

# Efficacy of Extended-Release Niacin With Lovastatin for Hypercholesterolemia

## Assessing All Reasonable Doses With Innovative Surface Graph Analysis

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**Background:** Combination therapy to improve the total lipid profile may achieve greater coronary risk reductions than lowering low-density lipoprotein cholesterol (LDL-C) alone. A new extended-release niacin (niacin ER)/lovastatin tablet substantially lowers LDL-C, triglyceride, and lipoprotein (a) levels and raises high-density lipoprotein cholesterol (HDL-C) level. We evaluated these serum lipid responses to niacin ER/lovastatin at all clinically reasonable doses.

**Methods:** Men (n = 85) and women (n = 79) with type IIa or IIb primary hyperlipidemia after diet were randomized among 5 parallel treatment arms. Each arm had 5 sequential 4-week treatment periods: niacin ER (starting at 500 mg/d, increasing in 500-mg increments to 2500 mg/d); lovastatin (starting at 10 mg, increasing to 20 mg, then 40 mg/d); and 3 combinations arms, each with a constant lovastatin dose and escalating niacin ER doses.

**Results:** For primary comparisons, mean LDL-C level reductions from baseline were greater with niacin

ER/lovastatin (1500/20 mg) than with lovastatin (20 mg) (35% vs 22%,  $P < .001$ ) and with niacin ER/lovastatin (2000/40 mg) than with lovastatin (40 mg) (46% vs 24%,  $P < .001$ ). Each 500-mg increase in niacin ER, on average, decreased LDL-C levels an additional 4% and increased HDL-C levels 8%. The maximum recommended dose (2000/40 mg/d) increased HDL-C levels 29% and decreased LDL-C levels 46%, triglyceride levels 38%, and lipoprotein(a) levels 14%. All lipid responses were dose dependent and generally additive. Graphs of the dose-response relationships as 3-dimensional surfaces documented the strength and consistency of these responses.

**Conclusions:** Niacin ER/lovastatin combination therapy substantially improves 4 major lipoprotein levels associated with atherosclerotic disease. Dose-response surfaces provide a practical guide for dose selection.

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**D**ESPITE RECENT ADVANCES in prevention and treatment, coronary heart disease (CHD) remains the leading cause of death and disability in the United States.<sup>1</sup> The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are highly effective at lowering low-density lipoprotein cholesterol (LDL-C) level and have lesser effects on high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels. In primary and secondary prevention trials with statin monotherapy, coronary events and strokes were reduced by about one third compared with placebo.<sup>2-7</sup> These major clinical benefits notwithstanding, new therapeutic strategies are clearly warranted to achieve further gains in cardiovascular risk reduction. Convergent lines of epidemiologic and clinical evidence suggest that low HDL-C levels and hypertriglyceridemia are also appropriate targets for intervention.<sup>8-13</sup> Niacin

(nicotinic acid) is the most potent agent available for elevating HDL-C level.<sup>14</sup> It also reduces TG and lipoprotein(a) [Lp(a)] levels but has a lesser effect on LDL-C level. In the Coronary Drug Project, niacin therapy reduced the rate of nonfatal myocardial infarction 27%, stroke 24%, and long-term mortality 11% compared with placebo.<sup>15,16</sup>

The rationale for combination therapy is based on well-established concepts.<sup>17-19</sup> Statins and niacin have complementary effects on the lipid profile and independent mechanisms of action and catabolism and have proven to be safe and effective in long-term studies. It is logical to combine these drugs, with the expectation that effects on clinical events might also be complementary. Recent evidence suggests that this approach may achieve substantial additional risk reductions. In the HDL Atherosclerosis Treatment Study (HATS), simvastatin plus niacin resulted in plaque regression and reductions in cardiovascular events of

60% to 90%, although the study was relatively small (n=160), as were the number of clinical events.<sup>20</sup>

The combination of niacin extended release (niacin ER) with lovastatin is the first prescription dual lipid-altering medication to be approved in the United States. Evaluation of innovative combinations for concurrent management of multiple plasma lipids presents new, challenging requirements. These include study design and data analysis to comprehensively evaluate efficacy and reporting results in a simple and clinically useful format. This report describes the results of a study design testing all clinically reasonable doses of niacin ER/lovastatin and analysis of the dose-response relationships by comparison of selected doses and by surface graphs.

## METHODS

### STUDY DESIGN

This 26-week, multicenter, randomized, double-blind, controlled trial enrolled patients with type IIa or IIb primary hyperlipidemia. All patients underwent a minimum 4-week dietary lead-in/drug washout and 2-week baseline evaluation phase. Patients were randomized to 20-week treatment with niacin ER/lovastatin, niacin ER alone, or lovastatin alone at scheduled escalating doses. Efficacy end points measured changes in serum lipid and lipoprotein levels. Safety was evaluated by clinical symptoms and chemistry studies. Informed consent was required before enrollment. Approval of the protocol by institutional review boards at the 16 sites was obtained.

### PATIENTS

Patients were eligible if they were 21 years or older and had CHD or diabetes and LDL-C level of 130 mg/dL or greater ( $\geq 3.4$  mmol/L); 2 or more CHD risk factors and LDL-C level of 160 mg/dL or greater ( $\geq 4.1$  mmol/L); or less than 2 risk factors but LDL-C level greater than 190 mg/dL ( $> 4.9$  mmol/L).<sup>21</sup> Baseline LDL-C levels needed to be within 12% of each other during 2 qualification visits 10 days or less apart. Baseline TG levels were required to be less than 800 mg/dL ( $< 9.0$  mmol/L). Dyslipidemia medications were withdrawn at least 6 weeks before qualifying lipid determinations. Medications with minor effects on lipoproteins were permitted if the dose remained stable. Vitamins or other preparations containing 30 mg of niacin or more were excluded.

Exclusions included hepatic dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]  $\geq 1.3 \times$  the upper limit of normal [ULN]); renal disease (serum creatinine  $> 1.4$  mg/dL [ $> 123.8$   $\mu$ mol/L]); recent (within 6 months) myocardial infarction, unstable angina, stroke syndrome, or revascularization; congestive heart failure, arterial bleeding, severe hypertension, active peptic ulcer, or gallbladder disease; type 1 or uncontrolled type 2 diabetes mellitus; active gout; substance abuse; and breast-feeding women or women of childbearing potential using inadequate contraception. Concomitant agents with adverse effects on hepatic function, skeletal muscle, or creatine kinase and certain agents metabolized by the cytochrome P-450 enzyme system were prohibited.

### INTERVENTION

Patients were instructed in the National Cholesterol Education Program Step I diet. Compliance with diet and medications was monitored during the 2-week baseline evaluation phase and during the trial. Dietary compliance was assessed by review of 3-day

diet logs at baseline and at weeks 12 and 28 or early termination visit. Compliance with medication regimen was assessed by pill counts at every visit. The 20-week treatment phase consisted of 5 parallel groups: 3 received niacin ER/lovastatin and 2 (active controls) received niacin ER or lovastatin alone. This factorial design tested 23 dose permutations. In each of the 3 combination groups, the lovastatin dose (10, 20, or 40 mg) remained constant, and the niacin ER dose was escalated 500 mg every 4 weeks to a maximum of 2500 mg at week 16. In the niacin ER group, the dose was escalated similarly. In the lovastatin group, the dose was doubled every 8 weeks, from 10 to 40 mg.

All patients took an identical number of tablets daily containing active niacin ER, lovastatin, and/or placebo. Medications were taken at bedtime with a low-fat snack. Aspirin (325 mg) use 30 minutes or less before dosing was permitted to limit flushing. Patients unable to tolerate symptoms during upward titration were withdrawn from the study. Patients were seen at 4-week intervals for dose titrations and assessments.

### ASSESSMENTS

Two primary comparisons were analyzed: mean change in LDL-C level from baseline with niacin ER/lovastatin (1500/20 mg) vs lovastatin (20 mg) alone and mean LDL-C level change with niacin ER/lovastatin (2000/40 mg) vs lovastatin (40 mg) alone. Secondary comparisons included effects on total cholesterol (TC), HDL-C, TG, very low-density lipoprotein cholesterol (VLDL-C), TC-HDL-C ratio, LDL-C-HDL-C ratio, and Lp(a).

All laboratory testing was performed at the Core Laboratory for Clinical Studies, Washington University, St Louis, Mo. Serum LDL-C concentrations were calculated using the Friedewald equation unless TG level exceeded 400 mg/dL (4.5 mmol/L), in which case LDL-C was measured using quantitative ultracentrifugation. High-density lipoprotein cholesterol levels were quantified after dextran sulfate precipitation, and TG and TC levels were measured by enzymatic assays. Very low-density lipoprotein cholesterol level was calculated as TG level divided by 5, and Lp(a) levels were quantified by immunoassay kit (Wako Chemicals USA, Richmond, Va). Cholesterol and TG analyses were referenced to lipid standards of the US Public Health Service Centers for Disease Control, Atlanta, Ga.

At each visit, patients were examined concerning adverse events and serum chemistry tests were performed (ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase, creatine kinase, fasting blood glucose, and uric acid). Elevations in ALT or AST greater than  $3 \times$  ULN that persisted on repeat testing within 1 week led to study withdrawal. Myopathy was defined as myalgia with creatine kinase elevation greater than  $10 \times$  ULN. A physical examination, urinalysis, hematologic profile, prothrombin time, and partial thromboplastin time were conducted at baseline and final visit.

### STATISTICAL AND GRAPHICAL ANALYSES

An estimated sample size of 24 patients per treatment group was required to detect a 9.1% difference in LDL-C level between groups with 80% power and 2-tailed  $\alpha$  level of .05. Categorical safety and efficacy variables were compared using Cochran-Mantel-Haenszel tests, and continuous variables were tested using 2-way analysis of variance. Mean levels of lipids and lipoproteins across visits were compared using repeated-measures analysis; between-group comparisons were done using 2-way analysis of variance model. At each time point, results are reported only for patients successfully titrated to target dose. The proportion of patients successfully titrated to maximum doses was 91% with lovastatin, 77% with niacin ER, and 82% with the combinations. Adverse events were tabulated for each treatment and compared using the  $\chi^2$  or Fisher exact test

**Table 1. Baseline Patient Demographics and Characteristics by Treatment Group\***

| Parameter                      | Niacin ER/Lovastatin,<br>10 mg<br>(n = 34) | Niacin ER/Lovastatin,<br>20 mg<br>(n = 34) | Niacin ER/Lovastatin,<br>40 mg<br>(n = 32) | Niacin ER Only<br>(n = 31) | Lovastatin Only<br>(n = 33) |
|--------------------------------|--|--|--|----------------------------|-----------------------------|
| <b>Demographics</b>            |  |  |  |                            |                             |
| Age, y                         | 59.0 ± 1.85                                | 61.2 ± 1.79                                | 60.1 ± 1.96                                | 58.2 ± 1.96                | 57.7 ± 2.4                  |
| BMI                            | 29.0 ± 0.94                                | 28.3 ± 0.92                                | 30.2 ± 1.47                                | 29.5 ± 1.37                | 28.4 ± 0.62                 |
| Men                            | 17 (50)                                    | 18 (53)                                    | 15 (47)                                    | 17 (55)                    | 18 (55)                     |
| Women                          | 17 (50)                                    | 16 (47)                                    | 17 (53)                                    | 14 (45)                    | 15 (45)                     |
| White                          | 29 (85)                                    | 25 (74)                                    | 27 (84)                                    | 25 (80)                    | 29 (88)                     |
| Black                          | 5 (15)                                     | 7 (21)                                     | 4 (13)                                     | 3 (10)                     | 3 (9)                       |
| Hispanic                       | 0  | 0  | 0  | 1 (3)                      | 0                           |
| Other                          | 0  | 2 (6)                                      | 1 (3)                                      | 2 (6)                      | 1 (3)                       |
| <b>Lipid parameters, mg/dL</b> |  |  |  |                            |                             |
| LDL-C                          | 199.5 ± 7.11                               | 191.4 ± 5.43                               | 204.9 ± 7.65                               | 201.6 ± 6.79               | 195.6 ± 4.59                |
| HDL-C                          | 45.3 ± 2.25                                | 43.2 ± 1.66                                | 45.4 ± 2.22                                | 41.8 ± 1.73                | 45.3 ± 2.00                 |
| TG                             | 187 ± 18.56                                | 177.3 ± 14.64                              | 189.5 ± 13.18                              | 181.9 ± 13.32              | 177.6 ± 13.37               |
| Lp(a)                          | 45.6 ± 8.61                                | 50.0 ± 8.64                                | 36.4 ± 6.14                                | 39.4 ± 7.86                | 46.0 ± 5.82                 |
| <b>No. of CAD risk factors</b> |  |  |  |                            |                             |
| 0                              | 2 (6)                                      | 5 (15)                                     | 4 (13)                                     | 1 (3)                      | 5 (15)                      |
| 1                              | 7 (21)                                     | 5 (15)                                     | 4 (13)                                     | 7 (23)                     | 6 (18)                      |
| 2                              | 14 (41)                                    | 11 (32)                                    | 12 (38)                                    | 11 (35)                    | 13 (39)                     |
| 3                              | 7 (21)                                     | 12 (35)                                    | 8 (25)                                     | 11 (35)                    | 9 (27)                      |
| ≥4                             | 4 (12)                                     | 1 (3)                                      | 4 (13)                                     | 1 (3)                      | 0                           |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CAD, coronary artery disease; ER, extended release; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TG, triglycerides.

SI conversion factors: To convert lipids to millimoles per liter, multiply by 0.0259 for LDL-C and HDL-C and by 0.0113 for TG; to convert Lp(a) to micromoles per liter, multiply by 0.0357.

\*Data are mean ± SE value or number (percentage) of patients.

when 2 or more patients in any group experienced an event. Discontinuation rates and reasons for dropout were analyzed between treatments.

Dose-response relationships for LDL-C, HDL-C, TG, and Lp(a) were analyzed by 3-dimensional graphs using a Microsoft PowerPoint 97 (Microsoft Corp, Redmond, Wash) spreadsheet.

## RESULTS

### BASELINE PATIENT CHARACTERISTICS

Of 299 patients screened, 164 qualified and were randomized. The 5 treatment arms were well-balanced regarding patient demographics and other baseline characteristics (**Table 1**). Mean age was approximately 59 years. There were similar numbers of men and women. About 70% of patients had 2 or more CHD risk factors. Mean baseline levels were 198.5 mg/dL (5.1 mmol/L) for LDL-C, 44.2 mg/dL (1.1 mmol/L) for HDL-C, 182.6 mg/dL (2.1 mmol/L) for TG, and 43.6 mg/dL (1.6 μmol/L) for Lp(a). Compliance with study medication regimens averaged 96% with lovastatin, 92% with niacin ER, and 96% with the combination.

### EFFICACY

For primary comparisons, mean reductions in LDL-C levels were significantly greater with niacin ER/lovastatin (1500/20 mg) (35%) than with lovastatin (20 mg) alone (22%;  $P \leq .001$ ) and significantly greater with niacin ER/lovastatin (2000/40 mg) (46%) than with lovastatin (40 mg) alone (24%;  $P \leq .001$ ; **Table 2**). Niacin ER/lovastatin produced incremental, dose-dependent de-

creases from baseline in LDL-C level from 22% at 500/10 mg/d to 47% at 2500/40 mg/d. These changes were approximately equal to the arithmetic sum of the decreases seen with the individual components. On average, each 500-mg increase in niacin ER dose was associated with an additional 4% decrease in LDL-C level.

For secondary efficacy parameters, increases in mean HDL-C level with niacin ER/lovastatin ranged from 9% at 500/10 mg/d to 33% at 2500/40 mg/d (Table 2). These changes were approximately equal to the arithmetic sum of the increases seen with the individual components, except at higher dose combinations containing niacin ER (2000 mg or 2500 mg), at which the response appeared to reach a plateau. On average, each 500-mg increase in niacin ER dose was associated with an additional 8% increase in HDL-C level. Niacin ER/lovastatin use decreased mean TC level 22% to 34%, TG level 9% to 38%, TC-HDL-C ratio 26% to 48%, and LDL-C-HDL-C ratio 33% to 57% at doses ranging from 500/20 mg/d to 2000/40 mg/d (**Table 3**). The changes in TC, TG, and VLDL-C levels were approximately equal to the sum of changes induced by the individual components. Lipoprotein(a) levels tended to increase slightly at lower doses of lovastatin and niacin ER but generally decreased progressively with niacin ER doses 1000 mg or above, alone or in combination.

The scope of the dose-response relationships for LDL-C, HDL-C, TG, and Lp(a) were analyzed by graphing the dose-response surfaces (**Figure**). For each lipid parameter, the 23 doses tested produced graded changes in serum levels represented by plotting the 23 corresponding responses in 3 dimensions, thus forming a rectangular grid of dose-response lines that delineates a surface. Three surfaces clearly demonstrate the progressive

**Table 2. Percent Change in LDL-C and HDL-C From Baseline With Niacin ER/Lovastatin Use\***

| Niacin ER Dose, mg | Lovastatin Dose, mg |               |               |              |
|--------------------|---------------------|---------------|---------------|--------------|
|                    | 0                   | 10            | 20            | 40           |
|                    | <b>LDL-C</b>        |               |               |              |
| 0                  |                     | -18.9† ± 1.80 | -21.5† ± 2.33 | -24.4 ± 2.41 |
| 500                | -3.3 ± 1.38         | -21.6 ± 1.81  | -29.4 ± 2.07  | -34.7 ± 1.61 |
| 1000               | -6.8 ± 1.92         | -24.7 ± 1.82  | -31.9 ± 2.55  | -37.8 ± 2.52 |
| 1500               | -12.2 ± 2.30        | -31.0 ± 2.08  | -34.9 ± 3.58  | -43.3 ± 2.58 |
| 2000               | -16.2 ± 2.57        | -33.7 ± 2.10  | -38.6 ± 3.42  | -45.6 ± 3.35 |
| 2500               | -19.7 ± 3.70        | -36.3 ± 2.36  | -36.4 ± 4.39  | -46.6 ± 4.48 |
|                    | <b>HDL-C</b>        |               |               |              |
| 0                  |                     | 5.4† ± 2.18   | 6.5† ± 2.43   | 9.5 ± 2.07   |
| 500                | 2.8 ± 1.39          | 8.6 ± 1.90    | 6.6 ± 1.74    | 11.3 ± 2.17  |
| 1000               | 9.9 ± 2.16          | 17.9 ± 3.10   | 17.5 ± 1.99   | 20.7 ± 3.09  |
| 1500               | 18.5 ± 3.60         | 28.0 ± 3.25   | 24.1 ± 3.22   | 26.9 ± 4.46  |
| 2000               | 28.9 ± 3.95         | 30.0 ± 3.66   | 25.3 ± 4.16   | 29.1 ± 4.58  |
| 2500               | 33.1 ± 3.60         | 37.2 ± 3.55   | 28.2 ± 4.74   | 32.9 ± 4.28  |

Abbreviations: ER, extended release; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. \*Data are mean ± SE percent change. Dose titration schedule for niacin ER (in 3 combination arms and alone): 500 mg through week 4, 1000 mg through week 8, 1500 mg through week 12, 2000 mg through week 16, and 2500 mg through week 20. Schedule for lovastatin alone: 10 mg through week 8, 20 mg through week 16, and 40 mg through week 20.

†Weighted average of responses at weeks 4 and 8 for lovastatin (10 mg) alone and at weeks 12 and 16 for lovastatin (20 mg) alone.

**Table 3. Percent Changes in Secondary Lipid Parameters From Baseline\***

| Treatment                   | TC           | TG           | TC/HDL-C     | LDL-C/HDL-C  | VLDL-C       | Lp(a)         |
|-----------------------------|--------------|--------------|--------------|--------------|--------------|---------------|
| Niacin ER/lovastatin, mg/mg |              |              |              |              |              |               |
| 500/20                      | -21.6 ± 1.47 | -9.4 ± 4.60  | -25.9 ± 1.95 | -33.2 ± 2.32 | -9.6 ± 4.60  | 2.9 ± 4.25    |
| 1000/20                     | -23.4 ± 1.87 | -24.1 ± 3.83 | -34.4 ± 2.06 | -41.4 ± 2.72 | -24.2 ± 3.75 | -4.6 ± 4.21   |
| 1000/40                     | -27.7 ± 2.18 | -28.9 ± 4.50 | -39.7 ± 1.93 | -48.1 ± 2.06 | -29.5 ± 4.12 | -6.6 ± 3.74   |
| 2000/40                     | -33.5 ± 3.15 | -37.8 ± 7.43 | -47.5 ± 2.89 | -56.9 ± 2.86 | -38.6 ± 6.79 | -14.3 ± 5.90  |
| 2500/40                     | -35.3 ± 3.88 | -50.6 ± 5.70 | -50.7 ± 3.09 | -59.0 ± 3.52 | -50.6 ± 5.60 | -22.1 ± 4.75  |
| Lovastatin, mg              |              |              |              |              |              |               |
| 20                          | -15.3 ± 1.19 | -8.1 ± 4.69  | -19.4 ± 1.80 | -25.3 ± 2.00 | -7.6 ± 4.90  | 7.1 ± 3.09    |
| 40                          | -18.0 ± 1.84 | -10.5 ± 5.96 | -24.3 ± 2.28 | -30.4 ± 2.67 | -10.7 ± 5.86 | 0.7 ± 3.58    |
| Niacin ER, mg               |              |              |              |              |              |               |
| 500                         | -2.3 ± 0.91  | -2.4 ± 4.84  | -4.8 ± 1.19  | -6.1 ± 1.40  | -2.3 ± 4.86  | 7.4 ± 5.05    |
| 1000                        | -4.8 ± 1.37  | -10.9 ± 5.08 | -12.8 ± 2.27 | -14.7 ± 2.37 | -11.3 ± 5.22 | -2.7 ± 5.08   |
| 2000                        | -11.1 ± 1.63 | -28.6 ± 6.24 | -29.5 ± 2.59 | -33.2 ± 3.21 | -28.6 ± 6.22 | -13.0 ± 10.91 |
| 2500                        | -15.8 ± 2.39 | -45.6 ± 3.57 | -35.4 ± 2.95 | -38.0 ± 3.84 | -45.6 ± 3.64 | -26.3 ± 5.64  |

Abbreviations: ER, extended release; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

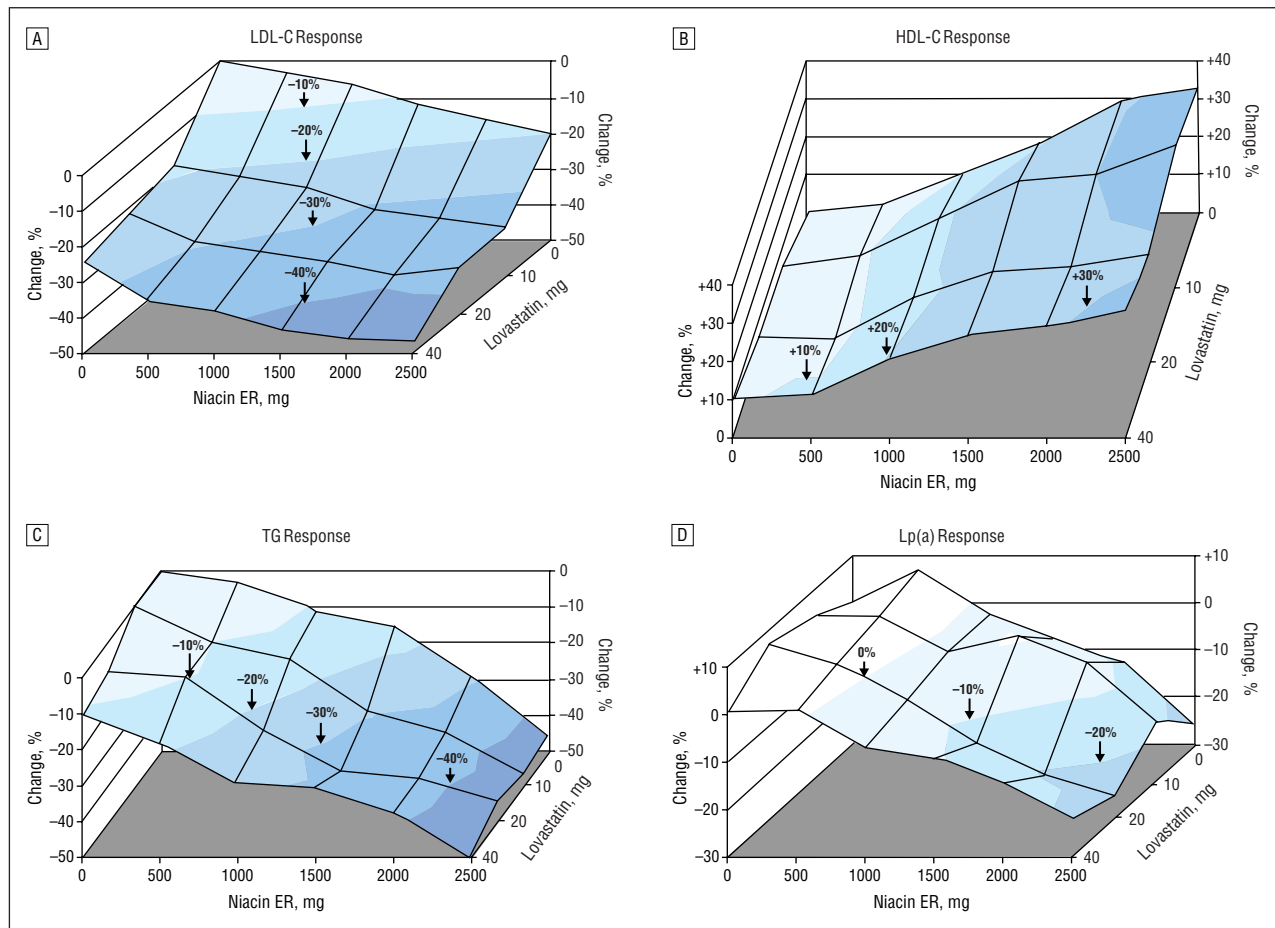
\*Data are mean ± SE percent change.

decreases in LDL-C and TG levels and increases in HDL-C level associated with escalating doses of niacin ER and lovastatin. Only the Lp(a) surface showed a biphasic response because of the small increases observed at the lowest doses. The consistency of the dose-response relationships among 23 doses for each of the 4 lipids documents the overall reliability of the observed effects and enables interpolation of responses for doses not tested.

### SAFETY

Of 164 patients, 35 (21%) discontinued treatment prematurely, 28 (17%) for adverse events. Differences in discontinuation rates in the niacin ER/lovastatin (18%) and niacin ER (23%) treatment arms, compared with the lovastatin group (9%), were due to niacin-related flushing (6% of niacin ER/lovastatin-treated and 10% of niacin ER-treated patients) or other cutaneous reactions such as rash or itching. Overall, 62% of patients treated with any niacin-containing formulation reported flushing, as did 15% of those randomized to lovastatin. Discontinuations for adverse events other than flushing were similar across all treatment groups.

The incidence of adverse events other than flushing, reported by more than 6% of patients, was similar in all 5 treatment groups (Table 4). Four patients receiving niacin ER/lovastatin had reversible increases in AST and/or ALT greater than 3 × ULN; in 3 of these patients, elevations occurred at the highest dose combinations (2500/20 mg or 2500/40 mg). Drug-induced myopathy was not reported. There was a dose-related rise in mean levels of creatine kinase with treatment regimens containing niacin doses greater than 1500 mg/d; however, no patient had an increase greater than 3 × ULN.



Dose-response surfaces for low-density lipoprotein cholesterol (LDL-C) (A); high-density lipoprotein cholesterol (HDL-C) (B); triglycerides (TG) (C); and lipoprotein(a) [Lp(a)] (D). The x-axis presents niacin doses, z-axis presents lovastatin doses, and y-axis presents lipid response as percent mean change in serum concentration from baseline. Each surface is delineated by 4 edges: (1) posterior edge shows responses to niacin extended release (niacin ER) alone; (2) left edge shows responses to lovastatin alone; (3) anterior edge shows responses to combinations of maximum lovastatin dose (40 mg) with escalating doses of niacin ER; and (4) right edge shows responses to combinations of maximum niacin ER dose (2500 mg) with escalating lovastatin doses. Surface interior presents all intermediate responses and is divided by isodose contour lines for niacin ER (parallel to right edge) and lovastatin (parallel to anterior edge), which form a rectilinear grid, with each intersect representing a tested combination. Surface is also subdivided by isoresponse contour boundaries delineating curvilinear zones of decile response (color coded) representing progressive 10% changes in lipid levels. Note that the recommended maximum dose of niacin ER/lovastatin is 2000/40 mg.

Overall, changes from baseline in other serum chemistries were modest and not clinically significant.

#### COMMENT

This study comprehensively evaluated the dose-response relationships of the first combination lipid modifier approved by the Food and Drug Administration using an innovative trial design and surface graph analyses. It tested all clinically reasonable doses in a cohort of patients distributed nationally among multiple clinics. Compliance with study medications was greater than 90%, providing a reasonable measure of efficacy. These procedures meet the requirements of a research model defining the efficacy of 2-drug lipid treatments.

Once-daily treatment with niacin ER/lovastatin resulted in complementary, dose-dependent changes in all lipid parameters tested. Each drug contributed to the lipid effects in different ways, with lovastatin producing a greater effect on LDL-C, and niacin ER producing greater effects on HDL-C, TG, and Lp(a). After 4 weeks of receiving the

maximum recommended dose of 2000 mg (niacin ER)/40 mg (lovastatin), mean levels for LDL-C, TG, and Lp(a) were reduced by 46%, 38%, and 14%, respectively, from baseline, while mean HDL-C level increased 29% from baseline. These results are equivalent to those reported in a prior open-label study, in which after 4 weeks, niacin ER/lovastatin (2000/40 mg/d) was associated with mean LDL-C level reductions of 47%, TG level reductions of 41%, and HDL-C level increases of 30% from baseline,<sup>22</sup> supporting the reliability of the present study. These lipid changes are similar to those associated with coronary plaque regression and reduction of cardiovascular events by 60% to 90% in HATS: LDL-C level was reduced by 46% in the present study vs 42% in HATS; TG level was reduced by 38% vs 36%, and HDL-C level increased 29% vs 26%.<sup>20</sup>

The effects of the individual drugs in combination were generally additive for LDL-C and TG and, except at higher doses, for HDL-C. This latter result may suggest a plateau effect for HDL-C above a niacin ER dose of 2000 mg. The effects of combination treatment were also much greater than those achieved by doubling the lovastatin dose alone.

**Table 4. Treatment-Emergent Adverse Events (Other Than Flushing) Reported by More Than 6% of Patients\***

| Adverse Event                    | Niacin ER/Lovastatin,<br>10 mg<br>(n = 34) | Niacin ER/Lovastatin,<br>20 mg<br>(n = 34) | Niacin ER/Lovastatin,<br>40 mg<br>(n = 32) | Niacin ER Only<br>(n = 31) | Lovastatin Only<br>(n = 33) |
|----------------------------------|--|--|--|----------------------------|-----------------------------|
| Patients with an adverse event   | 15 (44)                                    | 21 (62)                                    | 17 (53)                                    | 21 (68)                    | 17 (52)                     |
| Body as a whole                  | 4 (12)                                     | 8 (24)                                     | 5 (16)                                     | 7 (23)                     | 8 (24)                      |
| Asthenia                         | 3 (9)                                      | 1 (3)                                      | 2 (6)                                      | 2 (6)                      | 3 (9)                       |
| Headache                         | 1 (3)                                      | 1 (3)                                      | 0  | 1 (3)                      | 2 (6)                       |
| Infection                        | 0  | 2 (6)                                      | 0  | 0                          | 1 (3)                       |
| Pain                             | 1 (3)                                      | 2 (6)                                      | 0  | 2 (6)                      | 1 (3)                       |
| Abdominal pain                   | 0  | 3 (9)                                      | 2 (6)                                      | 1 (3)                      | 1 (3)                       |
| Digestive system                 | 3 (9)                                      | 10 (29)                                    | 5 (16)                                     | 10 (32)                    | 4 (12)                      |
| Diarrhea                         | 0  | 4 (12)                                     | 2 (6)                                      | 6 (19)                     | 0                           |
| Dyspepsia                        | 0  | 1 (3)                                      | 1 (3)                                      | 3 (10)                     | 1 (3)                       |
| Nausea                           | 1 (3)                                      | 1 (3)                                      | 2 (6)                                      | 4 (13)                     | 2 (6)                       |
| Vomiting                         | 0  | 0  | 1 (3)                                      | 4 (13)                     | 0                           |
| Metabolic and nutritional system | 4 (12)                                     | 4 (12)                                     | 3 (9)                                      | 3 (10)                     | 2 (6)                       |
| Hyperglycemia                    | 2 (6)                                      | 1 (3)                                      | 0  | 1 (3)                      | 0                           |
| AST and/or ALT >3 × ULN          | 1 (3)                                      | 1 (3)                                      | 2 (6)                                      | 0                          | 0                           |
| Nervous system                   | 4 (12)                                     | 3 (9)                                      | 1 (3)                                      | 1 (3)                      | 1 (3)                       |
| Dizziness                        | 2 (6)                                      | 0  | 0  | 0                          | 0                           |
| Paresthesia                      | 0  | 2 (6)                                      | 0  | 0                          | 0                           |
| Skin and appendages              | 4 (12)                                     | 7 (21)                                     | 5 (16)                                     | 6 (19)                     | 3 (9)                       |
| Pruritus                         | 1 (3)                                      | 3 (9)                                      | 2 (6)                                      | 4 (13)                     | 2 (6)                       |
| Rash                             | 1 (3)                                      | 3 (9)                                      | 2 (6)                                      | 2 (6)                      | 1 (3)                       |
| Urticaria                        | 0  | 3 (9)                                      | 0  | 0                          | 0                           |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ER, extended release; ULN, upper limit of normal.

\*Data are number (percentage) of patients.

The mean reductions in LDL-C levels of 32%, 35%, and 39% at the 1000/20-, 1500/20-, and 2000/20-mg doses, respectively, were significantly greater than the reductions seen with lovastatin (20 mg) (21%) or lovastatin (40 mg) (24%). Doubling the dose of a statin typically results in an additional 6% reduction in LDL-C level.<sup>23</sup> Although the LDL-C responses to 20 mg and 40 mg of lovastatin alone in the present study are on the low side, the difference between them is only 3%; they are consistent with and well within the range of results reported for other dose-ranging studies with this compound.<sup>24,25</sup> In addition, the lovastatin used in this trial has been shown to be bioequivalent to the brand name product.<sup>26</sup> This study also shows that for every 500-mg increase in the dose of niacin ER, LDL-C levels decreased an additional 4%, while HDL-C levels increased by 8%. Lipoprotein(a) levels also decreased progressively with escalating niacin doses of 1000 mg or greater. This study confirms the powerful effects of the combination on 4 parts of the lipid profile.<sup>22,27</sup>

Although this study was not of sufficient size or duration to evaluate safety, discontinuations for adverse events other than for flushing were similar among all treatment groups. Transient increases in liver function tests (>3 × ULN) were observed at the highest niacin ER dose (2500 mg) in 3 of 4 cases, which is higher than the maximum recommended dose in the combination formulation. No clinically significant myopathy was observed. Myopathy and rhabdomyolysis have been reported only rarely with niacin-statin combination therapy.<sup>28,29</sup> Thus, niacin ER/lovastatin at doses of 500/20 to 2000/40 mg was generally well tolerated.

Current opinion favors increasingly intensive lipid management, particularly for secondary prevention and

other high-risk groups.<sup>30</sup> Approximately 75% of patients with CHD who qualify for drug therapy require LDL-C level reductions greater than 30%.<sup>31</sup> Furthermore, most patients with CHD have more than 1 lipid abnormality.<sup>32</sup> While the current National Cholesterol Education Panel guidelines do not make a specific recommendation for treating low levels of HDL-C, 2 recent clinical studies indicate that treatment-induced increases in HDL-C levels favorably affect risk in CHD patients.<sup>13,20</sup> The Veterans Affairs HDL-C Intervention Trial (VA-HIT) provided the first clinical evidence that raising HDL-C and lowering TG levels, in the absence of any change in LDL-C level, was associated with significant reductions in coronary events.<sup>13</sup> Moreover, the substantial (60%-90%) risk reductions observed in HATS approximated the reduction predicted by epidemiologic studies based on the percent decrease in LDL-C level plus the percent increase in HDL-C level.<sup>20</sup> Furthermore, the 25% to 35% reductions in risk in coronary prevention studies with statins, while impressive, point to the need for more aggressive therapies to eliminate more of the residual risk that remains despite lowering LDL-C level (residual risk is two thirds to three quarters of the risk observed in the placebo groups).<sup>2-7</sup> Indeed, in the Heart Protection Study, among simvastatin-treated patients who entered the trial with LDL-C levels lower than 116 mg/dL (<3.0 mmol/L) and who had mean LDL-C levels of 70 mg/dL (1.8 mmol/L) during the study, the 5-year risk of a major vascular event was still 17.6%.<sup>7</sup> This would equate to a 10-year risk of 35%. Our data show that combination therapy with niacin and a statin results in favorable changes in all 4 lipoprotein classes that are independently associated with the risk of developing CHD. Future clinical trials are needed to directly compare combination therapy with

niacin and a statin against statin monotherapy to test the hypothesis that such broad control of dyslipidemia will result in greater reductions in coronary risk and will cause regression of arterial lesions of atherosclerosis.

Although clinicians are familiar with combination therapy for the management of hypertension, they are less familiar with its use in the management of dyslipidemia.<sup>33</sup> The dose-response surfaces provide unique documentation for enhanced understanding and clinical application of combination treatment for patients with multiple lipid abnormalities. Notably, the study's significant primary end points are contained in the dose-response surface for LDL-C. The surfaces concisely illustrate the continuous and uniform effects achieved by escalating doses of niacin ER and lovastatin. This is not clearly evident with conventional dose-response graphs in 2 dimensions, which require the reader to mentally synthesize the relationships that may exist between individual lines. The surfaces also facilitate the simultaneous comparison of treatment effects on all 4 lipid parameters. For the practicing clinician, the dose-response surfaces may be helpful to select and monitor treatment. After identifying a patient's treatment goals for LDL-C, HDL-C, TG, and, in selected cases, Lp(a) levels, the surfaces can be examined to select the most appropriate dose to achieve these multiple lipid targets. During treatment, the surfaces may aid in identifying the poorly adherent or biologically non-responsive patient by comparing the actual responses of 4 lipids with the expected responses.

In summary, niacin ER/lovastatin in a dual-component, single tablet has substantial and consistent dose-related efficacy on 4 major lipoprotein classes associated with atherosclerosis. Its lipid effects are expected to cause significant reductions in atherosclerotic morbidity and mortality.

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