Extended-Release Niacin vs Gemfibrozil for the Treatment of Low Levels of High-Density Lipoprotein Cholesterol

John R. Guyton, MD; Michael A. Blazing, MD; James Hagar, MD; Moti L. Kashyap, MD; Robert H. Knopp, MD; James M. McKenney, PharmD; David T. Nash, MD; Stephen D. Nash, MD; for the Niaspan-Gemfibrozil Study Group

Objective: To provide a direct comparison of agents that raise plasma levels of high-density lipoprotein cholesterol (HDL-C) to help devise strategies for coronary risk reduction.

Methods: In a multicenter, randomized, double-blind trial, we compared the effects of extended-release niacin (Niaspan), at doses increased sequentially from 1000 to 2000 mg at bedtime, with those of gemfibrozil, 600 mg given twice daily, in raising low levels of HDL-C. Enrollment criteria included an HDL-C level of 1.03 mmol/L or less (≤40 mg/dL), a low-density lipoprotein cholesterol level of 4.14 mmol/L or less (≤160 mg/dL) or less than 3.36 mmol/L (<130 mg/dL) with atherosclerotic disease, and a triglyceride level of 4.52 mmol/L or less (≤400 mg/dL).

Results: Among 173 patients, 72 (82%) of the 88 assigned to Niaspan treatment and 68 (80%) of the 85 assigned to gemfibrozil treatment completed the study. Niaspan, at 1500 and 2000 mg, vs gemfibrozil raised the HDL-C level more (21% and 26%, respectively, vs 13%), raised the apolipoprotein A-I level more (9% and 11% vs 4%), reduced the total cholesterol–HDL-C ratio more (−17% and −22% vs −12%), reduced the lipoprotein(a) level (−7% and −20% vs no change), and had no adverse effect on the low-density lipoprotein cholesterol level (2% and 0% change vs a 9% increase). Significance levels for comparisons between medications ranged from P<.001 to P<.02. Gemfibrozil reduced the triglyceride level more than Niaspan (P<.001 to P = .06, −40% for gemfibrozil vs −16% to −29% for Niaspan, 1000 to 2000 mg). Effects on plasma fibrinogen levels were significantly favorable for Niaspan compared with gemfibrozil (P<.02), as gemfibrozil increased the fibrinogen level (from 5% to 9%) and Niaspan tended to decrease the fibrinogen level (from −1% to −6%).

Conclusions: In patients with a low baseline HDL-C level, Niaspan at its higher doses provided up to 2-fold greater HDL-C increases, decreases in lipoprotein(a), improvements in lipoprotein cholesterol ratios, and lower fibrinogen levels compared with gemfibrozil. Gemfibrozil gave a greater triglyceride reduction but also increased the low-density lipoprotein cholesterol level, which did not occur with Niaspan.

Arch Intern Med. 2000;160:1177-1184

The inverse relation of plasma high-density lipoprotein (HDL) levels to coronary heart disease was first noted in the 1950s and was clearly established in the 1970s. In epidemiological studies, low HDL cholesterol (HDL-C) levels have predicted coronary risk as strongly as high levels of low-density lipoprotein cholesterol (LDL-C), and in some studies, HDL-C was a more significant predictor than LDL-C or total cholesterol. The hypothesis that treating low HDL-C levels with gemfibrozil can reduce recurrent coronary events was confirmed recently in the US Veterans Administration HDL Intervention Trial (VA-HIT).

Niacin raises HDL-C levels effectively and represents an alternative to fibric acid derivatives for patients with low HDL-C levels. Its drawbacks are flushing, which limits the tolerability of immediate-release niacin, and hepatic toxicity, which has occurred chiefly with slow-release niacin. A new extended-release niacin formulation, Niaspan, administered once daily at bedtime, has shown reduced flushing and has demonstrated hepatic safety.

The present study compares the increase in HDL-C level afforded by Niaspan vs gemfibrozil when these drugs are given to subjects with low HDL-C levels (≤1.03 mmol/L [≤40 mg/dL]). The results indicate that the highest dose of Niaspan (2000 mg daily) raised the HDL-C level twice as much as gemfibrozil (1200 mg daily). The effects on other lipoprotein risk factors and fibrinogen, the tolerability of the medica-
SUBJECTS AND METHODS

STUDY SUBJECTS

Male and female subjects between the ages of 21 and 75 years, totaling 399 subjects, were screened for the study, and 173 were randomized to receive the study drug. The protocol was approved by the Institutional Review Boards of the 11 participating institutions, and written informed consent was obtained from all participants. All lipid-lowering medications were withdrawn, and patients were counseled about a National Cholesterol Education Program Step I diet for a 4-week lead-in period. Baseline lipoprotein levels were mean values from consecutive blood samples taken 7 to 10 days apart after the dietary lead-in period. Stability of the HDL-C level was required, with the difference of 2 baseline values no greater than 15% of the higher value. Patients were eligible for randomization if the baseline HDL-C level was 1.03 mmol/L or less (≤40 mg/dL); triglyceride level, 4.5 mmol/L or less (≤400 mg/dL); and LDL-C level, 4.14 mmol/L or less (≤160 mg/dL) or less than 3.36 mmol/L (<130 mg/dL) if documented coronary heart disease was present. Excluded were patients with gallbladder or peptic ulcer disease; active gout or clinically significant hyperuricemia; nephric, hepatic, or other serious illness; or clinically significant cardiac arrhythmias or other serious cardiac abnormalities (stable coronary artery disease was not an exclusion). Most diabetic patients were excluded, but non–insulin-requiring diabetic patients with a hemoglobin A1C level within the normal range and a fasting glucose level of 6.66 mmol/L or less (≤120 mg/dL) were allowed in the study. Patients taking isotretinoin, cyclosporine, warfarin potassium, or warfarin sodium were excluded, but other medications with minor effects on lipoproteins were permitted if the dosage was expected to remain stable. Postmenopausal women undergoing or not undergoing replacement hormonal therapy were eligible, but premenopausal women were excluded unless surgically sterile or taking oral contraceptives.

STUDY DESIGN

In the double-blind, placebo-controlled treatment phase, patients were randomly assigned to receive either gemfibrozil or Niaspan. Gemfibrozil, 600 mg, or corresponding placebo was given twice daily, 30 minutes before the morning and evening meals. Niaspan or its placebo was administered once, at bedtime, after a low-fat snack. During an initial 3-week titration, Niaspan was given initially at 375 mg and increased at weekly intervals to 500 mg, then to 750 mg. Niaspan was subsequently administered at 1000 mg for 4 weeks, 1500 mg for 4 weeks, and 2000 mg for 8 weeks (Figure 1). Patients were advised to take aspirin, 325 mg, a half hour before the study medication at bedtime on an as-needed basis for prophylaxis of niacin-induced flushing. Gemfibrozil was administered at a total daily dose of 1200 mg for the entire 16-week period.

STUDY MEASUREMENTS

Blood samples were collected after a 12-hour fast. Analyses were performed at the Lipid Research Laboratory, Washington University, St Louis, Mo, which is certified by the Centers for Disease Control and Prevention’s Lipid Standardization Program. Total cholesterol and HDL-C levels were measured enzymatically (HDL after phosphotungstate precipitation), and triglyceride levels were determined by a glyceral-blanked enzymatic method. The LDL-C level was determined by the Friedewald calculation when triglyceride levels were less than 4.52 mmol/L (<400 mg/dL) or by β quantification when triglyceride levels were above 4.52 mmol/L (>400 mg/dL). Apolipoprotein A-I (apoA-I), apolipoprotein B, and lipoprotein(a) levels were determined at the Northwest Lipid Research Laboratory, Seattle, Wash, as previously described. Lipoprotein(a) measurement used a monoclonal antibody–based enzyme-linked immunosorbent assay. Fibrinogen was quantified by an automated Clauss method at the Core Laboratory for Clinical Studies, Washington University.

DATA ANALYSIS

The primary end point was the percentage change of the HDL-C level from baseline. Multiple comparisons analysis was used to determine statistical significance at each postbaseline visit. An analysis of variance was used to compare baseline levels and changes from baseline between the 2 groups. The same procedures were used to evaluate secondary lipoprotein, lipid, apolipoprotein, and chemistry end points.

RESULTS

PATIENTS

A total of 173 subjects met the enrollment criteria and were randomized to receive the study drug. The groups receiving Niaspan and gemfibrozil were well matched (Table 1). Four patients with diabetes (Table 1) were included in the overall group. Their responses were not statistically different, and the small number precluded meaningful analysis as a separate group. Among the 88 patients taking Niaspan, 72 (82%) completed the study, and of the 85 patients taking gemfibrozil, 68 (80%) completed the study. Patients dropped out for medical and nonmedical reasons, as detailed later.

LIPOPROTEIN EFFECTS

Niaspan–treated patients given 1000 mg at bedtime had an HDL-C level increase of 13.9%, not significantly different from the 11.8% increase in patients treated with gemfibrozil, 600 mg twice daily (Figure 2). At 1500 mg of Niaspan, the HDL-C level increase was 21.4%, significantly greater than the increase of 14.0% achieved with gemfibrozil. At 2000 mg of Niaspan, the HDL-C level increase was 26.0%, approximately double the increase of 13.3% achieved with gemfibrozil.

Gemfibrozil raised the LDL-C level by 8.6%, averaged over all visits (significant increase from baseline,
The mean percentage change in LDL-C level with Niaspan was minimal and nonsignificant ($P = .3$ to $.9$), ranging from $1.9\%$ to $-1.4\%$ at various times. Reduction of triglyceride levels was significantly greater with gemfibrozil than with Niaspan ($P$, $.02$ vs $1000$ and $2000$ mg of Niaspan and $P = .06$ vs $1500$ mg of Niaspan). The overall average decrease in triglyceride levels with gemfibrozil was $40.1\%$. The average decreases in triglyceride levels were $15.7\%$, $25.9\%$, and $29.5\%$, respectively, for $1000$, $1500$, and $2000$ mg of Niaspan.

At every dosage, Niaspan gave a significantly greater increase in apoA-I level compared with gemfibrozil ($Figure 3$). At $1500$ and $2000$ mg of Niaspan, the increases in apoA-I level were $9.1\%$ and $11.2\%$, respectively, compared with $4.1\%$ and $3.1\%$ for corresponding increases for gemfibrozil, $600$ mg given twice daily. Both drugs reduced serum apolipoprotein B levels from baseline, but differences in apolipoprotein B reductions between the 2 drugs did not reach statistical significance.

$Figure 4$ shows decreases in LDL-C/HDL-C and total cholesterol–HDL-C ratios. In every comparison, Niaspan afforded a significantly greater decrease in the ratio, except that the effects of Niaspan at $1000$ mg and gemfibrozil on the total cholesterol–HDL-C ratio were similar.

$Table 2$ gives correlations between baseline lipoprotein-lipid levels and subsequent changes in the levels in patients taking Niaspan or gemfibrozil. The negative correlation between baseline HDL-C level and percentage change in HDL-C level with Niaspan indicates that patients with a lower baseline HDL-C level had relatively greater increases when taking Niaspan. The correlations for LDL-C changes suggest that the interactive effects of drug treatment and baseline lipid values on LDL-C level were similar for the 2 drugs. For example, with both drugs, the tendency to elevate the LDL-C level was greatest when baseline triglyceride levels were high and when baseline LDL-C and HDL-C levels were low. However, across the entire patient group, Niaspan had no effect...
on LDL-C level (Figure 2), while gemfibrozil increased the average LDL-C level. Finally, the correlations for change in triglyceride levels indicate that gemfibrozil decreased triglyceride levels more effectively when baseline triglyceride levels were high and the HDL-C level was low.

Lipoprotein(a) levels were significantly reduced by 20% from baseline with 2000 mg of Niaspan ($P = .002$) (Figure 5). Lipoprotein(a) trended higher with gemfibrozil, but the effect was not statistically significant. Effects on fibrinogen level, another atherosclerotic risk factor, were small, but gemfibrozil significantly increased the fibrinogen level by 6% to 9% ($P = .04$), while Niaspan gave a nonsignificant trend toward lower fibrinogen levels (Figure 5). Niaspan, 2000 mg, had a significantly better effect on fibrinogen levels than gemfibrozil.

**ADVERSE EFFECTS AND ADVERSE EVENTS**

Flushing was significantly more frequent with Niaspan compared with gemfibrozil at every point. Overall, 69 (78%) of the 88 patients taking Niaspan, but no more than 9 (10%) of the 85 patients taking gemfibrozil, reported flushing 1 or more times. Half of all patients assigned to Niaspan reported flushing in the first 3 weeks of drug administration, when the dose was increased weekly from 375 to 500 to 750 mg.

Adverse events leading to discontinuation from the study were experienced by 13 patients in the Niaspan group, among whom 5 (5.7%) had intolerable flushing, 2 had itching, 1 had a rash, and 2 had gastrointestinal tract adverse effects. Three other patients were removed from the study for nonmedical reasons. Eight patients in the gemfibrozil group discontinued the study for various medical reasons, and 10 withdrew for nonmedical reasons.

Adverse effects were similar between the 2 groups, with 2 exceptions. Flu syndrome was experienced by significantly ($P = .006$) more patients assigned to Niaspan ($n = 14$) compared with gemfibrozil ($n = 3$). However, only 3 of the cases in patients taking Niaspan were con-
considered by the investigator to be at least remotely related to the study medication. Dyspepsia was reported by 13 patients taking gemfibrozil and 2 taking Niaspan. A significant ($P = .009$) difference in dyspepsia persisted when only events considered at least remotely related to the study medication were analyzed.

**EFFECTS ON LABORATORY VARIABLES**

Niaspan and gemfibrozil increased the mean levels of aspartate aminotransferase by 15% to 16% but did not affect the level of alanine aminotransferase (Table 3). No patient in the study had an aminotransferase level greater than 3 times the upper limit of normal. Effects of Niaspan on glucose, uric acid, amylase, phosphorus, and creatinine levels were consistent with previous experience.9,10 Small but statistically significant increases in phosphorus and urea nitrogen, and decreases in uric acid and creatinine, were observed in the gemfibrozil group. Table 4 shows the changes in hemotologic variables, the most substantial of which were a 11.6% increase in platelet count with gemfibrozil and a 12.8% decrease in platelet count with Niaspan. The changes in platelet count were not accompanied by clinical episodes of altered hemostasis.

**COMMENT**

This study in subjects selected for low HDL-C levels shows that Niaspan, 2000 mg daily, raised HDL-C levels by 26%, twice as much as the HDL-C increase afforded by gemfibrozil, 1200 mg daily. At a low dose of 1000 mg daily, Niaspan raised HDL-C levels by 14%, approximately the same as gemfibrozil. In an earlier study of patients with low HDL-C levels, Vega and Grundy14 found that immediate-release niacin, 1500 mg given 3 times daily, induced a 30% HDL-C increase, significantly more than the effects of gemfibrozil (10%) and lovastatin (6%). However, only 27 of 37 patients assigned to niacin therapy were able to take the full dose of 4500 mg daily. The present results indicate that a 2000-mg niacin dose, given once daily in a well-tolerated, extended-release formulation, can yield almost as great an increase in HDL-C levels as that described by Vega and Grundy. Other studies,8-10 in which Niaspan was administered to subjects selected for high LDL-C levels, have also shown HDL-C increases of 24% to 28%.

The favorable HDL-raising effect of Niaspan documented herein is consistent with a previous report10 showing comparable HDL-C increases provided by Niaspan and immediate-release niacin. In contrast, other delayed-release niacin formulations were less effective in raising HDL-C levels compared with immediate-release niacin.15-19 Since those studies usually used twice-daily dosing, the strategy of once-nightly dosing of Niaspan might play a role. Alternatively, the specific release characteristics of Niaspan could allow the favorable effect on HDL-C levels.10 Nevertheless, to our knowledge, no direct clinical comparison of Niaspan with other delayed-release preparations has been performed.

The mean effect of gemfibrozil in raising HDL-C levels by 13% in this study is in accord with previous data.20,21 In the VA-HIT, however, the increase of HDL-C level from baseline was only 7.5%.7 This discrepancy might be due to several factors. One difference in study populations.
Gemfibrozil, 600 mg twice daily. The following variables did not vary by more than 5% in either group: sodium, potassium, chloride, bicarbonate, albumin, total protein, calcium, and bilirubin.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (n = 88)</th>
<th>% Change (n = 71)†‡</th>
<th>Baseline Mean (n = 85)</th>
<th>% Change (n = 67)†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase, IU/mL</td>
<td>23.5</td>
<td>15.1‡</td>
<td>23.5</td>
<td>16.2‡</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/mL</td>
<td>27.8</td>
<td>0.6</td>
<td>27.7</td>
<td>−1.3</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/mL</td>
<td>79.9</td>
<td>1.3</td>
<td>81.8</td>
<td>6.4‡</td>
</tr>
<tr>
<td>Lactate dehydrogenase, IU/mL</td>
<td>151.7</td>
<td>7.6‡</td>
<td>147.6</td>
<td>−0.5</td>
</tr>
<tr>
<td>Amylase, IU/mL</td>
<td>51.0</td>
<td>14.2‡</td>
<td>53.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L (mg/dL)</td>
<td>5.3 (95.5)</td>
<td>4.5‡</td>
<td>5.2 (92.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Uric acid, mmol/L</td>
<td>0.36</td>
<td>11.1‡</td>
<td>0.37</td>
<td>−5.3‡</td>
</tr>
<tr>
<td>Phosphorus, mmol/L</td>
<td>0.97</td>
<td>−8.3†</td>
<td>1.00</td>
<td>5.9t</td>
</tr>
<tr>
<td>Blood urea nitrogen, mmol/L (mg/dL)</td>
<td>5.3 (14.8)</td>
<td>0.4</td>
<td>5.6 (15.6)</td>
<td>9.4‡</td>
</tr>
<tr>
<td>Creatinine, µmol/L (mg/dL)</td>
<td>88 (1.0)</td>
<td>−5.4‡</td>
<td>80 (0.9)</td>
<td>−3.6§</td>
</tr>
</tbody>
</table>

* The dosage of extended-release niacin was 2000 mg at bedtime; gemfibrozil, 600 mg twice daily. The following variables did not vary by more than 5% in either group: sodium, potassium, chloride, bicarbonate, albumin, total protein, calcium, and bilirubin.
† Mean percentage change from baseline.
‡P<.01.
§P<.05 by the matched-pair t test.

**Table 4. Hematologic Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (n = 88)</th>
<th>% Change (n = 71)†‡</th>
<th>Baseline Mean (n = 85)</th>
<th>% Change (n = 67)†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count, ×10^9/L</td>
<td>219</td>
<td>−12.8‡</td>
<td>222</td>
<td>11.6‡</td>
</tr>
<tr>
<td>White blood cell count, ×10^9/L</td>
<td>6.0</td>
<td>3.8</td>
<td>6.0</td>
<td>−6.1‡</td>
</tr>
</tbody>
</table>

* The dosage of extended-release niacin was 2000 mg at bedtime; gemfibrozil, 600 mg twice daily. Changes in hemoglobin and hematocrit were 1% or less and nonsignificant.
† Mean percentage change from baseline.
‡P<.01.

is the fact that all patients in the VA-HIT, as opposed to only 16% in our study, had coronary heart disease and consequently encountered serious illness and took multiple additional medications more frequently. Thus, a confounding effect of illness or perhaps agents such as β-adrenergic–blocking medications might have limited the HDL-C–raising effect of gemfibrozil in the VA-HIT.

Levels of LDL-C, a secondary end point in this study, were unchanged overall by Niaspan but were increased approximately 9% by gemfibrozil. These results were surprising, since previous studies often showed small decreases in LDL-C level induced by gemfibrozil and larger decreases induced by niacin. However, those studies were performed in patients with a high baseline LDL-C level. Gemfibrozil did not reduce the LDL-C level in the population with a low HDL level studied in the VA-HIT. Effects on LDL-C within our study population were dependent on baseline levels of LDL-C and triglycerides (Table 2).

Gemfibrozil reduced triglyceride levels more effectively than Niaspan at its maximum recommended dosage of 2000 mg daily. Niacin has been reported to achieve substantially greater triglyceride lowering than evident herein, but the better triglyceride lowering occurred in patients with high baseline triglyceride levels who received immediate-release niacin in doses of 3 g or more daily. Lipoprotein ratios predict atherosclerotic risk better than any single lipoprotein level in population studies. In this study, Niaspan at 1500- to 2000-mg daily doses improved LDL/HDL and total cholesterol–HDL-C ratios significantly more than gemfibrozil. One recent large clinical trial used the total cholesterol–HDL-C ratio as part of its enrollment criteria, but ratios are not recommended as treatment targets.

The effects of Niaspan on 2 other coronary risk factors, lipoprotein(a) and fibrinogen levels, were favorable compared with those of gemfibrozil. Lipoprotein(a) levels were reduced by Niaspan but were not affected by gemfibrozil. The difference in effects on fibrinogen was smaller. Fibrinogen levels rose 6% to 9% with gemfibrozil treatment. In previous studies, the effects of gemfibrozil on fibrinogen were variable, possibly depending on the particular fibrinogen assay used. Fibrinogen level trended lower with Niaspan in our results, and the difference between drug treatments was significant. These effects on lipoprotein(a) and fibrinogen levels raise the possibility of additional benefit from Niaspan, but no trial with clinical end points has featured interventional therapy aimed specifically at lipoprotein(a) or fibrinogen levels.

Medication adverse effects are obviously important in treatment decisions. Overall discontinuation rates in the groups taking Niaspan and gemfibrozil were similar and acceptable. Hepatic toxicity, signified by an amino-transferase level greater than 3 times the upper limit of normal, was not encountered in either group. These results extend the safety record of Niaspan as an extended-release niacin with minimal adverse effects on the liver. Among transient symptomatic adverse effects, flu syndrome was reported by significantly more Niaspan–treated patients. This effect did not appear in previous placebo-controlled trials and did not lead to study drug discontinuation. Conversely, gemfibrozil use was asso-
The Lipid Center, Louisville, Ky: Harold Bays, MD; Jackie Bourke; Sue Craven. The Watson Clinic, Lakeland, Fla: Alan Brenner, MD; Chris Clarke; Kim Pacheco. San Diego Cardiac Center, San Diego, Calif: Laurence Favrot, MD; Sue Harte. Duke University Medical Center, Durham, NC: John R. Guyton, MD; Stephanie Barrett. Long Beach Veterans Affairs Medical Center, Long Beach, Calif: Moti L. Kashyap, MD; Kumar Gogineni. Northwest Lipid Research Clinic, Seattle, Wash: Robert H. Knopp, MD; Linda Marichec; Sue Sigsart. Boston Heart Foundation, Cambridge, Mass: Robert Lees, MD; Norma Holmes. Heart Care Midwest, Peoria, Ill: Donald McElroy, MD; Rebecca Crutchfield; Cindy Ness. National Clinical Research, Inc, Richmond, Va: James M. McKenney, PharmD; Catherine Groden. Cholesterol Control Center, Syracuse, NY: David T. Nash, MD; Helene Wallace. Cleveland Clinic Foundation, Cleveland, Ohio: Dennis Sprecher, MD; Lisa Haines; Dana Wade.

Niaspan-Gemfibrozil Study Group

The Lipid Center, Louisville, Ky: Harold Bays, MD; Jackie Bourke; Sue Craven. The Watson Clinic, Lakeland, Fla: Alan Brenner, MD; Chris Clarke; Kim Pacheco. San Diego Cardiac Center, San Diego, Calif: Laurence Favrot, MD; Sue Harte. Duke University Medical Center, Durham, NC: John R. Guyton, MD; Stephanie Barrett. Long Beach Veterans Affairs Medical Center, Long Beach, Calif: Moti L. Kashyap, MD; Kumar Gogineni. Northwest Lipid Research Clinic, Seattle, Wash: Robert H. Knopp, MD; Linda Marichec; Sue Sigsart. Boston Heart Foundation, Cambridge, Mass: Robert Lees, MD; Norma Holmes. Heart Care Midwest, Peoria, Ill: Donald McElroy, MD; Rebecca Crutchfield; Cindy Ness. National Clinical Research, Inc, Richmond, Va: James M. McKenney, PharmD; Catherine Groden. Cholesterol Control Center, Syracuse, NY: David T. Nash, MD; Helene Wallace. Cleveland Clinic Foundation, Cleveland, Ohio: Dennis Sprecher, MD; Lisa Haines; Dana Wade.

Niacin has effects on HDL-C levels, triglyceride levels, and fibrinogen levels. Thus, Niaspan is a strong candidate for inclusion in future studies of reversing or limiting atherosclerosis in patients with low HDL-C levels.

Finally, gemfibrozil and niacin should not be regarded as mutually exclusive antiatherosclerotic agents, since they can be given safely in combination. Their mechanisms of action are also complementary. Because niacin decreases catabolism of apoA-I (the major protein of HDL), and gemfibrozil stimulates hepatic production of apoA-I, such a combination is expected to raise HDL more than either agent alone and more than if the mechanisms of action were similar. The combination of niacin with clofibrate, an earlier fibric acid derivative, appeared to be highly effective in preventing coronary deaths in a trial performed in Stockholm, Sweden. Combination therapy with gemfibrozil, niacin, and cholestyramine resin successfully inhibited atherosclerotic progression in a recent angiographic study of coronary disease in patients with low HDL-C levels.

Accepted for publication August 12, 1999.

This study was supported by Kos Pharmaceuticals, Inc, Miami, Fla.

We thank Phillip D. Simmons for his expert statistical assistance.

Reprints: John R. Guyton, MD, Department of Medicine, Campus Box 3510, Duke University Medical Center, Trent Drive, Durham, NC 27710 (e-mail: john.guyton@duke.edu).

REFERENCES


