Influence of Pravastatin and Plasma Lipids on Clinical Events in the West of Scotland Coronary Prevention Study (WOSCOPS)

West of Scotland Coronary Prevention Study Group

**Background**—The West of Scotland Coronary Prevention Study was a primary prevention trial that demonstrated the effectiveness of pravastatin (40 mg/d) in reducing morbidity and mortality from coronary heart disease (CHD) in moderately hypercholesterolemic men. The present analysis examines the extent to which differences in LDL and other plasma lipids both at baseline and on treatment influenced CHD risk reduction.

**Methods and Results**—Relationships between baseline lipid concentrations and incidence of all cardiovascular events and between on-treatment lipid concentrations and risk reduction in patients taking pravastatin were examined by use of Cox regression models and by division of the cohort into quintiles. Variation in plasma lipids at baseline did not influence the relative risk reduction generated by pravastatin therapy. Fall in LDL level in the pravastatin-treated group did not correlate with CHD risk reduction in multivariate regression. Furthermore, maximum benefit of an \( \approx 45\% \) risk reduction was observed in the middle quintile of LDL reduction (mean 24% fall); further mean decrements in LDL (up to 39%) were not associated with a greater decrease in CHD risk. Comparison of event rates between placebo- and pravastatin-treated subjects with the same LDL cholesterol level provided evidence for an apparent treatment effect that was independent of LDL.

**Conclusions**—We conclude that the treatment effect of 40 mg/d of pravastatin is proportionally the same regardless of baseline lipid phenotype. There is no CHD risk reduction unless LDL levels are reduced, but a fall in the range of 24% is sufficient to produce the full benefit in patients taking this dose of pravastatin. LDL reduction alone does not appear to account entirely for the benefits of pravastatin therapy. (Circulation. 1998;97:1440-1445.)

**Key Words:** cholesterol □ coronary disease □ risk factors

Clinical trials testing the “lipid hypothesis,” that lowering plasma cholesterol leads to decreased risk of CHD, were first conducted in the 1970s and 1980s. Results were generally positive and led with increasing conviction to the conclusion that MI could be prevented by lipid-lowering therapy. However, definitive proof that such treatment could reduce cardiovascular mortality and improve overall survival was not forthcoming until the recent publication of landmark studies in primary and secondary prevention. These trials used a new class of hypolipidemic agents, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (reductase inhibitors), which reduce plasma LDL by activating specific lipoprotein receptors in the liver. Effects on other lipoproteins (VLDL, HDL) are modest, although it is recognized that certain apolipoprotein B–containing particles such as chylomicron remnants, VLDL remnants, and IDLs are catalyzed by the same receptors and may be influenced by the therapy.

**Methods**

The conduct of WOSCOPS has been described in detail in publications explaining the design of the study and its clinical outcomes. The recruits were moderately hypercholesterolemic men 45 to 64 years old who had never had an MI. Their plasma lipid and lipoprotein concentrations (plasma triglyceride, plasma cholesterol, and VLDL, LDL, and HDL cholesterol) were measured according to the Lipid Research Clinics’ protocol in a central laboratory that participated in and met the quality criteria of the Lipid Standardization Program organized by the Centers for Disease Control and Prevention in Atlanta, Ga. Plasma lipids were measured twice during screening, and patients were included in the study if they had an LDL \( \geq 4.0 \) mmol/L (155 mg/dL) on both occasions and \( \geq 4.5 \) mmol/L (174 mg/dL) on one. If LDL exceeded 6.0 mmol/L (232 mg/dL) at both screening visits, the patient was excluded. Men were randomized to receive placebo or pravastatin 40 mg/d, and subsequent visits were conducted every 3 months. Fasting lipid profiles were obtained in LDL cholesterol and in HDL, respectively. In the present report, analysis of the WOSCOPS was undertaken to ascertain to what extent variations in baseline lipids and in plasma lipid levels during pravastatin treatment influenced outcome. The hypothesis was that benefit would be related principally to LDL reduction.
Comparison of CHD Risk in Placebo and Pravastatin Subjects With the Same LDL Cholesterol Level

Because this analysis involved both treatment arms of the study, compliance (rather than any LDL change) was the criterion used to identify adherence to the protocol. To be included in the overlap analysis, patients in both groups had to be >75% compliant (based on visit attendance and issue of study medication) and not have had an event in the first 6 months of follow-up. Investigation of the LDL cholesterol distribution in the placebo and pravastatin cohorts revealed that the region of 3.62 to 4.65 mmol/L (140 to 180 mg/dL) included substantial numbers of subjects in each treatment group who had overlapping LDL values (1071 receiving pravastatin and 1120 receiving placebo) throughout the treatment phase of the study. Risk of any cardiovascular event in these two groups was compared first by a log-rank test and then by a hierarchy of three Cox models. In the first, on-treatment LDL cholesterol was forced into a model even though it was not a significant predictor of risk (model A). In the second (model B), in addition to on-treatment LDL, baseline covariates were entered if they were significant at the $P = .05$ level and remained so during stepwise regression. Covariates were as stated before but excluded diabetes because an insufficient number of patients in this group suffered from the disorder and included a composite variable of self-reported angina or nitrate consumption as well as baseline lipid levels. In the third (model C), on-treatment values for plasma triglyceride and VLDL and HDL cholesterol levels were forced into model B. The effect of narrowing the overlap region to 3.88 to 4.39 mmol/L (150 to 170 mg/dL) was also tested. In this range, mean LDL cholesterol was virtually the same in the two treatment groups.

Comparison of Observed Event Rates Versus Those Predicted From the Framingham Risk Model

The equation published by the Framingham investigators permits calculation of the risk of a CHD event on the basis of sex, age, plasma cholesterol, HDL cholesterol, smoking habit, systolic blood pressure, and presence of diabetes. This model was used as a further approach to test the hypothesis that the event reduction seen in patients taking pravastatin could not be explained entirely by changes in plasma lipid levels. To generate compatibility with the Framingham coronary event definition, the end point was taken as definite nonfatal MI or CHD death plus revascularization (PTCA and CABG). Again, patients were omitted from the analysis if they had experienced a coronary event, had cancer, or had undergone angiography within 6 months of randomization. Men with preexisting vascular disease (self-reported angina, claudication, stroke, transient ischemic attack, or use of nitrates) were excluded. To be included, patients had to fall into the ranges of plasma cholesterol (4.13 to $7.23$ mmol/L; 160 to $280$ mg/dL) and blood pressure (diastolic, 70 to $105$ mm Hg; systolic, 110 to $170$ mm Hg) that characterized the Framingham population from which the risk equation was derived. They also had to comply with the treatment regimen (as described above). Risk was estimated from the point at which on-treatment lipid levels were available (6 months after randomization) over the remaining period of the trial (4.4 years, because the mean total length of follow-up was 4.9 years). Predicted event rates were derived for each patient by use of the mean (with separate evaluation was undertaken in which the mean of measured lipid values only was calculated and used as the on-treatment level. Associations between percent or absolute LDL fall as a continuous variable and risk reduction for the all-cardiovascular-event end point in the pravastatin group were sought by use of Cox regression models with and without adjustment for the baseline covariates (noted above). Because the hypothesis to be tested was that reduction in LDL was associated with decrease in risk, only subjects with a nominal >5% reduction from baseline in mean LDL were included (n = 2642). Similar analyses were performed for absolute change in HDL cholesterol and plasma triglyceride levels.
imputation when necessary) on-treatment level for plasma cholesterol and HDL cholesterol. After patients were grouped into quintiles of predicted risk, a Kaplan-Meier 4.4-year risk of an event was determined from the observed outcomes for each quintile. The numbers of predicted and observed events across the quintiles were compared for placebo and pravastatin groups by a $z$-score test. A total of 1251 patients in the placebo group and 1803 patients in the pravastatin group met the inclusion criteria for this analysis. The comparison of predicted versus observed risk was repeated without the restrictions on plasma lipids and blood pressure, the compliance threshold, or preexisting vascular disease but with a requirement that subjects taking pravastatin had a $>5\%$ reduction in LDL during treatment. In this instance, 3293 men taking placebo and 2605 men taking pravastatin were included in the analysis.

### Results

#### Baseline Lipids and CHD Risk

Patients were divided into quintiles of baseline lipid level (LDL cholesterol, HDL cholesterol, and triglyceride), each of which was related separately to the event rates observed in the placebo and pravastatin groups (Fig 1). Baseline LDL cholesterol was a weak predictor of risk in both groups (Table). Individuals in the top quintile of the placebo group experienced a rate for the all-cardiovascular-event end point of $12\%$ per 5 years compared with $9\%$ in the bottom quintile (Fig 1A). The proportionate reduction in risk of an event was similar across all quintiles in patients taking pravastatin. Baseline HDL cholesterol exhibited a clear negative association with event rate (Fig 1B) and was a major predictor of CHD risk in both treatment arms of the study. Again, the RR reduction was similar for all quintiles of this lipid fraction. The plasma triglyceride level at baseline was positively related to the risk of CHD (Fig 1C). Patients receiving placebo who had a baseline triglyceride level of $2.3 \text{ mmol/L (204 mg/dL)}$ had almost twice the event rate of patients with an initial triglyceride level of $1.2 \text{ mmol/L (106 mg/dL)}$ despite having similar baseline LDL levels (mean of $5.0 \text{ mmol/L (194 mg/dL)}$ in all quintiles of plasma triglyceride). On the basis of univariate analysis, the starting triglyceride value was a highly significant predictor of risk in both groups (Table). In line with previous observations, inclusion of baseline HDL in multivariate models led to a loss of significance of baseline plasma triglyceride as a predictor.

#### Pravastatin-Induced Changes in Plasma Lipids and CHD Risk

The percentage fall in LDL cholesterol during treatment varied (Fig 2) even in patients who complied with the treatment regimen (ie, they attended and had study medication issued on $75\%$ of the scheduled visits, data not shown). When the pravastatin group was divided into quintiles of percentage LDL reduction (based on measured plus imputed values), it was observed that the mean change varied from $0\%$ to $23\%$ (Fig 2A) and the absolute change from $0.0$ to $20.0$ mmol/L (10 mg/dL).

### Plasma Lipids as Univariate Predictors of CHD Risk in WOSCOPS

<table>
<thead>
<tr>
<th>Variable (Change)</th>
<th>Placebo Group Risk Ratio (CI)</th>
<th>$P$</th>
<th>Pravastatin Risk Ratio (CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LDL (0.5 mmol/L, 20 mg/dL)</td>
<td>1.10 (0.98 1.24)</td>
<td>.12</td>
<td>1.14 (1.00 1.31)</td>
<td>.055</td>
</tr>
<tr>
<td>Baseline HDL (0.25 mmol/L, 10 mg/dL)</td>
<td>0.78 (0.69 0.88)</td>
<td>.0001</td>
<td>0.71 (0.60 0.83)</td>
<td>.0001</td>
</tr>
<tr>
<td>Baseline triglyceride (log, 0.5)</td>
<td>1.23 (1.07 1.42)</td>
<td>.0029</td>
<td>1.23 (1.05 1.44)</td>
<td>.011</td>
</tr>
<tr>
<td>Percent fall LDL (10%)*</td>
<td></td>
<td>.67</td>
<td></td>
<td>.57</td>
</tr>
<tr>
<td>Absolute fall LDL (0.5 mmol/L, 20 mg/dL)</td>
<td>0.93 (0.81 1.08)</td>
<td>.33</td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>Absolute change HDL (0.25 mmol/L, 10 mg/dL)</td>
<td>0.86 (0.65 1.14)</td>
<td>.28</td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>Absolute change triglyceride (log, 0.25)</td>
<td>0.99 (0.86 1.14)</td>
<td>.91</td>
<td></td>
<td>.54</td>
</tr>
</tbody>
</table>

*Analysis carried out in pravastatin group for those with $>5\%$ decrease in LDL.
Figure 2. Relationship between LDL decrease and risk reduction. A, Patients receiving pravastatin were divided into quintiles of percentage decrease in LDL on treatment (with imputed values used where necessary). First 6 months of follow-up were excluded. Kaplan-Meier 4.4-year risks were calculated for each quintile. Bounds for each quintile of LDL change were 1 (+20% to −4%); 2 (−4% to −19%); 3 (−19% to −28%); 4 (−28% to −34%); and 5 (−34% to −57%). Similar results were seen without imputed values. B, Each quintile in A was compared with entire placebo group by a Cox proportional hazards model with adjustment for baseline covariates. RR and 95% CI are shown.

Figure 3. Overlap analysis. Frequency distribution for LDL cholesterol levels on treatment is given as separate histograms for placebo- and pravastatin-treated groups. Values represent mean of two visits in first year of follow-up. Overlap region of 3.62 to 4.65 mmol/L (140 to 180 mg/dL) LDL cholesterol was found to overlap substantially between the placebo and pravastatin groups. Values represent mean of two visits in first year of follow-up. Overlap region of 3.62 to 4.65 mmol/L (140 to 180 mg/dL) LDL cholesterol was found to overlap substantially between the placebo and pravastatin groups. Values represent mean of two visits in first year of follow-up. Overlap region of 3.62 to 4.65 mmol/L (140 to 180 mg/dL) LDL cholesterol was found to overlap substantially between the placebo and pravastatin groups.
Influence of Pravastatin on Clinical Events

![Figure 4. Framingham analysis. Predicted risk over 4.4 years for each subject was derived from Framingham risk equation.17 Subjects were then ranked into quintiles of predicted risk (continuous line), separately for placebo and pravastatin groups, and data were plotted against 4.4-year Kaplan-Meier estimate of an event obtained from observed rates in each quintile (circles). Only patients who fell into range of plasma lipid levels and blood pressure readings seen in Framingham population used to generate risk equation were included in analysis presented here. Overall predicted (pred) and observed (obs) rates were calculated for subjects in each group.

161 mg/dL for placebo- and pravastatin-treated subjects, respectively.

There was remarkable agreement between the observed CHD event rate in the placebo group and the value predicted from the Framingham model (Fig 4A). The predicted overall rate of 7.6 per 100 subjects was close to that observed (7.0 per 100). Treatment with pravastatin reduced total plasma cholesterol values and, as expected, diminished the risk of coronary events over the duration of the study (Fig 4B). However, in contrast to the placebo-treated cohort, those receiving pravastatin exhibited an observed reduction in events that, overall, was significantly (P = .026) greater than that predicted from the Framingham risk equation. According to the Framingham model, the cholesterol reduction that was achieved should have lowered the RR of a coronary event by 24%. In fact, the observed reduction was 35%. A similar result was obtained when the strict criteria for compatibility with the Framingham data set were relaxed, ie, an observed rate of 8.3/100 versus a predicted rate of 8.5/100 in patients receiving placebo (P = .86) and an observed rate of 5.1/100 versus a predicted rate of 6.1/100 in patients receiving pravastatin (P = .029). The elevated event rates in this second analysis reflect the inclusion of patients with higher lipid levels and blood pressure and those with preexisting vascular disease.

Discussion

Analysis of the relationship in WOSCOPS between the pravastatin-induced fall in LDL cholesterol and reduction in CHD risk did not yield the predicted result. On the basis of the earlier findings of the Lipid Research Clinic Coronary Primary Prevention Trial,10 we hypothesized that larger decreases in LDL would be associated with greater benefit. However, no clear, graded relationship was observed between LDL fall and risk reduction with pravastatin. Rather, the full benefit of an ≈45% risk reduction was seen in subjects who had a mean LDL fall in the range of 24%; further decreases in LDL were not associated with larger reduction in CHD risk. The findings of the quintile analysis were confirmed in regression models in which fall in LDL cholesterol failed to be a significant predictor of risk reduction. Attenuation of risk reduction as plasma cholesterol levels fall is to be expected from the curvilinear nature of the relationship between plasma cholesterol and coronary risk.21 Whether this fully explains our current observation is yet to be determined.

It was noteworthy that, in agreement with the 4S study,22 the benefit of therapy was independent of baseline LDL cholesterol and was also unaffected by baseline HDL cholesterol and plasma triglyceride levels. Likewise, as reported previously,16 the proportionate risk reduction during pravastatin treatment was not influenced by age, smoking status, or the signs or symptoms of CHD.

The possibility that treatment had an effect beyond that associated with LDL reduction was investigated by comparing event rates in subjects receiving pravastatin with those receiving placebo who had approximately the same on-treatment LDL cholesterol. In this exploratory analysis it was observed that, within the range of overlap of the two groups, those receiving pravastatin had a lower CHD risk than those receiving placebo. The difference could not be ascribed to an imbalance in the measured baseline risk factors; to changes in HDL cholesterol, plasma triglyceride, and VLDL cholesterol during treatment with pravastatin; or to differing levels of patient compliance. It is recognized that other confounding influences may have been present, but taken at face value, the observation suggests that in WOSCOPS, the influence of pravastatin on CHD risk could not be completely explained by the reduction in LDL cholesterol. Further support for this proposal came from the analysis in which the Framingham risk equation produced a coincidence between predicted and observed coronary event rate in the placebo group but underestimated the benefit of pravastatin therapy by ≈31%.

There are a number of possible explanations for this finding. First, patients in whom LDL cholesterol is reduced to a certain level may experience, at least for a time, a lower risk than those who naturally have an LDL at that concentration. Second, in addition to lowering LDL, pravastatin has been shown to promote the removal of triglyceride-rich remnant particles from the bloodstream.23 These lipoprotein species have been linked to the progression of atherosclerotic lesions,24-26 and their clearance, which is known to occur through receptor-mediated pathways,9 may lead to stabilization of plaques whose rupture would give rise to clinical events. Third, pravastatin may, through pathways not involving lipid lowering, beneficially affect atherosclerosis (eg, by decreasing a tendency for thrombosis).27-28 The latter two possibilities could account for the relatively early benefit seen during pravastatin therapy in WOSCOPS. It is noteworthy that other lipid-lowering therapies that work by stimulating receptor-mediated catabolism of LDL (ie, bile acid sequestrant resins and surgical biliary diversion) did not show an early treatment effect,7,29 although they did provide long-term risk reduction. This difference in response may arise because these therapeutic approaches enhance VLDL production in the liver and do not have the same impact on the plasma concentration of remnants of triglyceride-rich lipoproteins as do reductase inhibitors.30 The results described here are derived from post hoc analysis and therefore must be viewed...
cautiously. Nevertheless, they indicate that the benefit seen with pravastatin treatment, although obviously linked to a decrease in LDL, cannot be explained by this alone.

Appendix

This report was prepared by the publication committee of the West of Scotland Coronary Prevention Study: Christopher J. Packard, DSc, Department of Pathological Biochemistry, Glasgow Royal Infirmary; James Shepherd, FRCP, Department of Pathological Biochemistry, Glasgow Royal Infirmary; Stuart M. Cobbe, FRCP, Department of Medical Cardiology, Glasgow Royal Infirmary; Ian Ford, PhD, Robertson Center for Biostatistics, Database Unit, University of Glasgow; Christopher G. Isles, FRCP, Department of Medicine, Dumfries and Galloway Royal Infirmary; James H. McKillop, FRCP, University Department of Medicine, Glasgow Royal Infirmary; Peter W. Macfarlane, FRSE, Department of Medical Cardiology, Glasgow Royal Infirmary; A. Ross Lorimer, FRCP, Department of Medical Cardiology, Glasgow Royal Infirmary; in collaboration with John Norrie, MSc, Robertson Center for Biostatistics, University of Glasgow. A full list of Study Group members is given in Reference 8.

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References

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