduction (RRRs) in the LIPID, CARE, and Angiographic Trials*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Treatment Group</th>
<th>RRR (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prava + ASA</td>
<td>Prava Alone</td>
</tr>
<tr>
<td>LIPID (n = 3730)</td>
<td>(n = 782)</td>
<td>(n = 3698)</td>
</tr>
<tr>
<td>CHD death</td>
<td>5.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>7.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2.6</td>
<td>3.7</td>
</tr>
<tr>
<td>CHD death, nonfatal MI, CABG, PTCA, or ischemic stroke</td>
<td>23.5</td>
<td>26.9</td>
</tr>
<tr>
<td>CARE (n = 1742)</td>
<td>(n = 339)</td>
<td>(n = 1735)</td>
</tr>
<tr>
<td>CHD death or nonfatal MI</td>
<td>9.3</td>
<td>14.7</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>10.1</td>
<td>11.8</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2.0</td>
<td>4.1</td>
</tr>
<tr>
<td>CHD death, nonfatal MI, CABG, PTCA, or ischemic stroke</td>
<td>21.6</td>
<td>27.1</td>
</tr>
<tr>
<td>Angiographic studies† (n = 416)</td>
<td>(n = 315)</td>
<td>(n = 400)</td>
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<tr>
<td>Fatal or nonfatal MI</td>
<td>1.4</td>
<td>3.8</td>
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<tr>
<td>Stroke</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>CHD death, nonfatal MI, CABG, PTCA, or stroke</td>
<td>14.7</td>
<td>12.4</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, aspirin; CABG, coronary artery bypass graft; CARE, Cholesterol and Recurrent Events; CHD, coronary heart disease; LIPID, Long-term Intervention With Pravastatin in Ischaemic Disease; MI, myocardial infarction; Prava, pravastatin sodium; PTCA, percutaneous transluminal coronary angioplasty.

*Data are given as percentages unless otherwise indicated.
†Angiographic studies included the REGRESS, PLAC-I, and PLAC-II trials.

Figure 1. Relative risk reduction for pravastatin sodium (Prava) plus aspirin (ASA) vs ASA alone in the Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID) and Cholesterol and Recurrent Events (CARE) trials. The rectangles represent 2-sided 95% confidence Interval and the vertical line, the relative risk reduction. MI indicates myocardial infarction; CHD, coronary heart disease; CABG, coronary artery bypass graft; and PTCA, percutaneous transluminal coronary angioplasty.

Figure 2. The comparisons of the efficacy of the combined pravastatin and aspirin tended to be greater than the simple arithmetic sum of the benefits of each agent alone. Figure 3 shows the analysis for the end point of fatal or nonfatal MI, which indicated that the probability of synergy was 0.92.

A significant 23.6% RRR in the composite end point (P < .001) Among patients randomized to pravastatin, aspirin use was associated with a significant RRR of 38.9% in CHD death or nonfatal MI (P = .002). For the other prespecified end points, aspirin use was associated with a nonsignificant RRR of 17.6% in fatal or nonfatal MI (P = .27), but with significant RRRs of 51.3% in ischemic stroke (P = .02) and 22.5% in the composite end point (P = .03) (Table).

In the 3 smaller angiographic trials with clinical CVD end points, 1444 patients with CHD were randomized to pravastatin (40 mg/d almost exclusively, as only 21 patients were taking lower dosages) or placebo and treated for a mean of 2 years. The percentage of aspirin users in the 3 regression trials was 54.4% in REGRESS, 67.5% in PLAC I, and 42.7% in PLAC II. For aspirin users, the RRR in fatal or nonfatal MI for pravastatin vs placebo was 75.2% (P = .002) and for the composite end point was 29.4% (P = .04). For stroke (not classified as ischemic or hemorrhagic), there was a possible but nonsignificant 7.9% increase (P = .94). Among patients randomized to pravastatin, aspirin use was associated with a significant 64.5% RRR in fatal or nonfatal MI (P = .04), but with nonsignificant increases of 81.8% in stroke (P = .63) and 14.5% in the composite end point (P = .52) (Table).

In the LIPID and CARE trials, the RRRs for pravastatin plus aspirin vs aspirin alone were remarkably similar (Figure 1). In the meta-analysis of all 5 trials, the RRRs for fatal or nonfatal MI were 31% for pravastatin plus aspirin and 26% for pravastatin plus aspirin vs pravastatin alone. For ischemic stroke, the corresponding values were 29% and 31%. For the composite end point, the values were 24% and 13%. All these RRRs were statistically significant (Figure 2). The results were remarkably consistent in the analyses of the LIPID and CARE data alone and in meta-analyses using each of 3 different assumptions (results not shown).

The comparisons of the efficacy of the combination vs placebo only (non–aspirin users randomized to placebo) are shown in Figure 2. The RRRs for the combination vs placebo were 40% for fatal or nonfatal MI, 39% for ischemic stroke, and 27% for the composite end point. All these RRRs were statistically significant.

We also explored whether the benefits of combined pravastatin and aspirin tended to be greater than the simple arithmetic sum of the benefits of each agent alone. Figure 3 shows the analysis for the end point of fatal or nonfatal MI, which indicated that the probability of synergy was 0.92.
In all analyses using various Cox proportional hazards models of the LIPID and CARE trial data, the combination of pravastatin plus aspirin consistently showed greater efficacy than pravastatin or aspirin alone. These findings were also present in meta-analyses of these 2 large-scale trials and in additional meta-analyses comprising 3 smaller angiographic trials, namely, REGRESS, PLAC I, and PLAC II. The findings were also present in 2 additional meta-analyses using different assumptions. Furthermore, the findings were consistent across a range of individual and composite CVD end points that included (but were not limited to) MI, stroke, and CHD death.

The finding of additive benefits of pravastatin and aspirin over pravastatin or aspirin alone is not surprising based on the well described and different mechanisms of action of each of these drugs. In randomized trials of secondary prevention in stable patients, pravastatin has a predominantly delayed antiatherogenic effect, as evidenced by clinical benefit becoming apparent more than 1 year after the initiation of therapy, when the statistically significant and clinically important reductions in CVD events become manifest. In randomized trials of secondary prevention, aspirin has a predominantly immediate antiplatelet effect, as evidenced by the clinical benefit becoming apparent within months after the initiation of therapy, when the statistically significant and clinically important reductions in CVD events become manifest.

The observation of a high probability that the benefits of pravastatin and aspirin are synergistic is intriguing. The additive benefits of pravastatin and aspirin are predicted for the primarily antiatherogenic effect of the former and antiplatelet effect of the latter. With regard to synergy, it is tempting to speculate that the documented anti-inflammatory properties of pravastatin and possibly aspirin may contribute to a finding of greater than additive benefits.

In theory, there are several possible alternative explanations for the observed findings, namely, chance, bias, and confounding. Chance seems unlikely, as the principal findings are highly statistically significant and derived from 2 large-scale trials that randomized and observed 13173 patients for 5 to 6 years and from meta-analyses with more than 73900 patient-years of observation. Bias also seems unlikely, because the data are prospective and there were virtually no losses to follow-up. Furthermore, the possibility of bias is lessened by the uniformly high and equal rates of aspirin use in the pravastatin and placebo groups. Despite the fact that all the trials were randomized for pravastatin use, residual confounding is plausible because the analyses were observational for aspirin use. Several factors, however, render this possibility less likely. First, we controlled for a large number of potential confounding variables. Second, the results were consistent in the analyses of the individual trials and in meta-analyses using 3 different assumptions. Third, the aspirin results were consistent with the most recent findings in the Antithrombotic Trialists’ Collaboration, which included 287 randomized trials of secondary prevention, most with aspirin, involving more than 135000 patients. Fourth, while aspirin use was defined at baseline, 97% of patients were still taking the drug at the end of the trials. Furthermore, the likely effect, if any, of drop-ins would be to dilute the magnitude of observed effects. Fifth, while information was not available on dosage, it is clear from the Antithrombotic Trialists’ Collaboration that the cardiovascular benefits of aspirin are virtually identical across a wide range of daily dosages, from 75 mg to higher than 1800 mg. Despite these and perhaps other limitations, we believe these analyses represent the best evidence on the question of the additive benefits of pravastatin and aspirin on CVD. We further believe that the most plausible interpretation of the findings is that the combination of pravastatin and aspirin is superior to either agent alone, each
of which confers statistically significant and clinically important benefits in the secondary prevention of CVD.

The population that would benefit from combined pravastatin and aspirin is large. In the United States, there are more than 12.4 million patients who have survived a prior CVD event and are candidates for use of statins and aspirin, of whom approximately 3% have a contraindication to pravastatin use and approximately 16% to aspirin use, leaving 10.4 million who would benefit from the combination. With respect to current use patterns, in a nationwide survey of 165,000 patients with CHD and no contraindication or intolerance to statins or aspirin, only 37% were prescribed statins and 77% were prescribed aspirin at discharge. Viewed in the context of their underuse, the data herein demonstrating additive benefits of pravastatin and aspirin to decrease risks of CVD in secondary prevention suggest that simply increasing use of the combination to the current level of aspirin use would avoid tens of thousands of premature deaths in the United States each year alone.

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REFERENCES


