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 the rise 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.
at 6-month intervals during the follow-up period. In this analysis, baseline plasma lipid levels were taken as the mean of the values observed at the two screening visits. As noted in the publication of baseline characteristics, there was no significant difference in any lipid variables between these visits. To provide the most accurate measure of plasma lipid concentration during follow-up, on-treatment lipid values were calculated as the mean of all lipid measurements made after randomization until the patient had an event or reached the end of the study. If a lipid value was missing at a visit but study medication had been issued at the previous visit (3 months earlier), the most recent measurement that had been preceded by a medication issue was carried forward. If before the visit no such on-treatment measurement existed, then the baseline value was imputed. Baseline value was also imputed if no medication had been issued at the previous visit and the present lipid level was missing. Plasma triglyceride concentration was log-transformed.

The end point used in this report is all cardiovascular events, defined as the occurrence of definite or suspected fatal MI, other cardiovascular death, definite or suspected nonfatal MI, or CAGB or PTCA as a first event. This provided ~40% more events than the primary end point and hence enhanced power to detect associations and differences. CAGB and PTCA as separate end points showed similar risk reduction on pravastatin to the primary end point. The relationships described below between plasma lipids and CHD risk based on the all-cardiovascular-events end point were evident also for the primary end point (data not shown).

Baseline Lipids Versus CHD Risk
All 6595 randomized patients were used to calculate quintiles of baseline LDL cholesterol, HDL cholesterol, and plasma triglyceride. The Kaplan-Meier 5-year risk of any cardiovascular event was then determined separately for each quintile of the placebo and pravastatin groups. Baseline lipids as continuous variables were related to risk of any cardiovascular event in the two groups separately by Cox regression11 both univariately and then multivariately with other baseline covariates (as described in Reference 16) to test their independence as predictors. The covariates used in the adjustment were age, smoking, blood pressure, body mass index, family history of premature death from CHD, and nitrate use.

Change in Plasma Lipids and Treatment Effect
Percent change from baseline in LDL cholesterol (based on mean values with imputation as described above) was calculated for the pravastatin group. The Kaplan-Meier 4.4-year risk of any cardiovascular event was determined for each quintile of percent LDL reduction. Each quintile was then compared with the whole placebo group in a Cox model. In these analyses, the first 6 months of follow-up in both groups were excluded, because no on-treatment lipid values were available for patients who had an event before this time had elapsed. The difference between treatments was assessed with adjustment for potential baseline covariate imbalance (covariates as above) and expressed as risk ratios relative to placebo with 95% confidence limits. To determine whether quintiles differed from each other with respect to risk of any cardiovascular event, quintiles 1 through 4 were compared with quintile 5 (highest percent change in LDL) in Cox multivariate models. A similar exercise was undertaken for absolute fall in LDL cholesterol (ie, mean baseline level minus mean on-treatment value). To rule out the possibility that the quintile analysis was biased by the use of imputed values, a 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.

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 6.45 mmol/L (140 to 240 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 investigators17–19 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,17–19 the end point was taken as definite nonfatal MI or CHD death plus revascularization (PTCA and CAGB). 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

Selected Abbreviations and Acronyms
CABG = coronary artery bypass graft surgery
CHD = coronary heart disease
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
RR = relative risk
WOSCOPS = West of Scotland Coronary Prevention Study
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 $\geq 2.3$ mmol/L (204 mg/dL) had almost twice the event rate of patients with an initial triglyceride level of $< 1.2$ mmol/L (106 mg/dL) despite having similar baseline LDL levels (mean of 5.0 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, the 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 $239\%$ (Fig 2A) and the absolute change from 0.0 to $2.3$ mmol/L (90 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>.555</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>0.96 (0.82 1.11)</td>
<td>.57</td>
<td>0.82 (0.65 1.04)</td>
<td>.33</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>0.86 (0.65 1.14)</td>
<td>.28</td>
</tr>
<tr>
<td>Absolute change HDL (0.25 mmol/L, 10 mg/dL)</td>
<td>0.99 (0.86 1.14)</td>
<td>.28</td>
<td>0.82 (0.68 1.00)</td>
<td>.12</td>
</tr>
<tr>
<td>Absolute change triglyceride (log, 0.25)</td>
<td>0.99 (0.86 1.14)</td>
<td>.91</td>
<td>0.82 (0.65 1.04)</td>
<td>.33</td>
</tr>
</tbody>
</table>

*Analysis carried out in pravastatin group for those with $> 5\%$ decrease in LDL.

Figure 1. Baseline lipids and CHD risk. Patients in placebo- and pravastatin-treated groups were divided into quintiles according to mean baseline levels of LDL cholesterol, HDL cholesterol, and plasma triglyceride levels. Kaplan-Meier 5-year estimated event rates were derived for each quintile. Significance of associations for each treatment group are revealed in univariate risk ratios (Table). Solid columns indicate placebo; open columns, pravastatin. To convert mmol/L cholesterol to mg/dL, multiply by 38.7; to convert mmol/L triglyceride to mg/dL, multiply by 88.5.
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. A 34% (CI, 9% to 56%) lower risk (Fig 2B). This revealed that individuals in quintile 1 who achieved no LDL reduction gained no risk reduction. The full benefit in terms of reduction in risk of a cardiovascular event was seen in patients in quintile 3, who had a mean 24% decrease in LDL. No further significant decrement in risk was apparent in those in quintile 5, who experienced a mean 39% LDL decrease (range, 34% to 57% decrease).

When quintiles of absolute reduction in LDL were examined, the relationship with risk was found to be similar to that seen for percent fall. That is, as noted above, RR of any cardiovascular event was similar to placebo in the quintile of least reduction (quintile 1), whereas quintiles 2 through 5 had significant risk reductions, with maximum benefit first present in quintile 3. The mean change from baseline and the RR compared with the placebo group was, for quintile 1, 0.0 mmol/L, RR = 1.06 (CI, 0.81, 1.38); for quintile 2, −0.60 mmol/L (−23 mg/dL), RR = 0.70 (0.50, 0.96); for quintile 3, −1.16 mmol/L (−45 mg/dL), RR = 0.57 (0.41, 0.81); for quintile 4, −1.52 mmol/L (−59 mg/dL), RR = 0.64 (0.47, 0.89); and for quintile 5, −2.01 mmol/L (−78 mg/dL), RR = 0.57 (0.41, 0.78). Pravastatin affected both plasma triglyceride (mean 12% reduction) and HDL cholesterol (mean 7% increase), but neither of these perturbations was associated with change in risk (Table).

Lipid Values and CHD Risk in Pravastatin- and Placebo-Treated Groups

The distribution of mean LDL cholesterol during treatment was found to overlap substantially between the placebo and pravastatin groups (Fig 3), with 2191 patients lying in the interval of 3.62 to 4.65 mmol/L (140 to 180 mg/dL) LDL cholesterol. This provided an opportunity to explore further the relationship between LDL cholesterol and CHD risk in the two treatment arms of the study. Mean LDL cholesterol levels in this interval were 4.38 mmol/L (170 mg/dL) for placebo-treated patients and 4.10 mmol/L (159 mg/dL) for pravastatin-treated patients. Event rates for the two subgroups differed markedly. Pravastatin treatment was associated with a 36% (CI, 9% to 56%) lower risk (P = .014, Fig 3), a finding that did not appear to be due to an imbalance in baseline risk factors or to differences in on-treatment LDL (or on-treatment plasma triglyceride, VLDL cholesterol, or HDL cholesterol). Similar differences were obtained on examination of a narrower 3.88 to 4.39 mmol/L (150 to 170 mg/dL) overlap, a region in which the on-treatment LDL values were virtually equal in the two groups (4.23 versus 4.15 mmol/L [164 versus 159 mg/dL]).
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 $\approx 45\%$ 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 disproportionate 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 $\approx 31\%$.

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,8 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

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