Coronary Heart Disease in Patients With Low LDL-Cholesterol

Benefit of Pravastatin in Diabetics and Enhanced Role for HDL-Cholesterol and Triglycerides as Risk Factors

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Background—In two large secondary prevention trials of pravastatin, risk reduction was not significant in participants who had low baseline LDL-C concentrations (that is, <125 mg/dL). We conducted exploratory analyses of participant characteristics, lipid risk factors, and risk reduction in this group.

Methods and Results—Among 13 173 participants with coronary heart disease (CHD), 2607 had baseline LDL-C <125 mg/dL. Those with LDL-C <125 compared with ≥125 mg/dL were more likely to be diabetic (15% versus 9%), hypertensive (46 versus 41%), and male (89% versus 83%); they had higher triglycerides (169 versus 154 mg/dL), lower HDL-C (36.5 versus 38 mg/dL), and similar body mass index (27 kg/m²); and pravastatin lowered their LDL-C by 36 mg/dL (32%) versus 45 mg/dL (29%). During 5.8-year (mean) follow-up, HDL-C and triglycerides were both significantly stronger predictors of recurrent CHD events in participants with LDL-C <125 than ≥125 mg/dL. In diabetic participants with low LDL-C, pravastatin decreased CHD events from 34% to 22% (relative risk, 0.56; 95% CI, 0.37 to 0.83; P = 0.004), significantly different from the effect in nondiabetic participants with low LDL-C (P interaction, 0.005) (event rate, 21%; relative risk, 1.06 [95% CI, 0.89 to 1.27]). There were trends toward risk reduction in smokers and in those with low HDL-C, <40 mg/dL.

Conclusions—Among patients with CHD who have low LDL-C, diabetics have much higher subsequent CHD event rates than do nondiabetics. Pravastatin reduced the event rate in diabetics to that of nondiabetic participants. The results also suggest enhanced therapeutic potential for improving HDL-C and triglycerides in patients with CHD who have low LDL-C concentrations. (Circulation. 2002;105:1424-1428.)

Key Words: cholesterol ■ coronary disease ■ diabetes mellitus ■ lipoproteins ■ drugs

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reating patients with coronary heart disease (CHD) with 3-hydroxy 3-methyl glutaryl coenzyme A reductase inhibitors (statins) prevents coronary events and extends survival.1-3 Relative risk reductions have been consistent across all groups of patients studied and throughout the population ranges of the plasma lipid risk factors total cholesterol, HDL-C, and triglycerides. In a combined analysis of two secondary prevention trials with pravastatin, Cholesterol And Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), only patients with low pretreatment LDL-C (<125 mg/dL) did not show significant risk reduction.4 The two studies included 2607 such participants (20% of the two cohorts). The other large statin trials that have been reported had very few if any participants with pretreatment LDL-C in this range.1,5 We conducted an exploratory analysis of these participants in an attempt to understand their characteristics, the roles of triglycerides and HDL-C as risk factors, and risk reduction by pravastatin treatment in specific patient types.

Methods

This analysis is part of the Prospective Pravastatin Pooling Project,6 initiated in 1992 before completion of any of the constituent trials,
and includes data from the two secondary prevention trials, CARE and LIPID. The design and results of the pooling project and the constituent trials have been published. The studies were approved by institutional review boards, the participants gave their informed consent, and the procedures followed were in accordance with institutional guidelines. CARE and LIPID were similar randomized, double-blind, placebo-controlled trials of 40 mg pravastatin taken once per day. CARE was conducted in the United States and Canada in 4159 men and women 21 to 75 years of age with average lipid levels (baseline LDL-C range, 115 to 174 mg/dL [3.0 to 4.5 mmol/L]) and a myocardial infarction 3 to 20 months before randomization. LIPID was conducted in Australia and New Zealand in 9014 men and women 31 to 75 years of age with a history of myocardial infarction or unstable angina 3 to 36 months before randomization and a wider range of LDL-C than CARE (46 to 274 mg/dL [1.2 to 7.1 mmol/L]). Mean follow-up time was 5 years for CARE and 6 years for LIPID. Study end points were adjudicated blindly with predefined definitions. The primary end point used in this analysis was one used previously to gain power to detect effects in subgroups, namely the compound end point CHD death, nonfatal myocardial infarction, or coronary revascularization (CABG or PTCA). Laboratory methods have been described previously. LDL-C concentration was determined by calculation. Baseline characteristics of participants with LDL-C <125 mg/dL were compared with those with LDL-C ≥125 mg/dL, and significance of differences was assessed by t tests (for continuous factors) and χ² tests (for categorical factors). Changes from baseline to 1 year in LDL-C, HDL-C, and triglycerides were determined, and the effects of pravastatin were compared with placebo.

The interrelations between LDL-C, HDL-C, and triglyceride levels as predictors of risk of CHD events were evaluated in the placebo group by Cox proportional hazards regression, which included as covariates the trial (CARE or LIPID), age, sex, history of hypertension or diabetes, systolic and diastolic blood pressure, smoking status, body mass index, LDL-C, HDL-C, triglycerides, and the interaction terms, LDL-C×HDL-C, LDL-C×triglycerides, and HDL-C×triglycerides. Plasma lipids were analyzed as continuous variables, and for presentation they are divided into quintiles. A backward elimination variable selection procedure was used to determine which 2-way interactions were most strongly associated with events. Separate models were studied that included only one of these interaction terms. We hypothesized that triglycerides would be a stronger predictor of events in participants with low as opposed to average or high LDL-C, as suggested by a previous report.

Exploration of relations between treatment assignment and event-free follow-up in subgroups of participants with LDL-C <125 mg/dL was performed with 2-way tables to estimate event rates and simple proportional hazards regression models that included only treatment group and an indicator of trial (CARE or LIPID). Relative risks and 95% CIs were computed for pravastatin compared with placebo treatment. The subgroups considered were age (<60 years, ≥60 years), sex, history of hypertension, a self-reported history of diabetes, smoking status, body mass index (<27 kg/m², ≥27 kg/m²), LDL-C (<40 mg/dL, ≥40 mg/dL), and triglycerides (<150 mg/dL, ≥150 mg/dL). All analyses were performed on an intention-to-treat basis.

Results
Baseline mean LDL-C was 113±12 mg/dL (range, 46 to 125 mg/dL) and 155±21 mg/dL (range, 125 to 274 mg/dL) in the groups with LDL-C <125 versus ≥125 mg/dL, respectively. Participants with LDL-C <125 compared with ≥125 mg/dL had higher mean triglycerides (169±89 versus 154±69 mg/dL, P<0.0001) and slightly lower mean HDL-C (36.5±10.6 versus 38.0±8.9 mg/dL, P<0.0001); they were more likely to be diabetic (15% versus 9%, P<0.0001), hypertensive (46% versus 41%, P=0.003), and male (89% versus 83%, P<0.0001); they had similar mean body mass index (27 kg/m²), mean age (60 years), current smoking status (11% versus 12%, NS), aspirin use (84% versus 82%, NS), and unstable angina as their qualifying event (26% versus 24%, NS). Among the diabetic participants, 21% to 22% were taking insulin.

In participants with baseline LDL-C <125 mg/dL, pravastatin compared with placebo lowered LDL-C by 36 mg/dL (32%) (P<0.001), raised HDL-C by 2 mg/dL (6%), and lowered triglycerides by 26 mg/dL (14%) (all P<0.001). In those with baseline LDL-C ≥125 mg/dL, pravastatin lowered LDL-C by 45 mg/dL (29%), raised HDL-C by 2 mg/dL (6%), and lowered triglycerides by 21 mg/dL (13%) (all P<0.001).

In participants assigned to placebo, HDL-C and triglycerides had greater predictive values for occurrence of CHD.
events in those with LDL-C <125 mg/dL, than in those with LDL-C ≥125 mg/dL (Figure 1). Tests for interaction between HDL-C and LDL-C and between triglycerides and LDL-C as predictors of events were significant in models in which each interaction was tested individually ($P_{0.0008}$ for HDL-C and LDL-C; $P_{0.005}$ for triglycerides and LDL-C). For a 10-mg/dL increase in HDL-C, the event rate decreased by 29% in participants with LDL-C <125 mg/dL, but by only 10% in those with LDL-C ≥125 mg/dL (results calculated from the data in Figure 1). For a 10-mg/dL increase in triglycerides, the event rate increased by 2.5% in participants with LDL-C <125 mg/dL but only 0.5% in those with LDL-C ≥125 mg/dL. When the two interaction terms, LDL-C×HDL-C and LDL-C×triglycerides, were included together in the multivariate model, LDL-C×HDL-C only was significant ($P_{0.02}$). There was no interaction between HDL-C and triglyceride concentrations and CHD events, indicating that prediction of CHD events by HDL-C is not affected by the triglyceride concentrations, nor vice versa.

Among the subgroups of participants with LDL-C <125 mg/dL, risk reduction with pravastatin was significant only in those with diabetes (Table and Figure 2). In diabetic participants with low LDL-C, pravastatin decreased CHD events during 5.5 years from 34% to 22% (relative risk, 0.56; 95% CI, 0.37 to 0.83, $P_{0.004}$). This risk reduction was significantly different from that in participants without diabetes ($P_{interaction, 0.005}$) (event rate in the placebo group, 21%; relative risk, 1.06 [95% CI, 0.89 to 1.27]). When analysis of treatment effect in diabetic participants with LDL-C <125 mg/dL was restricted to those with fasting glucose >125 mg/dL (n=112 placebo, 115 pravastatin), the relative risk for those assigned to the pravastatin group was 0.59 (0.36 to 0.97).

The characteristics of participants with baseline LDL-C <125 mg/dL who did or did not have diabetes were 12%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Coronary Events/Total Participants (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Pravastin Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td>Age ≥60 y</td>
<td>178/790 (23)</td>
<td>187/788 (24)</td>
</tr>
<tr>
<td>Age &lt;60 y</td>
<td>106/526 (20)</td>
<td>105/503 (21)</td>
</tr>
<tr>
<td>Women</td>
<td>26/170 (15)</td>
<td>30/147 (20)</td>
</tr>
<tr>
<td>Men</td>
<td>258/1146 (23)</td>
<td>262/1144 (23)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>138/549 (25)</td>
<td>158/594 (27)</td>
</tr>
<tr>
<td>No hypertension</td>
<td>146/767 (19)</td>
<td>134/697 (19)</td>
</tr>
<tr>
<td>Smoking</td>
<td>24/123 (20)</td>
<td>40/137 (29)</td>
</tr>
<tr>
<td>Nonsmoking</td>
<td>260/1193 (22)</td>
<td>252/1154 (22)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39/181 (22)</td>
<td>65/189 (34)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>245/1135 (22)</td>
<td>227/1102 (21)</td>
</tr>
<tr>
<td>BMI ≥27 kg/m²</td>
<td>147/612 (24)</td>
<td>154/596 (26)</td>
</tr>
<tr>
<td>BMI &lt;27 kg/m²</td>
<td>136/702 (19)</td>
<td>137/693 (20)</td>
</tr>
<tr>
<td>HDL-C &lt;40 mg/dL</td>
<td>217/945 (23)</td>
<td>240/900 (27)</td>
</tr>
<tr>
<td>HDL-C ≥40 mg/dL</td>
<td>67/371 (18)</td>
<td>52/391 (13)</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
<td>150/638 (25)</td>
<td>159/625 (25)</td>
</tr>
<tr>
<td>Triglycerides &lt;150 mg/dL</td>
<td>124/678 (18)</td>
<td>133/665 (20)</td>
</tr>
</tbody>
</table>

Relative risks and 95% CIs determined by Cox regression analysis. BMI indicates body mass index.

* $P$ for risk reduction in smokers = 0.075; $P$ for a difference in risk reduction (interaction) between smokers and nonsmokers = 0.09.

† $P$ for risk reduction in diabetics = 0.004; $P$ for a difference in risk reduction (interaction) between diabetics and nondiabetics = 0.005.

‡ $P$ for relative risk in HDL-C groups = 0.06; $P$ for a difference in risk reduction (interaction) according to HDL-C concentration analyzed as a continuous variable = 0.06.
versus 11% women, 8% versus 11% smokers, 58% versus 44% with hypertension, 76% versus 85% taking aspirin, and 21% versus 27% with unstable angina as the qualifying event; mean age was 62 versus 60 years, and mean body mass index was 28.5 kg/m² versus 26.9 kg/m²; mean baseline lipids were LDL-C, 113 mg/dL versus 113 mg/dL; HDL-C, 34 mg/dL versus 37 mg/dL; and triglycerides 191 mg/dL versus 165 mg/dL, respectively. Among the diabetic participants, 21% were taking insulin. In the diabetic compared with the nondiabetic participants with baseline LDL-C <125 mg/dL, pravastatin lowered LDL-C by 33 mg/dL (30%) versus 37 mg/dL (32%), raised HDL-C by 0.9 mg/dL (1.6%) versus 2.3 mg/dL (6.5%), and lowered triglycerides by 32 mg/dL (14%) versus 25 mg/dL (14%) (all \( P < 0.001 \), except for HDL-C in diabetics, \( P = 0.17 \)).

There were trends toward risk reduction in cigarette smokers and in participants with low HDL-C (Table); however, tests for interaction were not significant.

**Discussion**

Combined analysis of the CARE and LIPID studies, undertaken to increase power to examine effects in subgroups, had shown significant benefit from pravastatin treatment in all prespecified subgroups of participants with preexisting CHD.\(^4\) However, participants with baseline LDL-C <125 mg/dL, the lowest 20% of the LDL-C range, did not show significant risk reduction.\(^4\) We therefore conducted exploratory analysis in this group. Participants with LDL-C <125 mg/dL compared with those with LDL-C \( \geq 125 \) had greater prevalence of diabetes and hypertension and higher mean triglycerides and lower HDL-C levels. Although each of these differences was small, together they would have contributed to the high rate of recurrent CHD events, 23% over 6 years (similar to the rate of 28% in those with LDL-C \( \geq 125 \) mg/dL), and partially mitigated the protective effect of their low LDL-C levels. These observations underscore the multifactorial risk for CHD.

It is unlikely that baseline differences explain the lack of overall benefit in the group with LDL-C <125 mg/dL compared with those with LDL-C \( \geq 125 \) mg/dL. In the total cohorts of CARE and LIPID, there was no heterogeneity of treatment effects of pravastatin according to presence or absence of diabetes, nor with different levels of triglycerides or HDL-C.\(^2\)–\(^4\) Furthermore, within the group with LDL-C <125 mg/dL, these risk factors were not associated with reduced risk reduction; in fact, participants with diabetes or low HDL-C showed greater risk reduction. Lack of risk reduction may have been due to the lower pretreatment LDL-C itself, the smaller absolute reduction in LDL-C (36 mg/dL in those with baseline LDL <125 mg/dL versus 45 mg/dL in those with baseline LDL \( \geq 125 \) mg/dL), or the lack of sufficient power to examine effects reliably.

HDL-C and triglycerides were stronger predictors of CHD events in participants with low compared with higher LDL-C levels. A similar result has been previously reported for triglycerides and LDL-C.\(^8\) The very small probability value for test of interaction (0.0008 for HDL-C, 0.005 for triglycerides) makes it unlikely that these are chance findings. These interactions may not have been specifically evaluated in other cohorts. The clinical implications are that low HDL-C and high triglyceride levels would have heightened clinical importance in patients with low LDL-C because their effects on risk are stronger in that LDL-C range. By extension, we speculate that raising HDL-C and lowering triglycerides would have greater potential for clinical benefit, expressed both in terms of absolute and relative event reduction, when LDL-C levels are low rather than average or high. This concept could be evaluated by stratified or multivariate analysis of clinical trials of fibrates, niacin, or other classes of drugs being developed.

The findings in patients with diabetes are particularly important because of increasing rates of diabetes in many population surveys and the persistently and substantially elevated CHD risk in diabetes. Diabetic participants with low LDL-C received substantial benefit from pravastatin treatment, as has been previously reported in the total CARE and LIPID populations.\(^4\) CHD events were reduced from 34% to 22%, a relative risk reduction of 44%. We caution that enhanced relative risk reduction for diabetic patients was not a prespecified hypothesis, and it emerged from exploratory analysis of many subgroups. Thus, even with strong probability values for risk reduction and heterogeneity in risk reduction between diabetic and nondiabetic groups, the observation may have been due to chance. Plasma lipid changes overall were not more favorable in diabetic compared with nondiabetic participants. It could be speculated that diabetes renders patients more susceptible to the adverse effects of LDL; that LDL is more atherogenic in diabetic patients than in nondiabetics; or that effects of pravastatin on atherogenic lipoproteins that were not measured or on vascular inflammation could be stronger or more important in diabetic patients. These observations may be pertinent to the initial report of benefit of simvastatin in reducing CHD events in diabetics and other high-risk patients with low baseline LDL-C in the very large Heart Protection Study (American Heart Association Scientific Sessions, November 2001). Current guidelines for CHD prevention for people with diabetes advocate reducing LDL-C to <100 mg/dL regardless of the starting level.\(^10\)\(^11\) This study of the CARE and LIPID trials provides direct evidence in support of such an intensive approach to lipid management in diabetes, at least in those with known CHD.

**Acknowledgments**

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