Combined Therapy of Niacin, Colestipol, and Fat-Controlled Diet in Men with Coronary Bypass

Effect on Blood Lipids and Apolipoproteins

Sharon A. Nessim, H. P. Chin, Petar Alaupovic, and David H. Blankenhorn

The effects of colestipol (30 grams/day), niacin (7.3 grams/day), and diet on blood lipids and apolipoproteins after one year of therapy are reported. Men selected on the basis of previous coronary artery bypass surgery were randomly assigned to drug or control treatments in an angiographic study of atherosclerosis progression and regression. In 14 men, drugs and diet produced the following changes: Baseline total cholesterol 245 mg/dl, triglyceride 189 mg/dl, and LDL cholesterol 164 mg/dl were decreased by 73 mg/dl (29%), 83 mg/dl (41%) and 69 mg/dl (40%) respectively. Baseline HDL cholesterol, 44 mg/dl was increased 13 mg/dl (33%). Baseline apolipoprotein B, 124 mg/dl and apolipoprotein C-III (heparin precipitate) 5.6 mg/dl were decreased 40 mg/dl (31%) and 2.4 mg/dl (41%) respectively. All these changes are significant, p < 0.01. Apolipoprotein A-I and apolipoprotein C-III (heparin supernate) were not significantly changed. In the controls, placebo and diet produced no significant decrease in blood lipid or lipoproteins, with the exception that baseline apolipoprotein B, 111 mg/dl increased 18 mg/dl (12%), p < 0.05.

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The combination of diet and treatment with bile acid binding resins plus niacin has been shown to be effective in treatment of heterozygous familial hypercholesterolemia.1,2 This topic has recently been reviewed by Kane and Malloy.3 Total plasma cholesterol levels were reduced 45% and LDL cholesterol levels, 55% when 30 grams per day of resin and up to 7.5 grams per day of niacin were administered to 18 xanthomatosis patients whose pretreatment plasma cholesterol averaged 424 mg/dl.1 There is an indication that the size of cutaneous and tendon xanthomas can be reduced with prolonged therapy.1,4 Goodman and co-workers5 have demonstrated that bile acid binding resin therapy increases the turnover rate of cholesterol in a rapidly exchangeable pool and it seems reasonable that this effect contributes to a reduction in xanthoma size and may assist in mobilizing stored cholesterol. The average total cholesterol level of patients studied by Goodman was 303 mg/dl. These results suggest that primary prevention of ischemic heart disease (IHD) in heterozygous familial hypercholesterolemia may be possible with these agents through reduction of arterial wall cholesterol deposits. Kuo and co-workers6 have demonstrated that coronary atherosclerotic lesions appear to remain stable in vigorously treated patients with familial hypercholesterolemia and established IHD. The average pretreatment level of patients reported by Kuo was 384 mg/dl.

Patients with familial hypercholesterolemia constitute an instructive, but relatively small, segment of the total population who develop IHD. Most patients with overt IHD have lower total cholesterol and LDL cholesterol levels, and in studies where patients are selected on the basis of having survived myocardial infarction, average total cholesterol levels in the range of 250 mg/dl are typical.7 Although the usual patient with IHD does not exhibit the high cholesterol

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level of patients with familial hyperlipoproteinemia, and only rarely has tendon xanthomata or other external evidence of abnormal tissue cholesterol stores, patients with IHD have excessive arterial wall cholesterol deposits. It is, therefore, reasonable to consider secondary prevention based on efforts to reduce arterial wall cholesterol stores.

The current view of the role of plasma lipoproteins in atherogenesis suggests the utility of lowering the LDL level and/or increasing the HDL level. A reduction of plasma LDL cholesterol level could reduce the influx of LDL cholesterol into the arterial wall, as suggested by the proportionality between LDL plasma levels and LDL entry rates into the arterial wall noted by Smith et al. and Niehaus et al. A reduction of plasma apolipoprotein B (apo B) level might have particular value in candidates for secondary IHD prevention who have relatively normal plasma lipid levels. The plasma variable that is the most reliable in predicting angiographic severity of coronary atherosclerosis in patients with total plasma cholesterol less than 265 mg/dl has been found to be the Apo B level. An elevation of plasma HDL cholesterol could facilitate the redistribution of cholesterol from the arterial wall to other body sites and might also reduce the cytotoxicity of LDL on arterial smooth and endothelial cells. An additional rationale for these changes in plasma lipid levels is obtained from epidemiologic studies which indicate that the correlation between the total cholesterol and the LDL cholesterol level with IHD prevalence is positive, but that the correlation between HDL and IHD prevalence is negative. Although much has been published about drug therapy for lowering major elevations of plasma lipid level, there is little published data on the aggressive treatment to reduce plasma lipid levels in persons with less extreme lipid values. The reports on the effectiveness of bile acid binding resin therapy and/or niacin for normolipemic subjects typically describe short periods of therapy. This paper reports on plasma lipid levels obtained after 1 year on a combined therapy of bile acid binding resin, niacin, and diet during an angiographic secondary prevention trial which studies the effects of lipid lowering on atherosclerotic lesion size. The subjects were candidates for secondary IHD prevention after coronary artery bypass surgery. Their average pretreatment plasma cholesterol (246 mg/dl) level was similar to patients studied in the Coronary Drug Project.

Because only a relatively small number of individuals can be included in an angiographic trial, the power of the experiment depends greatly on the magnitude of the expected differences in atherosclerotic lesion change rates in the test and control groups. To maximize the possibility of obtaining rapid changes in atherosclerotic lesions, aggressive therapy shown to be effective in heterozygous familial hypercholesterolemia has been assigned to the members of a treatment group. We report here changes in blood lipids, lipoproteins, and apolipoproteins after one year of therapy.

**Subjects**

The subjects for this study were 29 men, 40 through 59 years of age, with entry cholesterol of 185 to 350 mg/dl, who were currently nonsmokers, and who had had coronary artery bypass surgery. Of the men studied, 13 had plasma cholesterol values above 245 mg/dl. Five of these had Fredrickson and Lees' Type II hyperlipoproteinemia, four had Type IV hyperlipoproteinemia, and four had mixed (Type II B) hyperlipoproteinemia.

All participants passed a 6-week drug pretrial phase which began after the third screening visit, in which a treatment of niacin (3 g per day) and colestipol (30 g per day) had lowered serum cholesterol by at least 15%. The pretrial was adopted to screen out poor responders and compliers. Of the men screened, 25% had pretrial drops of less than 15% and were subsequently excluded from the trial. Values obtained at Visit 1 for relative weight, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, LDL cholesterol, and family incidence of diagnosed coronary heart disease or heart-related death before age 65 did not differ significantly in those who subsequently failed or passed the pretrial. HDL cholesterol was significantly lower at Visit 1 (p = 0.05) in those who subsequently failed the drug pretrial.

Those who passed the drug pretrial continued to take pretrial levels of medication up to their random assignment and the beginning of treatment. The average period between the end of the pretrial and their assignment to a group was 25 days. All participants gave written informed consent on forms approved by the Los Angeles County-University of Southern California Medical Center's Human Research Committee.

**Treatment**

The men were randomly assigned to treatment by nutritional intervention and placebo (Control Group), or to treatment by nutritional intervention plus 30 g/day of colestipol and 3–12 g/day of niacin (Drug Group). The average daily dose of niacin was 7.3 g/day. Compliance was monitored through scores assigned by dietitians after interviewing the participants at each clinic visit. In the Drug Group, 100% (14/14) of the subjects were reported as having excellent niacin compliance (seldom or only occasionally deviating from the protocol), and 71% (10/14) were reported as having excellent colestipol compliance. In the Control Group, 67% (10/15) had excellent niacin placebo compliance and 47% (7/15) had excellent colestipol placebo compliance.

The nutritional intervention program consisted of a core of individual counseling sessions with registered dietitians held at each study visit. The goals of this program for the Control Group were to change eating behaviors to include a dietary intake of 27% total fat, 5% saturated fat, a cholesterol intake of no...
more than 250 mg/day, and a polyunsaturated/saturated fat ratio of 2:1. Assuming an average American diet on entry, the expected reduction in total plasma cholesterol due to diet change was 7%.16 The goal of nutrition intervention in the Drug Group was to attain a dietary intake of 23% total fat, 4% saturated fat, a cholesterol intake of no more than 125 mg/day, and a polyunsaturated/saturated fat ratio of 2.5:1. Assuming an average American diet on entry, the expected reduction of total cholesterol was 14%.15 Diet compliance in both groups was monitored with a modification of the four-point scale developed for the Multiple Risk Factor Intervention Trial Program.16 In this trial, 36% (5/14) of the Drug Group and 53% (8/15) of the Control Group were scored as having excellent compliance (seldom or only occasionally deviated from the dietary program).

Blood Lipid and Apolipoprotein Analyses

Cholesterol,17 triglyceride,17 and HDL18 were measured at each screening visit and at 2-month intervals once on treatment. LDL was calculated as: 
\[ \text{LDL} = \text{cholesterol} - \text{HDL} - \text{triglyceride}/5 \]

for persons with triglyceride values of less than 500 mg/dl.19 In one case, the triglyceride value exceeded this and LDL was not calculated. All lipid measurements were carried out using procedures17-18 standardized with reference materials supplied by the National Center for Disease Control. Replicate analysis of pooled controls conducted in parallel with unknown specimens during the period of this study yielded coefficients of variation of 1.6% for total cholesterol, 4.3% for HDL cholesterol, and 3.2% for serum triglyceride.

The electroimmunoassay of apolipoproteins was carried out by previously described procedures for apolipoprotein A-I (apo A-I),20 apo B,21 and apolipoprotein C-III (apo C-III).22 Total apo C-III was measured (apo C-III-WS) in the heparin-precipitated (apo C-III-HP) and heparin-nonprecipitated (apo C-III-HS) lipoproteins. The ratio of apo C-III-HS to apo C-III-HP (apo C-III ratio) was calculated.23 Heparin-precipitated lipoproteins isolated by the procedure of Burstein et al.24 were dissolved in 10% NaHCO3 for the measurement of apo C-III. Apo C-III-HS approximates the quantity of apo C-III in HDL, while apo C-III-HP approximates that in VLDL plus LDL. All analyses were carried out in duplicate, and measurements were repeated if they disagreed by more than 5%. In 10 plasma samples analyzed every other day for 2 weeks, the within- and between-assay coefficients of variation were 5% and 7% respectively for both apo A-I and apo B; and 6% and 8% respectively for apo C-III. Apolipoprotein assays were also monitored by examining values obtained on all subjects at entry into the study. There was no evidence for drift in levels over a 26-month period.

Data Analysis

Baseline values were measured at the third screening visit, before treatment commenced. Post-treatment values were analyzed after one year of treatment. Data were examined for change using two-sided t-tests on lipid and apolipoprotein differences from baseline to one year of treatment. All testing was done at the 0.05 level.

Results

Lipid results at the third screening visit and after one year of treatment are shown in Table 1. In the Control Group, there were no significant lipid changes. In the Drug Group there were statistically significant decreases in cholesterol (-73 mg/dl; -29%), triglyceride (-83 mg/dl; -41%), and LDL-cholesterol (-69 mg/dl; -40%). An increase was seen in HDL-cholesterol (+13 mg/dl; +33%). The LDL/HDL ratio decreased from 3.9 to 1.7, with an average reduction of 54%. Significant correlations

<p>| Table 1. Effect of Therapeutic Diet with Placebo or with Niacin and Colestipol on Lipids (Drug Group = 14, Placebo Group = 15) |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Lipids</th>
<th>mg/dl (mean ± SEM)</th>
<th>Treatment group</th>
<th>Baseline (Visit 3)</th>
<th>One Year on Treatment</th>
<th>Change</th>
<th>Percent Change</th>
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<tbody>
<tr>
<td>Total cholesterol</td>
<td>Drug</td>
<td>245 ± 8</td>
<td>172 ± 7</td>
<td>-73 ± 11*</td>
<td>-29</td>
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<tr>
<td></td>
<td>Control</td>
<td>247 ± 10</td>
<td>246 ± 12</td>
<td>1 ± 10</td>
<td>0</td>
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<tr>
<td>Triglyceride</td>
<td>Drug</td>
<td>189 ± 22</td>
<td>106 ± 11</td>
<td>-83 ± 19*</td>
<td>-41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>193 ± 32</td>
<td>168 ± 31</td>
<td>-25 ± 13</td>
<td>-12</td>
<td></td>
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<tr>
<td>LDL cholesterol</td>
<td>Drug</td>
<td>164 ± 7</td>
<td>95 ± 6</td>
<td>-69 ± 9*</td>
<td>-40</td>
<td></td>
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<tr>
<td></td>
<td>Control</td>
<td>168 ± 10</td>
<td>173 ± 9</td>
<td>5 ± 9</td>
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<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Drug</td>
<td>44 ± 3</td>
<td>57 ± 4</td>
<td>13 ± 3*</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>40 ± 2</td>
<td>42 ± 2</td>
<td>2 ± 2</td>
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<td></td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>Drug</td>
<td>3.9 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td>-2.2 ± 0.3*</td>
<td>-54</td>
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<tr>
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<td>Control</td>
<td>4.4 ± 0.4</td>
<td>4.3 ± 0.3</td>
<td>-0.1 ± 0.3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at the 0.01 level.
between baseline lipid values and decreases in level were observed for total cholesterol \( (r = 0.81) \), triglyceride \( (r = 0.87) \), LDL-cholesterol \( (r = 0.78) \), and the LDL/HDL ratio \( (r = 0.82) \). The correlation between baseline level and increase in level for HDL-cholesterol was nonsignificant \( (r = -0.17) \).

The results of apolipoprotein analyses are summarized in Table 2. In the Control Group, the only significant change from baseline was seen in apo B \( (+18 \text{ mg/dl}; +12\%) \). The Drug Group showed a marked decrease in apo B \( (-40 \text{ mg/dl}; -31\%) \) and a large increase in the apo C-III ratio \( (+1.3; +136\%) \). The apo C-III ratio increase was due to a large decrease in apo C-III-HP \( (-2.4 \text{ mg/dl}; -41\%) \) paired with an increase in apo C-III-HS \( (+1.1 \text{ mg/dl}; +26\%) \) although this last change was not statistically significant. There were no statistically significant changes in apo A-I or apo C-III-WS. Significant correlations between baseline values and decreases in level were observed for apo C-III-WS \( (r = 0.62) \), apo C-III-HS \( (r = 0.55) \), and apo C-III-HP \( (r = 0.57) \). The correlations were nonsignificant for apo B \( (r = 0.46) \), apo A-I \( (r = 0.24) \), and the apo C-III ratio \( (r = -0.17) \).

### Discussion

Although the individual contributions of diet, colestipol, and niacin therapy could be separated in our experiment, the total effect on plasma lipid levels was similar to those observed with regimens which have been reported to stabilize coronary atherosclerosis lesions in familial hypercholesterolemia, reduce the size of early femoral atherosclerosis in hyperlipoproteinemic subjects, and retard progression in advanced femoral atherosclerosis in hyperlipoproteinemics with claudication. The effect on LDL reported here is also similar to those now being tested in a secondary prevention trial that uses partial ileal bypass to reduce plasma lipids in survivors of myocardial infarction. An increase in HDL has regularly been found by others using colestipol plus niacin therapy but has not been observed in patients treated by partial ileal bypass. The magnitude of the HDL increase that we observed may have been accentuated because our study was confined to non-smokers and exsmokers. The reports of other investigators suggest roughly an equal impact of niacin and colestipol on total and LDL-cholesterol, while changes in triglyceride and HDL-cholesterol appear principally attributable to niacin.

The results of apolipoprotein analyses confirm and extend further the information provided by plasma and lipoprotein lipids about the drug-induced changes in lipoprotein particles. A significant decrease of apo B levels commensurate with that of LDL-cholesterol indicates a reduction in cholesterol ester-rich lipoprotein B particles, considered the most atherogenic lipoproteins. Similarly, the significant decreases of apo C-III-HP and triglyceride point to a reduction of potentially atherogenic triglyceride-rich lipoproteins. A more efficient degradation of triglyceride-rich lipoproteins as suggested by a significant increase in the apo C-III ratio appears to be primarily responsible for an equally significant elevation of HDL cholesterol levels. It is interesting that levels of apo A-I are not changed significantly, suggesting that the main contributors to increased...
HDL-cholesterol levels may be triglyceride-poor apo C- and apo E-containing particles released during lipolysis of their corresponding triglyceride-rich lipoproteins. At present, we do not have an explanation for the increase in apo B exhibited by the placebo-treated men.

The Drug Group demonstrated significant positive correlations between baseline values and decrease for most of the lipids and apolipoproteins studied. This resulted from the larger initial values being associated with larger decreases. For HDL cholesterol, where the treatment effect was to increase HDL values, lower HDL values tended to have the greater increases, but this correlation was nonsignificant.

The results reported here were obtained in men who had been screened on the basis of short-term cholesterol response to diet and drug therapy before random assignment. This drug pretrial was adopted to improve comparability between study groups by eliminating potential drug-related dropouts before assignment and to screen out gross noncompliers and others in whom drug therapy would not be effective. The goal of this screening procedure was to create treatment groups which efficiently tested the cholesterol response to diet and drug therapy before random assignment and to screen out gross noncompliers and others in whom drug therapy would not be effective. The goal of this screening procedure was to create treatment groups which efficiently tested whether lowering of plasma LDL and elevation of plasma HDL has a beneficial effect on the progress of atherosclerotic disease. To increase the difference between Drug and Control Groups, the drug treatment group was given a more rigorous dietary program.

One possible area of controversy regarding this experiment is the treatment of men with plasma cholesterol levels under 220 mg/dl. The report of Kannel and Gordon of a steep gradient of coronary heart disease risk on serum cholesterol that persists in the lowest quintile of the Framingham data (total serum cholesterol 114–193 mg/dl) argues in favor of treatment for this group.

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References


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