Relationship Between Lipid Levels and Clinical Outcomes in the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Trial

To What Extent Is the Reduction in Coronary Events With Pravastatin Explained by On-Study Lipid Levels?

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Background—The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial showed that pravastatin significantly reduced mortality and coronary heart disease (CHD) events in 9014 patients with known CHD and total cholesterol 4.0 to 7.0 mmol/L at baseline. Secondary objectives included assessment of CHD event reduction according to lipid levels.

Methods and Results—We investigated the relationships of baseline and on-study lipids with subsequent CHD events in separate Cox models. Treatment effect on CHD event reduction was examined by baseline lipids and after adjustment for on-study lipid levels. Baseline lipids were significant predictors of CHD events. The adjusted relative risk per mmol/L (on placebo) was 1.24 (P=0.004) for total cholesterol, 1.28 (P=0.002) for low-density lipoprotein cholesterol, and 0.52 (P=0.004) for high-density lipoprotein cholesterol. Apolipoproteins A1 and B were strong predictors (each P=0.001). Pravastatin reduced the risk of the composite outcome of fatal CHD or nonfatal myocardial infarction by 24% (95% confidence interval [CI], 15% to 32%) and the expanded end point of fatal CHD, nonfatal myocardial infarction, unstable angina, or coronary revascularization by 17% (95% CI, 10% to 24%). Similar relative effects were observed for different categories of baseline lipids. The proportion of treatment effect explained by on-study lipid levels was 67% (95% CI, 27% to 106%) for the composite and 97% (95% CI, 49% to 145%) for the expanded end point. The most important lipids associated with event reduction were apolipoprotein B, low-density lipoprotein cholesterol, and the combination of total and high-density lipoprotein cholesterol.

Conclusions—Changes in lipid levels can explain all or most of the observed benefit of pravastatin. Some treatment effect may also be mediated through nonlipid changes. (Circulation. 2002;105:1162-1169.)

Key Words: lipids ■ coronary disease ■ atherosclerosis ■ apolipoproteins ■ cholesterol

Epidemiological studies have shown a continuous association between the level of cholesterol, particularly low-density lipoprotein (LDL) cholesterol, and the risk of subsequent coronary heart disease (CHD) events, in populations with and without prior CHD.1-3 These data and overviews of cholesterol-lowering trials4-6 provided the rationale for the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial.7 This assessed the effects of cholesterol-lowering treatment with pravastatin in patients with a previous acute coronary syndrome and average baseline cholesterol of 4.0 to 7.0 mmol/L (155 to 271 mg/dL).7 The study reported significant reductions in CHD mortality (24%; 95% confidence interval [CI], 12% to 35%), total mortality (22%; 95% CI, 13% to 31%), and all other prespecified cardiovascular events.

The purpose of this analysis was to assess the following: baseline and on-study lipid levels as independent risk factors for subsequent CHD events, effects of pravastatin on lipid concentrations and on CHD events according to baseline lipid levels, and the proportion of the treatment
Study Design and Patients
In the LIPID study, 9014 patients, aged 31 to 75 years, with a history of acute myocardial infarction (MI) or a diagnosis of unstable angina 3 to 36 months before registration, a baseline plasma total cholesterol 4.0 to 7.0 mmol/L (155 to 271 mg/dL), and fasting triglycerides <5.0 mmol/L (<445 mg/dL) were randomized to 40 mg of pravastatin or matching placebo daily.

Lipid Measurements
Plasma cholesterol levels were measured at baseline (4 weeks before and at randomization), 6 months later, yearly after randomization, and at study end. Fasting high-density lipoprotein (HDL) cholesterol, triglyceride, and apolipoprotein levels were measured at baseline; 1, 3, and 5 years later; and at study end. LDL cholesterol was estimated indirectly using the Friedewald formula. Apolipoproteins A1 and B were measured by the nephelometric method using Behring antibodies.

Clinical Outcomes
The primary study end point of the LIPID trial was death from CHD. Secondary end points included death from any cause, MI, stroke, and coronary revascularization. An adjudication committee blinded to treatment reviewed all deaths, MIs, and strokes. The prespecified primary end point for subgroup analyses was a composite of CHD death and nonfatal MI. An additional analysis used an expanded end point of CHD death, nonfatal MI, hospitalization for unstable angina, and coronary revascularization.

Statistical Methods
The association between baseline lipid levels and subsequent CHD events for patients in each treatment group was assessed in separate multivariate regression analyses using the Cox proportional-hazards model. In addition, in those assigned pravastatin, the association between on-study lipid levels and CHD events was assessed in a Cox model for patients both alive and with an on-study lipid measurement at 12 months. Baseline factors included in these models were age, sex, history of hypertension, diabetes, smoking, stroke or transient ischemic attack, peripheral vascular disease, previous coronary revascularization, stable angina, and qualifying event, based on the risk-factor model developed from LIPID. Lipid concentrations were analyzed as continuous linear variables (for tests of association) and by quartiles of lipid concentrations (for graphical presentation). Measurement error (regression-dilution bias) was adjusted for by regression calibration of lipid levels based on measurement-error variance estimated from repeated lipid observations in the placebo group.

The effects of pravastatin on lipid levels and CHD events were based on intention-to-treat analyses. Variation in treatment effect was assessed according to baseline lipid levels (as continuous linear variables) with tests for interaction in the Cox model.

The PTE explained by on-study lipid parameters, examined in a Cox regression analysis using the landmark method, was estimated as follows:

\[
\text{log hazard ratio for treatment} = \frac{1 - \text{log hazard ratio (effect unadjusted)}}{\text{effect adjusted for lipid parameter}}
\]

All PTE analyses were adjusted for the significant nonlipid risk factors identified in the LIPID risk-factor model and for measurement error, with CIs constructed using the paired bootstrap with 500 replications.

Baseline Lipid Levels and CHD Risk
Baseline lipids were balanced in the treatment groups, although patients assigned to pravastatin had slightly higher triglyceride levels (Table 1).

The association between baseline lipid levels and subsequent CHD events in the placebo group is shown in Figure 1 (unadjusted analysis) and in Table 2. Total cholesterol, LDL cholesterol, and apolipoprotein B were positively associated with CHD events, whereas apolipoprotein A1 and HDL cholesterol were negatively associated.

After adjustment for other risk factors and correction for measurement error, each mmol/L increase in total cholesterol was associated with a 24% higher CHD risk and each mmol/L increase in LDL cholesterol with a 28% higher risk. The total/HDL cholesterol ratio was the strongest predictor of risk (Figure 1) and the only significant lipid factor in a multivariate model. By contrast with the placebo group, there was little association between baseline lipids and CHD events in those assigned pravastatin (Figure 2).

Effects of Pravastatin on Lipid Levels
After 12 months, pravastatin (relative to placebo) reduced plasma total cholesterol by 1.16 mmol/L (20%), calculated LDL cholesterol by 1.09 mmol/L (28%), plasma triglycerides by 0.22 mmol/L (12%), and apolipoprotein B by 0.32 g/L (24%). HDL cholesterol was increased by 0.06 mmol/L (6%) and apolipoprotein A1 by 0.04 g/L (3%) (each P<0.001).
The average differences in total and LDL cholesterol had diminished by 5 years to 16% and 23%, respectively, because of discontinuation of active treatment (from 6% of patients at 12 months to 16% at 5 years) and commencement of open-label cholesterol-lowering treatment for those assigned placebo (from 3% at 12 months to 18% at 5 years).

The effect of pravastatin on cholesterol levels according to baseline cholesterol is shown in Figure 3. Smaller

**TABLE 2. Baseline Lipid Levels and the Risk of Subsequent CHD Death or Nonfatal MI in the Placebo Group (n=4502)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Unadjusted Analysis†</th>
<th>Adjusted Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio* (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>1.12 (1.02–1.23)</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.15 (1.04–1.27)</td>
<td>0.008</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.53 (0.37–0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.07 (0.99–1.66)</td>
<td>0.09</td>
</tr>
<tr>
<td>Apolipoprotein A1, g/L</td>
<td>0.48 (0.34–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>1.64 (1.21–2.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio</td>
<td>1.14 (1.08–1.19)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Relative risk for each unit change in lipid level (mmol/L for total, LDL, and HDL cholesterol, and triglycerides; g/L for apolipoprotein A1 and B).
† Analysis unadjusted (univariate) or adjusted for other nonlipid risk factors plus measurement error.
‡ Only significant lipid parameter in multivariate analysis.
absolute differences in cholesterol levels were seen among patients with lower baseline levels (each \( P < 0.001 \)). However, percentage differences in lipid levels were similar for patients in the highest and lowest quartiles (20% for both groups for total cholesterol, and 30% and 27%, respectively, for LDL cholesterol).

**Treatment Effects of Pravastatin According to Baseline Lipid Levels**

Pravastatin treatment, compared with placebo, was associated with a significant reduction in the composite outcome, CHD death, or nonfatal MI, of 24% (95% CI, 15% to 32%, \( P < 0.001 \)). The treatment effect did not vary significantly according to baseline lipid level (each \( P > 0.10 \)), as illustrated for total and LDL cholesterol in Figure 3. Nor was there significant variation of relative risk for the expanded end point. The absolute risk reduction was larger in patients with higher baseline lipids, who were at higher risk. If a common relative risk reduction is assumed for each quartile, 35 and 28 CHD events were prevented per 1000 patients treated in the highest and lowest quartiles of LDL cholesterol, respectively.
On-Study Lipid Levels and Subsequent CHD Risk (Pravastatin Group)

The associations between lipid levels at 12 months and subsequent CHD events appeared weaker in the group assigned to pravastatin (Figure 4) compared with placebo, but similar after adjustment for other risk factors and measurement error (Table 3). After adjustment, each mmol/L increase in total cholesterol was associated with a 25% higher CHD risk and each mmol/L increase in LDL cholesterol with a 20% increase in CHD risk. Important lipid parameters more strongly associated with CHD event rates were apolipoprotein B and the total/HDL cholesterol ratio. The only lipid

![Figure 4](Image)

**Figure 4.** Average lipid levels to 12 months, grouped by quartile, and subsequent risk of CHD death or nonfatal MI for the pravastatin group. Relative risk of each group (with 95% CIs) is plotted relative to the study average, depicted by the dotted line.

**TABLE 3.** On-Study Lipid Levels at 12 Months and the Risk of Subsequent CHD Death or Nonfatal MI in the Pravastatin Group (n=4386)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Unadjusted Analysis†</th>
<th>Adjusted Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio* (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>1.11 (0.99–1.24)</td>
<td>0.09</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.08 (0.94–1.23)</td>
<td>0.29</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.73 (0.49–1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.11 (1.01–1.21)</td>
<td>0.03</td>
</tr>
<tr>
<td>Apolipoprotein A1, g/L</td>
<td>0.61 (0.39–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>1.49 (1.02–2.17)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol/HDL ratio</td>
<td>1.03 (1.00–1.06)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Relative risk for each unit change in lipid level.
†Analysis unadjusted (univariate) or adjusted for other nonlipid risk factors plus measurement error.
TABLE 4. PTE Explained by Lipid Parameters: for the Composite Outcome (CHD Death or Nonfatal MI) and for the Expanded End Point (CHD Death, Nonfatal MI, Unstable Angina, or Coronary Revascularization)*

<table>
<thead>
<tr>
<th>Lipid Parameters</th>
<th>Risk Reduction, † ‰ (95% CI)</th>
<th>P</th>
<th>PTE, ‰ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD death and nonfatal MI (n=8202)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25 (14–34)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>14 (–1–26)</td>
<td>0.069</td>
<td>48 (9–88)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>13 (–2–26)</td>
<td>0.994</td>
<td>52 (10–94)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>22 (12–32)</td>
<td>&lt;0.001</td>
<td>11 (2–20)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>23 (12–32)</td>
<td>&lt;0.001</td>
<td>9 (1–17)</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>22 (12–32)</td>
<td>&lt;0.001</td>
<td>11 (3–19)</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>9 (–6–22)</td>
<td>0.233</td>
<td>67 (24–110)</td>
</tr>
<tr>
<td>Total cholesterol, HDL</td>
<td>9 (–7–22)</td>
<td>0.267</td>
<td>67 (27–106)</td>
</tr>
<tr>
<td>Expanded end point (n=7613)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17 (10–24)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5 (–5–14)</td>
<td>0.306</td>
<td>72 (28–116)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3 (–7–13)</td>
<td>0.519</td>
<td>82 (34–130)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>16 (8–22)</td>
<td>&lt;0.001</td>
<td>12 (–2–25)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>16 (9–23)</td>
<td>&lt;0.001</td>
<td>8 (–5–21)</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>16 (8–22)</td>
<td>&lt;0.001</td>
<td>11 (–2–24)</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>2 (–7–12)</td>
<td>0.615</td>
<td>87 (40–134)</td>
</tr>
<tr>
<td>Total cholesterol, HDL</td>
<td>1 (–10–11)</td>
<td>0.847</td>
<td>97 (49–145)</td>
</tr>
</tbody>
</table>

*Analyses used data from patients with 1-year measures of all 6 lipid fractions and who did not experience an end point event during the first year. Analyses adjusted for measurement error and other nonlipid baseline risk factors.
†Percentage risk reduction for pravastatin, estimated from the hazard ratio either adjusted for the lipid parameters listed in column 1 or unadjusted (lipid parameters=none).
NA indicates not applicable.

Factors significant in a multivariate analysis of all lipid parameters were total cholesterol (P=0.001) and apolipoprotein A1 (P=0.002)

PTE Explained by On-Study Lipid Levels

Before adjustment for on-study lipid levels, pravastatin treatment was associated with a 25% (95% CI, 14% to 34%) reduction in CHD death or nonfatal MI after 12 months and a 17% (95% CI, 10% to 24%) reduction in the expanded end point. After adjustment for on-study total cholesterol, LDL cholesterol, or apolipoprotein B levels at 1 year, these reductions were no longer significant (Table 4). Consequently, these lipids explain a moderate to large amount of the effect of pravastatin on events. The PTE explained by LDL cholesterol was estimated at 52% for CHD events and 82% for the expanded end point; the PTE explained by apolipoprotein B was estimated at 67% and 87%, respectively, but with wide CIs.

Total and HDL cholesterol together explained the greatest PTE, as follows: 67% for the composite outcome and 97% for the expanded end point. A multivariate analysis considering all lipid parameters simultaneously gave almost identical results, 67% and 96% explained, respectively, whereas the PTEs explained for patients compliant with treatment or placebo at 12 months were 61% and 100%, respectively. Analyses that also adjusted for baseline lipids gave similar results.

Discussion

Lipid Levels and CHD Risk

The association between the usual plasma cholesterol level (and LDL cholesterol) and CHD events in epidemiological data is continuous and curvilinear. However, when plotted on a semilog scale, and after allowing for regression-dilution bias, the data are consistent with a log-linear relationship without a definite threshold level. Overall, a cholesterol level 1 mmol/L lower appears associated over many years with a reduction in CHD risk of ≈40%,13 The hypothesis that a similar benefit of cholesterol lowering might apply to those with lower cholesterol levels (but at higher risk from other factors) as for patients with a higher cholesterol level but at a similar overall risk is now supported by results from large-scale trials.14,15 Our analysis of patients on placebo shows an association between baseline lipids and subsequent CHD events, although it is weaker than seen in long-term epidemiological studies, ie, ≈25% relative reduction in risk for each mmol/L reduction in cholesterol. This may reflect the shorter follow-up period of 6 years and/or the patient selection process.

Effects of Pravastatin Treatment

Pravastatin treatment was associated with a 1.1 mmol/L greater fall in LDL cholesterol and a 0.06 mmol/L greater rise in HDL cholesterol, compared with placebo. These lipid changes and the relative risk reduction for CHD events of 24% are consistent with the association between lipids and CHD events in the placebo group. However, analyses of the West of Scotland Coronary Prevention Study (WOSCOPS) have suggested treatment effects significantly larger than those attributable to lipid changes.16

Summary data from the large-scale trials of statins are consistent with a similar relative treatment effect per unit of absolute change in lipids.14 Within the individual trials in patients with elevated cholesterol levels, the relative effects of treatment were similar for various levels of baseline cholesterol, whereas exploratory analyses of the Cholesterol and Recurrent Events (CARE) trial suggested a possible threshold, with little or no treatment effect with LDL cholesterol below 125 mg/dl (3.2 mmol/L).17

In LIPID, there was no significant variation in the relative treatment effect according to baseline lipid levels. There was a trend to a lower effect for patients in the lowest LDL-cholesterol quartile, but also less LDL cholesterol reduction was achieved in these patients. Consequently, a similar CHD event reduction per absolute change in lipid levels was seen across all quartiles. The effect of treatment has been examined prospectively in the combined data sets of LIPID and CARE.18 This showed a possible interaction, with a smaller relative reduction in CHD events for those with a lower baseline LDL cholesterol. These data are consistent either with a threshold effect, a diminishing benefit of treatment for those with lower baseline lipids, or with the original hypothesis in LIPID that a similar relative reduction in risk might
accompany each unit of change in LDL cholesterol. The recently reported results of the Heart Protection Study substantiate the latter hypothesis by showing similar and significant relative reductions in risk irrespective of baseline lipid levels, even for patients with baseline LDL cholesterol <2.58 mmol/L (100 mg/dL).15

Implications for Therapy
These different explanations point to different treatment recommendations. In the case of a threshold effect, little would be gained by more aggressive therapy for those with low levels. Alternatively, the log-linear model would indicate that, for patients with low baseline lipid levels, a standard dose reduces lipids less and has less effect on reducing coronary events, suggesting that more aggressive treatment may be needed. In either case, treatment would be less cost-effective for patients with low levels.

The importance of lowering LDL cholesterol has been explored indirectly in many trials, which are examining on-study lipid levels and CHD events. In the Lipid Research Clinics trial using cholestyramine19 and the Scandinavian Simvastatin Survival Study,20 CHD event reduction was strongly associated with LDL reduction. In contrast, in the CARE study21 and WOSCOPS,16 provided some LDL lowering occurred, its degree appeared unrelated to the treatment benefit of pravastatin.

In those assigned pravastatin in LIPID, the relationships between on-study lipid levels and CHD events were apparently weaker than for the placebo group, suggesting a lesser role for lipid changes. However, the stronger relationship after adjustment for other risk factors and measurement error points to possible confounding.

PTE Explained by Lipid Levels
The PTE explained by on-study lipid levels provides a less biased measure of the role of lipid changes on CHD events. However, this method is still an indirect comparison and can be statistically unstable, with wide CIs, although this provides a useful indication of the uncertainty inherent in explaining treatment mechanisms. Our PTE estimates are comparable with those reported in CARE, in which 83% of the event reduction could be accounted for by on-study concentrations of LDL and HDL cholesterol and triglycerides.21 However, CARE did not report the wide CIs associated with such an analysis. Consequently, both of our analyses are consistent with all or most of the treatment effect being mediated through lipid levels, but do not rule out non–lipid-mediated effects of treatment.

Although LDL cholesterol appears important in predicting outcomes, other lipids also matter. HDL cholesterol predicted CHD events, and the total/HDL cholesterol ratio was the best single lipid predictor. Moreover, changes in total and HDL cholesterol combined explained a greater PTE than LDL cholesterol alone. The concept that lipid changes in addition to LDL cholesterol may contribute to clinical event reduction is supported by the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial, in which lipid-modifying treatment with gemfibrozil reduced the rate of CHD events but not LDL cholesterol levels.22

Apolipoprotein B level was a stronger predictor of the risk of CHD events than LDL cholesterol and the best single predictor of the PTE explained. This may relate to error in the indirect estimate of LDL cholesterol. Alternatively, because apolipoprotein B signifies the number of lipoprotein particles and indirectly the amount of small, dense LDL cholesterol, it may have important clinical relevance. This is also supported by analyses from the Air Force Texas Coronary Atherosclerosis Prevention Study.23

Mechanisms of Pravastatin Effect
Other potential mechanisms for reduction in CHD events by pravastatin are now well recognized. These pleiotropic effects include ameliorating endothelial dysfunction, stabilizing atherosclerotic plaque, inhibiting inflammatory processes, antioxidant effects, antithrombotic effects, and possible protection for smooth muscle proliferation.24 These may bear on coronary plaque rupture and acute coronary occlusion. Some may be mediated through changes in lipids, and several have been reported for other statins as well.24

The LIPID trial has shown coronary event reduction with pravastatin across a broad spectrum of patients. Treatment effects are consistent with changes in lipid concentrations, but do not exclude other treatment mechanisms. Either way, a strategy of cholesterol treatment for almost all patients with prior CHD should now be considered routinely.

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References


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