Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results
Effect of Patient Characteristics on Lovastatin-Induced Changes in Plasma Concentrations of Lipids and Lipoproteins

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Background. Lovastatin produces consistent dose-related reductions in plasma levels of low density lipoprotein (LDL) cholesterol along with variable decreases in triglycerides and increases in high density lipoprotein (HDL) cholesterol. Patient characteristics from the Expanded Clinical Evaluation of Lovastatin (EXCEL) study were examined to determine their association with the magnitude of lovastatin-induced changes in these lipids and lipoproteins.

Methods and Results. After a baseline period consisting of dietary therapy, 8,245 patients with moderate hypercholesterolemia were randomized to five groups that received 48 weeks of treatment with either placebo or daily doses of lovastatin ranging from 20 to 80 mg. By use of linear statistical models, 20 different patient characteristics were examined for modification of the dose-dependent responses observed. For LDL cholesterol, the following were associated with enhanced lowering (p < 0.05; percent changes are placebo-corrected, adjusted mean changes from baseline for the 80-mg/day lovastatin group): full drug compliance (~41.9%) versus 80% compliance (~20.3%); an age of 65 (~43.4%) versus 45 years (~38.1%) for women; white race (~40.9%) versus black race (~38.0%); and 4.5-kg weight gain (~42.6%) versus 4.5-kg weight loss (~37.9%). Similar relations for enhanced triglyceride lowering were found with older age and weight gain. Patients with initially low HDL cholesterol (<0.91 mmol/l) and high triglycerides (>2.26 mmol/l) had enhanced responses for these parameters: placebo-corrected percent changes at 80 mg/day were ~27.4% for triglycerides and +12.3% for HDL cholesterol.

Conclusions. Overall, patient characteristics had very little impact of clinical importance on the dose-dependent LDL cholesterol lowering found with lovastatin. In patients with initially high levels of triglycerides and low levels of HDL cholesterol, the elevation of HDL cholesterol produced by lovastatin appears to be enhanced. (Circulation 1992;85:1293–1303)

Key Words • hypercholesterolemia • lipoproteins • cholesterol

Lovastatin is a specific, competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes the reduction of HMG-CoA to mevalonic acid. The inhibition of this early step in de novo cholesterol synthesis produces a pronounced and consistent dose-related decrease in plasma concentrations of total and low density lipoprotein (LDL) cholesterol.2–9 Less dramatic and inconsistent increases in plasma levels of high density lipoprotein (HDL) cholesterol and reductions in triglycerides have also been observed.2–9 The results of the Expanded Clinical Evaluation of Lovastatin (EXCEL) study, a large, randomized, double-blind, placebo-controlled, multicenter study of lovastatin in 8,245 patients with moderate hypercholesterolemia, have recently been reported.6 Dose-dependent, stable, and statistically significant placebo-corrected decreases from baseline in both LDL cholesterol (24–40%) and triglycerides (14–23%) and increases in HDL cholesterol (4.6–7.5%) were observed.6 In this report, we present the results of analyses undertaken to identify characteristics of patients in the EXCEL study that may be associated with the magnitude of lovastatin-induced changes in lipids and lipoproteins.
Methods

Patients and Study Design

The design of the EXCEL study and characteristics of patients at baseline have been presented in detail elsewhere. Briefly, after a baseline period consisting of a cholesterol-lowering diet alone, patients with moderate hypercholesterolemia (total cholesterol, 6.21–7.76 mmol/l [240–300 mg/dl]; LDL cholesterol, ≥4.14 mmol/l [≥160 mg/dl]; and triglycerides, <3.95 mmol/l [<350 mg/dl]) were randomized into five parallel treatment groups that received lovastatin either 20 mg once daily, 40 mg once daily, 20 mg twice daily, or 40 mg twice daily or matching placebo. Patients were instructed to maintain their cholesterol-lowering diets during the 48-week drug treatment period.

Fasting plasma total cholesterol was analyzed enzymatically by quantification of quinoneimine dye formation after hydrolysis and oxidation. HDL cholesterol was analyzed after precipitation of very low density lipoprotein and LDL with phosphotungstic acid and magnesium chloride and subsequent reaction with cholesterol esterase and cholesterol oxidase. Triglycerides were determined after conversion to free fatty acids and glycerol by absorbance of the reaction of glycerol with glycerol kinase and pyruvate kinase at 340 nm. LDL cholesterol was calculated by the Friedewald equation. A patient’s lipid and lipoprotein profile at baseline was characterized as the average of two measurements in the baseline period; the average of up to four measurements obtained every 12 weeks characterized the treatment period and the resulting change from baseline. For LDL cholesterol, from 90.8% to 92.3% of patients in each treatment group had two measurements that characterized their baseline value, and from 93.8% to 95.5% had two or more measurements that characterized their treatment period average.

The five treatment groups were well balanced at baseline, with an average patient age of 56 years; 59% were men, 92% were white, 29% had preexisting coronary heart disease, and 62% were characterized as high risk by National Cholesterol Education Program guidelines. Average lipid and lipoprotein levels at baseline were 4.65 mmol/l (180 mg/dl) for LDL cholesterol, 1.16 mmol/l (45 mg/dl) for HDL cholesterol, and 1.75 mmol/l (155 mg/dl) for triglycerides.

Statistical Methods

The question addressed was whether or not patient characteristics were associated with a differential response in lovastatin-induced changes in LDL cholesterol, HDL cholesterol, or triglycerides. The patient characteristics included in these analyses are shown in Table 1 and include baseline demographic, medical, biochemical, and health habit descriptors. Treatment observations were also evaluated and included weight change (the average of the last two postrandomization weight measurements minus the baseline measurement), change in self-reported dietary compliance (the shift from baseline to the last reported category on treatment), self-reported study drug com-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Observations</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.8±9.7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>White (%)</td>
<td>91.7</td>
</tr>
<tr>
<td>Black (%)</td>
<td>5.6</td>
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<td>Other (%)</td>
<td>2.7</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Men (%)</td>
<td>58.9</td>
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<tr>
<td>Women (%)</td>
<td>41.1</td>
</tr>
<tr>
<td>Lipids/lipoproteins</td>
<td></td>
</tr>
<tr>
<td>LDLC (mmol/l)</td>
<td>4.65±0.5</td>
</tr>
<tr>
<td>HDLC (mmol/l)</td>
<td>1.16±0.3</td>
</tr>
<tr>
<td>Triglycerides (median) (mmol/l)</td>
<td>1.74</td>
</tr>
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<td>Cigarette smoking</td>
<td></td>
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<tr>
<td>None (%)</td>
<td>44.3</td>
</tr>
<tr>
<td>1–7 drinks/wk (%)</td>
<td>13.7</td>
</tr>
<tr>
<td>&gt;7 drinks/wk (%)</td>
<td>13.7</td>
</tr>
<tr>
<td>Strenuous exercise</td>
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<tr>
<td>None (%)</td>
<td>67.0</td>
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<td>1–2 times/wk (%)</td>
<td>7.4</td>
</tr>
<tr>
<td>&gt;2 times/wk (%)</td>
<td>25.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.0±4.2</td>
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<td>Dietary compliance</td>
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<tr>
<td>&lt;1/2 the time (%)</td>
<td>3.5</td>
</tr>
<tr>
<td>≥1/2 the time (%)</td>
<td>96.5</td>
</tr>
<tr>
<td>Preexisting coronary heart disease (%)</td>
<td>28.7</td>
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<tr>
<td>Hypertension (%)</td>
<td>39.6</td>
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<tr>
<td>Exogenous sex hormone use</td>
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<tr>
<td>Estrogens only (%)</td>
<td>2.9</td>
</tr>
<tr>
<td>Combination or progestogen only (%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Thyroid hormone use (%)</td>
<td>5.3</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>101.9±11.8</td>
</tr>
<tr>
<td>Treatment period observations</td>
<td></td>
</tr>
<tr>
<td>Weight change (lb)</td>
<td>1.3±6.8</td>
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<tr>
<td>Change in dietary compliance</td>
<td></td>
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<tr>
<td>≥ one category worse (%)</td>
<td>28.3</td>
</tr>
<tr>
<td>No change (%)</td>
<td>58.2</td>
</tr>
<tr>
<td>≥ one category better (%)</td>
<td>13.5</td>
</tr>
<tr>
<td>Study drug compliance</td>
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</tr>
<tr>
<td>&lt;50% (%)</td>
<td>0.5</td>
</tr>
<tr>
<td>50–75% (%)</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;75% (%)</td>
<td>99.0</td>
</tr>
<tr>
<td>Fasting at measurement</td>
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<tr>
<td>&lt;50% (%)</td>
<td>0.3</td>
</tr>
<tr>
<td>50–75% (%)</td>
<td>2.4</td>
</tr>
<tr>
<td>&gt;75% (%)</td>
<td>97.3</td>
</tr>
</tbody>
</table>

*All treatment groups are combined; sample sizes vary by characteristic and range from a minimum of 8,222 for baseline observations to a minimum of 7,745 for treatment period observations. LDLC, low density lipoprotein cholesterol; HDLC, high density lipoprotein cholesterol.
pliance (100 minus percentage of study days in which the patient reported taking no tablets), and self-reported fasting at the time of a lipid/lipoprotein measurement (percentage of measurements).

A linear statistical model was developed separately for LDL cholesterol, HDL cholesterol, and triglycerides and was carried out by use of SAS PROC REG. The dependent variable for each was the observed percent change from baseline. Models to assess the effects of patient characteristics (covariates) on lovastatin-induced changes in lipids were developed in a hierarchical fashion. All patient characteristics were initially entered into each model to detect significant covariates by stepwise regression techniques. In addition, 15 two-way interactions between pairs of the following covariates that have been shown to affect lipid/lipoprotein levels were included a priori: age, sex, weight change, exercise, alcohol intake, and smoking. At this initial stage of model development, a value of \( p < 0.05 \) was used to screen for potentially important covariates. Subsequently, interactions of the covariates (two-way for individual covariates and three-way for pairs of covariates) with treatment group were assessed. Blockwise backward elimination of nonsignificant \( (p > 0.05) \) terms was used for model reduction: three-way interactions were tested and eliminated first, then two-way interactions, and finally main effects.

The validity of the models was assessed by standard diagnostic techniques; special modeling techniques were used to cope with multicollinearity in the regressors and influence in the observations. Mean-centered continuous covariates and deviations from means coding for categorical covariates were used in all models. In the LDL cholesterol and HDL cholesterol models, however, the general intercept term and indicator variables for race, treatment, and race-by-treatment interactions led to severe multicollinearity. This was alleviated by elimination of the general intercept term and use of race-specific intercepts and race-specific deviations from means coding for treatment terms ("modular coding"). The models were also refined by use of two alternative approaches to assess robustness of the original models to influential observations (excluding outliers as defined by Cook’s \( D > 99\% \) and weighted least squares by weighting on the number of treatment period lipid/lipoprotein measurements). A final model was thereby obtained that was free of collinearity and robust to influential observations.

Because the main interest of the modeling results was the interaction of patient characteristics with treatment group, only these results are presented in detail. For selected levels of patient characteristics, model estimated means are tabulated for each treatment group. As an index of the differential magnitude of the lovastatin-induced effects associated with various patient characteristics, we refer to the placebo-corrected, adjusted mean percent change for various daily doses of lovastatin. This was defined as the difference in the adjusted mean response in the placebo group from that in the corresponding lovastatin group. Placebo correction was performed to eliminate effects not truly associated with lovastatin treatment (e.g., regression to the mean).

As triglycerides and HDL cholesterol are metabolically related and were found to be significantly correlated in this study \( (r = -0.44 \) at baseline), we also present unadjusted changes observed by stratification on levels of these characteristics to provide additional perspectives on the relations found.

In all, 7,721, 7,569, and 7,737 patients were included in the LDL cholesterol, HDL cholesterol, and triglyceride models, respectively. They represent 92–94% of all patients randomized. Those not included had no treatment-period lipid/lipoprotein measurements or were missing a value for a patient characteristic examined. A detailed description of the statistical modeling procedures is available from the authors.

**Results**

**Variability in Response to Treatment**

The variability in response to lovastatin treatment is shown in Table 2 for LDL cholesterol, triglycerides, and HDL cholesterol. The responses for each of these parameters have previously been shown to have statistically significant, dose-dependent relations that were stable over time. For LDL cholesterol, from 67% of patients at 20 mg daily to 95% of patients at 80 mg daily of lovastatin have a \( >20\% \) decrease from baseline; only 2% of placebo patients had this magnitude of decrease. When no change or an increase from baseline in LDL cholesterol was used as a measure of nonresponse, from 2.8% of patients at 20 mg daily to 0.8% of patients at 80 mg daily were nonresponders; nonresponse was 50.4% for placebo group patients. For triglycerides, the percentage of patients with a \( >30\% \) reduction ranged from 14% at 20 mg daily to 27% at 80 mg daily of lovastatin, whereas 6% of placebo patients showed this degree of response. For HDL cholesterol, from 20% (at 20 mg daily) to 28% (at 80 mg daily) of the lovastatin groups and 10% of the placebo group had a \( >15\% \) increase from baseline in HDL cholesterol. Analyses attempting to explain the variability in response are described below.

**LDL Cholesterol**

Of the total variability in percentage change from baseline in LDL cholesterol, 66% \( (R^2, p < 0.001) \) was explained by the statistical model. Patient characteristics that predicted change in LDL cholesterol uniformly among treatment groups (placebo and lovastatin equally and therefore not associated with a differential treatment effect) included baseline LDL cholesterol level, cigarette smoking, body mass index, preexisting coronary heart disease, and fasting at the time of a lipid measurement. The coefficients for these characteristics predicted only a small degree of change (data not shown). The largest degree of predicted change that was found to be uniform among the treatment groups was attributable to baseline LDL cholesterol. For this characteristic, regression-to-the-mean effects were seen, in that baseline LDL cholesterol levels that deviated 0.26 mmol/l (10 mg/dl) from
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo [% (n)]</th>
<th>20 qpm [% (n)]</th>
<th>40 qpm [% (n)]</th>
<th>20 bid [% (n)]</th>
<th>40 bid [% (n)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL cholesterol (% reduction)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>&gt;60</td>
<td>...</td>
<td>...</td>
<td>0.1 (2)</td>
<td>0.4 (6)</td>
<td>1.2 (19)</td>
</tr>
<tr>
<td>41–60</td>
<td>...</td>
<td>4.0 (62)</td>
<td>15.2 (235)</td>
<td>25.9 (401)</td>
<td>53.3 (826)</td>
</tr>
<tr>
<td>21–40</td>
<td>2.2 (34)</td>
<td>63.3 (979)</td>
<td>69.6 (1,075)</td>
<td>64.4 (996)</td>
<td>41.0 (635)</td>
</tr>
<tr>
<td>0–20</td>
<td>47.4 (738)</td>
<td>29.9 (463)</td>
<td>13.2 (204)</td>
<td>8.0 (124)</td>
<td>3.6 (56)</td>
</tr>
<tr>
<td>No change or increase</td>
<td>50.4 (785)</td>
<td>2.8 (43)</td>
<td>1.9 (29)</td>
<td>1.3 (20)</td>
<td>0.8 (13)</td>
</tr>
<tr>
<td><strong>Triglycerides (% reduction)</strong></td>
<td></td>
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<tr>
<td>&gt;45</td>
<td>1.5 (23)</td>
<td>2.7 (42)</td>
<td>3.7 (57)</td>
<td>4.4 (68)</td>
<td>7.2 (111)</td>
</tr>
<tr>
<td>31–45</td>
<td>4.5 (70)</td>
<td>11.0 (171)</td>
<td>16.3 (252)</td>
<td>17.2 (266)</td>
<td>19.9 (308)</td>
</tr>
<tr>
<td>16–30</td>
<td>15.3 (240)</td>
<td>25.0 (387)</td>
<td>28.4 (439)</td>
<td>29.2 (452)</td>
<td>31.5 (489)</td>
</tr>
<tr>
<td>0–15</td>
<td>22.8 (358)</td>
<td>28.8 (447)</td>
<td>24.5 (379)</td>
<td>24.9 (386)</td>
<td>21.9 (340)</td>
</tr>
<tr>
<td>No change or increase</td>
<td>55.9 (877)</td>
<td>32.4 (502)</td>
<td>27.2 (421)</td>
<td>24.3 (377)</td>
<td>19.5 (303)</td>
</tr>
<tr>
<td><strong>HDL cholesterol (% increase)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>6.4 (101)</td>
<td>12.1 (188)</td>
<td>13.4 (208)</td>
<td>15.0 (232)</td>
<td>17.5 (272)</td>
</tr>
<tr>
<td>16–20</td>
<td>4.0 (62)</td>
<td>8.1 (125)</td>
<td>10.1 (157)</td>
<td>9.0 (140)</td>
<td>10.1 (156)</td>
</tr>
<tr>
<td>11–15</td>
<td>8.9 (139)</td>
<td>14.3 (221)</td>
<td>12.0 (185)</td>
<td>17.7 (274)</td>
<td>14.6 (227)</td>
</tr>
<tr>
<td>6–10</td>
<td>13.8 (217)</td>
<td>16.5 (256)</td>
<td>16.9 (262)</td>
<td>16.7 (258)</td>
<td>19.5 (302)</td>
</tr>
<tr>
<td>0–5</td>
<td>20.6 (323)</td>
<td>20.4 (316)</td>
<td>18.3 (284)</td>
<td>15.9 (246)</td>
<td>14.3 (222)</td>
</tr>
<tr>
<td>No change or decrease</td>
<td>46.3 (725)</td>
<td>28.6 (443)</td>
<td>29.2 (452)</td>
<td>25.8 (399)</td>
<td>24.0 (372)</td>
</tr>
</tbody>
</table>

*Excludes patients who had no treatment-period lipid/lipoprotein measurements; qpm, once daily; bid, twice daily; LDL, low density lipoprotein; HDL, high density lipoprotein.

the mean regressed toward the mean by 1% over the study period.

Characteristics found to predict percent change in LDL cholesterol differentially among treatment groups included study drug compliance, race, weight change, an interaction of age with gender, and an interaction of alcohol consumption with exercise level. Table 3 presents the estimated magnitude of differential responses for these characteristics, which are described below.

Compliance with the study drug regimen 100% of the time was associated with a placebo-corrected, adjusted mean 25.2% decrease in LDL cholesterol for 20 mg/day lovastatin; at 80% compliance, the reduction was 8.2%. The corresponding reductions at 80 mg/day were 41.9% and 20.3% for 100% and 80% compliance, respectively. A substantial portion of the reduction in the effectiveness of lovastatin at 80% compliance was a result of an unexpected 6.9% increase in LDL cholesterol when 100% versus 80% compliant placebo group patients were compared; it should be noted that less than 3% of patients in each treatment group reported <90% compliance with study drug regimen and less than 1% reported <80% compliance.

White patients in the lovastatin treatment groups had a placebo-corrected 2.9% (at 80 mg/day) to 6.3% (at 40 mg once daily) additional lowering in LDL cholesterol relative to blacks (p = 0.005). The black and other-race groups were small in size (n ranged from 75 to 90 for blacks and 35 to 44 for other races in each treatment group), and when hyperinfluential observations (outers) were excluded from the LDL cholesterol model, the additional lowering among white patients relative to blacks was reduced to 0.0% to 2.3% (p = 0.143). No statistically significant differences were found in LDL cholesterol lowering when whites were compared with other races (p = 0.161).

In the placebo group, a 4.5-kg (10-lb) weight gain versus 4.5-kg weight loss was associated with a 6.0% increase in LDL cholesterol. This increase associated with weight gain diminished progressively with increasing dosage of lovastatin: at 20 mg/day a 5.7% increase was seen, whereas at 80 mg/day only a 1.3% increase was seen. Viewed in another way, the placebo-corrected, adjusted mean percent lowering in LDL cholesterol for 80 mg/day lovastatin was greater with weight gain (−42.6%) than with weight loss (−37.9%).

Age interacted with sex in that enhanced lovastatin-induced LDL cholesterol lowering was found among older patients, especially among older women. In the comparison of 65-year-olds with 45-year-olds, a 4.4% (at 20 mg once daily) to 6.3% (at 20 mg twice daily) additional placebo-corrected lowering was found in women, and a 0.4% (at 20 mg twice daily) to 2.0% (at 20 mg once daily) additional lowering was found in men in the lovastatin treatment groups.

The interaction of alcohol consumption with exercise level showed no consistent pattern of enhancement or attenuation of LDL cholesterol lowering in the lovastatin treatment groups.

As the statistical model identified compliance as a substantial contributor to LDL cholesterol response, we
reexamined the percentage of patients who had no change or an increase from baseline in LDL cholesterol (Table 2) that could be explained by a lack of compliance. After patients who were <90% compliant were removed (n=186), the percentage of patients with no change or an increase in LDL cholesterol was reduced only slightly from 2.8% to 2.7% at 20 mg daily and from 0.8% to 0.7% at 80 mg daily. Having failed to identify nonresponse by removing noncompliers, we examined the effect of measurement variability by removing patients who had only a single LDL cholesterol measurement that characterized their treatment period level. This resulted in reduction of the proportion of nonresponders to 2.1% at 20 mg daily and 0.2% at 80 mg daily.

**Triglycerides**

The model for triglycerides explained 22% (p<0.001) of the variability in percentage change from baseline. Patient characteristics that predicted change uniformly among the lovastatin and placebo groups (with no two-way or higher order of interaction) included race, hypertension, body mass index, alcohol consumption, glucose level, study drug compliance, and fasting at the time of a lipid measurement. In general, the effects of these characteristics were relatively small, with the largest effect seen for race (data not shown). Across all treatment groups during the study period, blacks had a 2.9% larger decrease in triglycerides than whites; the other-races group had a 6.0% smaller decrease than whites.

Differential changes in triglycerides between treatment groups (p<0.05) were found for baseline HDL cholesterol, age, weight change, and an interaction of sex with cigarette smoking (Table 4). Details of these interactions follow.

An enhancement of lovastatin-induced triglyceride lowering was found when baseline HDL cholesterol was low. For example, at a baseline HDL cholesterol of 0.91 mmol/l (35 mg/dl), the placebo-corrected, adjusted

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**Table 3. LDL Cholesterol: Adjusted Mean Percent Change From Baseline for Patient Characteristics Showing Treatment Group Interactions**

<table>
<thead>
<tr>
<th>Patient characteristic (probability value)</th>
<th>Placebo [% (SEM)]</th>
<th>20 qpm [% (SEM)]</th>
<th>40 qpm [% (SEM)]</th>
<th>20 bid [% (SEM)]</th>
<th>40 bid [% (SEM)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug compliance (p&lt;0.001, df=4)†</td>
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<td></td>
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<tr>
<td>80%</td>
<td>-6.3 (1.8)</td>
<td>-14.5 (1.5)</td>
<td>-22.1 (1.5)</td>
<td>-25.1 (1.5)</td>
<td>-26.6 (1.6)</td>
</tr>
<tr>
<td>90%</td>
<td>-2.9 (0.9)</td>
<td>-19.5 (0.8)</td>
<td>-26.6 (0.8)</td>
<td>-29.7 (0.7)</td>
<td>-34.0 (0.8)</td>
</tr>
<tr>
<td>100%</td>
<td>+0.6 (0.3)</td>
<td>-24.6 (0.3)</td>
<td>-31.1 (0.3)</td>
<td>-34.2 (0.3)</td>
<td>-41.3 (0.3)</td>
</tr>
<tr>
<td>Race (p=0.005 for white vs. black, df=4; p=0.161 for white vs. other)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>+0.3 (0.3)</td>
<td>-24.1 (0.3)</td>
<td>-30.7 (0.3)</td>
<td>-33.8 (0.3)</td>
<td>-40.6 (0.3)</td>
</tr>
<tr>
<td>Black</td>
<td>-0.9 (1.2)</td>
<td>-21.0 (1.1)</td>
<td>-25.6 (1.2)</td>
<td>-30.4 (1.1)</td>
<td>-38.9 (1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>-1.9 (1.6)</td>
<td>-23.6 (1.6)</td>
<td>-33.0 (1.8)</td>
<td>-32.2 (1.6)</td>
<td>-38.1 (1.7)</td>
</tr>
<tr>
<td>Weight change (p&lt;0.001, df=4)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5-kg (10-lb) loss</td>
<td>-3.3 (0.5)</td>
<td>-27.2 (0.5)</td>
<td>-32.7 (0.6)</td>
<td>-35.8 (0.5)</td>
<td>-41.2 (0.5)</td>
</tr>
<tr>
<td>No change</td>
<td>-0.3 (0.3)</td>
<td>-24.4 (0.3)</td>
<td>-30.8 (0.3)</td>
<td>-33.9 (0.3)</td>
<td>-40.5 (0.3)</td>
</tr>
<tr>
<td>4.5-kg (10-lb) gain</td>
<td>+2.7 (0.5)</td>
<td>-21.5 (0.4)</td>
<td>-28.9 (0.4)</td>
<td>-32.0 (0.4)</td>
<td>-39.9 (0.4)</td>
</tr>
<tr>
<td>Sex/age interaction (p=0.019, df=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 years old</td>
<td>+0.3 (0.5)</td>
<td>-22.8 (0.5)</td>
<td>-29.0 (0.5)</td>
<td>-33.2 (0.5)</td>
<td>-39.3 (0.5)</td>
</tr>
<tr>
<td>65 years old</td>
<td>-0.1 (0.5)</td>
<td>-25.2 (0.5)</td>
<td>-31.1 (0.5)</td>
<td>-34.0 (0.5)</td>
<td>-40.9 (0.5)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 years old</td>
<td>-0.3 (0.9)</td>
<td>-22.0 (0.8)</td>
<td>-28.8 (0.9)</td>
<td>-30.7 (0.9)</td>
<td>-38.4 (0.8)</td>
</tr>
<tr>
<td>65 years old</td>
<td>+0.6 (0.6)</td>
<td>-25.5 (0.6)</td>
<td>-32.7 (0.5)</td>
<td>-36.1 (0.6)</td>
<td>-42.8 (0.6)</td>
</tr>
<tr>
<td>Exercise/alcohol intake interaction (p=0.027, df=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drinks</td>
<td>-0.1 (0.4)</td>
<td>-25.1 (0.4)</td>
<td>-31.4 (0.4)</td>
<td>-33.8 (0.4)</td>
<td>-40.5 (0.4)</td>
</tr>
<tr>
<td>14/wk</td>
<td>+0.5 (0.9)</td>
<td>-21.2 (0.9)</td>
<td>-28.9 (0.9)</td>
<td>-35.4 (0.9)</td>
<td>-40.0 (0.9)</td>
</tr>
<tr>
<td>Exercise ≧3 times/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drinks</td>
<td>+0.1 (0.6)</td>
<td>-22.9 (0.6)</td>
<td>-30.7 (0.6)</td>
<td>-32.3 (0.7)</td>
<td>-40.8 (0.6)</td>
</tr>
<tr>
<td>14/wk</td>
<td>+1.1 (1.1)</td>
<td>-24.8 (1.2)</td>
<td>-27.0 (1.3)</td>
<td>-32.7 (1.1)</td>
<td>-40.2 (1.2)</td>
</tr>
</tbody>
</table>

*Patient characteristics shown are those interacting with treatment group at p<0.05. Patient characteristics not shown here but included in Table 1 did not show a statistically significant treatment group interaction.
†Probability values are for the interaction of the covariates specified with treatment group adjusted for all other covariates in the model. qpm, once daily; bid, twice daily.
mean decrease for lovastatin 80 mg/day was 25.9%; when baseline HDL cholesterol was 1.42 mmol/l (55 mg/dl), the estimated decrease was 21.7%. The magnitude of additional lowering was similar at other dosage levels. Because HDL cholesterol and triglycerides are metabolically related and the statistical model adjusted for baseline levels of triglycerides, HDL cholesterol, and their interaction, we also examined the relation between these variables and change in triglycerides by stratification (Figure 1). With the placebo-corrected, mean percent change (unadjusted) for lovastatin 80 mg/day as the index of response, patients with low baseline triglyceride levels (<1.69 mmol/l; <150 mg/dl) had a 32.3% decrease in triglycerides when their baseline HDL cholesterol level was also low (<0.91 mmol/l; <35 mg/dl) compared with a 20.9% decrease in triglycerides when baseline HDL cholesterol was high (>1.16 mmol/l; >45 mg/dl). The corresponding reductions at 20 mg/day were 22.5% and 11.7%, respectively. The attenuation of lovastatin-induced triglyceride lowering with increasing baseline HDL cholesterol was less marked and inconsistent in subgroups with higher baseline levels of triglycerides.

As with LDL cholesterol, a differential response in triglycerides was seen for age and weight change. Older patients had enhanced triglyceride lowering: a 20-year increase in patient age was associated with a 2.5% (at 20 mg twice daily) to 5.5% (at 20 mg once daily) additional placebo-corrected decrease in triglycerides. Increasing doses of lovastatin attenuated the detrimental effect of weight gain; in the placebo group, a 9-kg increase was associated with a 17.0% increase in triglycerides compared with a 9.5% increase in the lovastatin 80-mg/day group.

The interaction of sex with cigarette smoking produced no consistent pattern of attenuation or enhancement of triglyceride lowering in the lovastatin treatment groups.

**HDL Cholesterol**

The model for HDL cholesterol explained 21% (p<0.001) of the variability in percentage change from baseline. Among the patient characteristics that predicted change uniformly among treatment groups and had no higher order of interaction were sex, preexisting coronary heart disease, glucose level, exercise level, body mass index, cigarette smoking, weight change, dietary compliance at baseline, shift in dietary compliance, and compliance with study drug regimen. The
largest uniform change noted was for sex (increase of 4.6% among women relative to men).

A differential response ($p<0.05$) in the lovastatin-induced increase in HDL cholesterol was found with baseline triglyceride level, race, and an interaction of patient age with alcohol consumption (Table 5). A description of these interactions follows.

An enhancement in the lovastatin-induced increase in HDL cholesterol was found when baseline triglyceride levels were high. For example, at a baseline triglyceride level of 2.82 mmol/l (250 mg/dl), a 5.3% placebo-corrected, adjusted mean increase for lovastatin 20 mg/day was estimated from the model. This increase was reduced to 4.5% when baseline triglycerides were 1.69 mmol/l (150 mg/dl). At 80 mg/day, the corresponding increases were 9.2% and 7.0%, respectively. As previously noted for the triglycerides model, because of the interrelations between triglycerides and HDL cholesterol, we also examined the relation between these variables and change in HDL cholesterol by stratification (Figure 2). With the placebo-corrected, mean percent change for lovastatin 80 mg/day as the index of response, patients with low baseline HDL cholesterol (<0.91 mmol/l; <35 mg/dl) had a 12.3% increase when baseline triglycerides were high (>2.26 mmol/l; >200 mg/dl) and a 7.2% increase when triglycerides were low (<1.69 mmol/l; <150 mg/dl). When baseline HDL cholesterol was high (>1.16 mmol/l; >45 mg/dl), the placebo-corrected, mean percent increase for lovastatin 80 mg/day was 6.9% for patients with high baseline triglyceride levels (>2.26 mmol/l) and 6.0% for patients with low baseline triglyceride levels (<1.69 mmol/l). These relations were consistent at the other dosage levels of lovastatin.

Although an overall treatment group interaction with race for HDL cholesterol was significant ($p=0.035$), treatment interactions in whites versus blacks ($p=0.093$) and other races versus whites ($p=0.071$) were borderline significant. The placebo-corrected, adjusted mean percent change for lovastatin 80 mg/day was +3.3% for blacks, +7.5% for whites, and +11.2% for other races. The results for the black and other-race groups were tenuous because of large 95% confidence bounds on the adjusted mean percent change ($\pm 3\%$ and $\pm 4\%$) as a result of small sample size. In addition, the differences of the other-race group relative to whites diminished ($p=0.224$) when hyperinfluentual observations were excluded from the statistical model.

The interaction of age with alcohol consumption produced no consistent alterations in the lovastatin-induced increase in HDL cholesterol.

**Discussion**

Lovastatin is used as an adjunct to dietary therapy for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (types IIa and IIb) when response to diet and other nonpharmacological measures alone has been inade-
TABLE 5. HDL Cholesterol: Adjusted Mean Percent Change From Baseline for Patient Characteristics Showing Treatment Group Interactions*

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Placebo [ % (SEM)]</th>
<th>20 qpm [ % (SEM)]</th>
<th>40 qpm [ % (SEM)]</th>
<th>20 bid [ % (SEM)]</th>
<th>40 bid [ % (SEM)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline triglycerides† (mmol/l) (p&lt;0.001, df=4)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.69 (150 mg/dl)</td>
<td>+7.2 (0.4)</td>
<td>+11.7 (0.4)</td>
<td>+12.2 (0.4)</td>
<td>+13.2 (0.4)</td>
<td>+14.2 (0.4)</td>
</tr>
<tr>
<td>2.26 (200 mg/dl)</td>
<td>+6.7 (0.4)</td>
<td>+11.6 (0.4)</td>
<td>+11.7 (0.4)</td>
<td>+13.6 (0.4)</td>
<td>+14.8 (0.4)</td>
</tr>
<tr>
<td>2.82 (250 mg/dl)</td>
<td>+6.3 (0.5)</td>
<td>+11.6 (0.5)</td>
<td>+11.3 (0.5)</td>
<td>+13.9 (0.5)</td>
<td>+15.5 (0.5)</td>
</tr>
<tr>
<td>Race (p=0.093 for white vs. black, df=4; p=0.071 for white vs. other, df=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>+1.7 (0.3)</td>
<td>+6.2 (0.3)</td>
<td>+6.7 (0.3)</td>
<td>+8.1 (0.3)</td>
<td>+9.2 (0.3)</td>
</tr>
<tr>
<td>Black</td>
<td>+3.8 (1.4)</td>
<td>+8.2 (1.3)</td>
<td>+6.6 (1.4)</td>
<td>+6.9 (1.3)</td>
<td>+7.1 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>−1.4 (1.8)</td>
<td>+10.7 (1.8)</td>
<td>+6.6 (2.0)</td>
<td>+8.5 (1.8)</td>
<td>+9.8 (2.0)</td>
</tr>
<tr>
<td>Age (yr)/alcoholic intake interaction (p=0.034, df=4) 45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 drinks/wk</td>
<td>+1.3 (0.6)</td>
<td>+6.4 (0.6)</td>
<td>+4.8 (0.6)</td>
<td>+6.8 (0.6)</td>
<td>+7.6 (0.6)</td>
</tr>
<tr>
<td>7 drinks/wk</td>
<td>+2.1 (0.6)</td>
<td>+6.4 (0.6)</td>
<td>+6.6 (0.6)</td>
<td>+8.1 (0.6)</td>
<td>+9.2 (0.6)</td>
</tr>
<tr>
<td>14 drinks/wk</td>
<td>+2.9 (1.1)</td>
<td>+6.4 (1.1)</td>
<td>+8.3 (1.2)</td>
<td>+9.4 (1.2)</td>
<td>+10.8 (1.1)</td>
</tr>
<tr>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 drinks/wk</td>
<td>+1.6 (0.5)</td>
<td>+5.5 (0.5)</td>
<td>+7.4 (0.5)</td>
<td>+8.7 (0.5)</td>
<td>+9.8 (0.5)</td>
</tr>
<tr>
<td>7 drinks/wk</td>
<td>+2.2 (0.5)</td>
<td>+7.6 (0.6)</td>
<td>+8.2 (0.6)</td>
<td>+8.4 (0.6)</td>
<td>+9.9 (0.6)</td>
</tr>
<tr>
<td>14 drinks/wk</td>
<td>+2.9 (1.0)</td>
<td>+9.8 (1.2)</td>
<td>+8.9 (1.2)</td>
<td>+8.2 (1.1)</td>
<td>+10.1 (1.1)</td>
</tr>
</tbody>
</table>

*Patient characteristics shown are those interacting with treatment group at p<0.05. Patient characteristics not shown here but included in Table 1 did not show a statistically significant treatment group interaction.
†Adjusted mean percent change in high density lipoprotein (HDL) cholesterol is estimated at baseline HDL cholesterol level of 0.91 mmol/l (35 mg/dl).
‡Probability values are for the interaction of the covariates specified with treatment group adjusted for all other covariates in the model.

quantified.
The low HDL cholesterol/high triglyceride pattern has been linked with hyperinsulinemia and insulin resistance, truncal obesity, and high coronary artery disease risk. \(^\text{18,19}\) Low HDL cholesterol is not uncommon; in the Framingham offspring cohort, low HDL cholesterol (<0.91 mmol/l; <35 mg/dl) was present in 11.5% of adults, about half as frequent as elevated LDL cholesterol (>4.14 mmol/l; >160 mg/dl). \(^\text{20}\) Although the increase in HDL cholesterol from 6.2% to 12.3% found with 20–80 mg/day of lovastatin for the low HDL cholesterol/high triglyceride subgroup should not influence the type of patient who should receive lovastatin, this effect may provide an additional benefit in patients who are treated with lovastatin to reduce elevated LDL cholesterol.

The finding of an enhanced lovastatin-induced lowering of LDL cholesterol (especially in women) and triglycerides with advancing age is noteworthy, because the attributable risk of cholesterol-associated coronary heart disease also increases with age. \(^\text{21}\) The effect of age appeared to be independent of dose, ranging from 4% to 6% additional lowering in LDL cholesterol among women and from 3% to 6% in triglycerides when 45- and 65-year-old patients are compared. It is not known whether this finding results from age-related differences in the pharmacokinetics of lovastatin or other age-associated factors that influence lipid metabolism. The reason for the slightly smaller lovastatin-induced LDL cholesterol reduction (which was partially explained by hyperinfluential observations) and HDL cholesterol elevation in blacks is also obscure but may have been influenced by their small representation in the overall study.
Lovastatin appeared to attenuate, but not totally reverse, the detrimental effect of weight gain on LDL cholesterol and triglyceride levels. A 9-kg (20-lb) relative weight gain was associated with an estimated 6% increase in LDL cholesterol and 17% increase in triglycerides in the placebo group compared with increases of 5.7% and 15.8%, respectively, in patients who took 20 mg of lovastatin daily. At 80 mg/day, the increases were reduced to 1.3% and 9.5%, respectively. It would be medically inappropriate to suggest a relaxation of recommendations for weight optimization based on these findings, because lipid levels were still adversely affected by weight gain, and obesity has other health consequences.\(^{22}\) The finding of an enhanced overall impact of lovastatin on plasma levels of LDL cholesterol and triglycerides with weight gain may indicate that the effect of lovastatin is greater in the metabolic setting of an overproduction of apolipoprotein B–containing lipoproteins. Grundy and Vega\(^{23}\) have reported plasma LDL cholesterol decreases in response to lovastatin therapy without a dramatic change in the LDL fractional catabolic rate, whereas apolipoprotein B production was decreased. In addition, decreased apolipoprotein B synthesis has been observed with lovastatin treatment in other patients.\(^{24}\) These observations suggest the possibility for an additional mechanism of action of lovastatin besides the increased receptor-mediated catabolism of these particles.

In summary, except for compliance with medication, no patient characteristic was found to substantially modify the dose-dependent LDL cholesterol lowering found withLovastatin. Percentage elevations in HDL cholesterol associated withLovastatin appear to be enhanced when pretreatment levels of HDL cholesterol are low and triglycerides are high. The variations in response toLovastatin that were found suggest the possibility that mechanisms other than receptor-mediated catabolism of apolipoprotein B–containing particles may be involved in the effect of Lovastatin on lipoprotein metabolism.

Acknowledgments

The authors thank the investigators (listed in Reference 10) and patients who made this study possible. We also thank Patience VanderBusch for her editorial assistance during the preparation of the manuscript and Prof. Ronald Helms for advice on statistical analysis approaches.

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