Prediction of Angiographic Change in Native Human Coronary Arteries and Aortocoronary Bypass Grafts

Lipid and Nonlipid Factors

David H. Blankenhorn, MD, Petar Alaupovic, PhD, Emily Wickham, MS, H.P. Chin, PhD, and Stanley P. Azen, PhD

A within-group risk factor analysis was conducted to predict angiographic change in the Cholesterol Lowering Atherosclerosis Study, a randomized, placebo-controlled trial of colestipol plus niacin therapy in men with previous coronary bypass surgery. Global angiographic change, including both native coronary arteries and bypass grafts after 2 treatment years, was the end point. Risk factors included on-trial clinical measures, plasma lipids, lipoproteins, and apolipoproteins. Univariate analysis indicated that risk factors previously observed by others in epidemiologic investigation of ischemic heart disease—total cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, apolipoprotein B, and diastolic blood pressure—had significant effects in the placebo-treated group. Univariate analysis indicated significant effects of apolipoprotein C-III in drug- and placebo-treated groups. Multivariate analysis indicated the predominant risk factor predicting the probability of global coronary progression was non-HDL cholesterol in placebo-treated subjects and the content of apolipoprotein C-III in high density lipoproteins of drug-treated subjects. Both drug- and placebo-treated group findings point to an important role for triglyceride-rich lipoproteins in progression and regression of human atherosclerosis. (Circulation 1990;81:470-476)

Three controlled clinical trials (the Lipid Research Clinics Coronary Primary Prevention Trial, the Helsinki Heart Study, and the Coronary Drug Project) have shown that the incidence rate of coronary heart disease can be reduced by drugs that lower total plasma cholesterol.1-3

Although reduction of total plasma cholesterol was a common feature of these trials, the drugs tested reduced cholesterol levels through different mechanisms and produced widely different patterns of lipoprotein transport. The mechanism(s) of benefit in these trials is believed due to a primary effect of lowering blood lipids or lipoproteins on coronary atherosclerosis at the level of the arterial wall.

Angiographic trials have provided additional evidence about lipoprotein and other risk factor effects on coronary atherosclerosis. Evidence from two angiographic trials that did not demonstrate a significant per patient therapy effect, the Leiden Intervention Trial4 and the National Heart, Lung, and Blood Institute (NHLBI) Type II Coronary Intervention Study,5 suggested that the ratio of total cholesterol, or LDL cholesterol (LDL-C) to HDL cholesterol (HDL-C), can influence lesion progression. The Leiden trial, which was nonrandomized, treated 39 subjects with a single vegetarian diet. Plasma lipid and lipoprotein response to diet varied among subjects and higher ratios of plasma total cholesterol to HDL-C were found to be significantly related to the occurrence of progression. The NHLBI trial, which was a randomized test of cholestyramine versus placebo in 116 subjects, showed that progression of lesions that exhibited more than 50% stenosis was significantly related to higher ratios of LDL-C to HDL-C.

A third trial, the Cholesterol Lowering Atherosclerosis Study (CLAS) of the University of Southern California, provided stronger evidence for therapeutic benefit.6 One hundred sixty-two men with coronary artery bypass grafts were randomized to placebo

From the Atherosclerosis Research Institute, Departments of Medicine and Preventive Medicine, University of Southern California, Los Angeles; and the Oklahoma Medical Research Foundation, Oklahoma City.

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Address for reprints: David H. Blankenhorn, MD, University of Southern California, School of Medicine, 2025 Zonal Avenue, RMR 102, Los Angeles, CA 90033.

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niacin. The percent of subjects who developed new lesions in both native coronary arteries ($p<0.03$) and grafts ($p<0.04$) was reduced by drug treatment. The percent of subjects with progression in existing lesions was reduced by drug treatment in both coronary arteries ($p<0.03$) and grafts ($p<0.03$). In addition, the percent of subjects with improved overall coronary status, as judged by a coronary global change score, was significantly ($p<0.007$) increased with treatment. In the present study, CLAS data are used to compare the predictive power of plasma lipids, lipoproteins, apolipoproteins, and other coronary risk factors in progression of global coronary change within each of the CLAS treatment groups.

**Methods**

**Study Groups and Experimental Design**

The CLAS study design has been described elsewhere. Briefly, CLAS was a randomized, placebo-controlled, angiographic trial testing the combined therapy of colestipol-hydrochloride and niacin in 162 (of 188) randomized, nonsmoking men 40–59 years old with progressive atherosclerosis and previous coronary bypass surgery (80 men in the drug-treated group and 82 in the placebo-treated group). Entry fasting blood cholesterol levels were in the range of 180–335 mg/dl. Average ($\pm$SEM) age at entry of all subjects was 54.1 $\pm$ 0.4 years, and average blood pressure (determined at three screening visits) was 122 $\pm$ 1.0/80 $\pm$ 0.7 mm Hg. Forty-one percent of drug-treated subjects and 37% of placebo-treated subjects were treated for mild hypertension, principally with $\beta$-adrenergic blockade. Thirty percent of all subjects never smoked, and 70% were ex-smokers for more than 6 months. Nonsmoking status was monitored every 6 months with urinary nicotine and cotinine determinations.

Placebo-treated group subjects received diet intervention with a prescription for 26% of energy from total fat calories and less than 250 mg/day cholesterol intake. The prescription for drug-treated group subjects was 22% of energy from total fat calories and less than 125 mg/day cholesterol intake. Diet intervention was planned with different diet composition to enhance the differential in blood cholesterol responses due to therapy between the two groups. Body weight was recorded at each clinic visit and caloric intake for the preceding 7 days estimated from a computerized diet diary. These data were used to estimate habitual levels of energy expenditure that were equal in both groups throughout the trial and compatible with moderate physical activity. Subjects were evaluated angiographically before randomization to obtain baseline data on the atherosclerotic disease of the carotid, femoral, and coronary arteries as well as of the coronary bypass grafts. Subjects then were followed at specified intervals for 2 years, at which time a repeat angiogram was performed.

**Lipid Analysis**

All blood samples were obtained after an overnight (8 hours or more) fast. Cholesterol, triglycerides, and cholesterol from HDL-C isolated by precipitation of the low-density species were analyzed by AAI methodology and standardized against reference materials supplied by the Standardization Program of the Centers for Disease Control. For persons with triglyceride values of less than 500 mg/dl, cholesterol from LDL-C was calculated as follows: LDL-C = cholesterol − HDL-C − triglyceride/5. Cholesterol, triglyceride, and HDL-C were measured at each screening visit, at 1-month intervals for the first 6 months on treatment, and at 2-month intervals thereafter.

**Apolipoprotein Analysis**

Plasma samples for apolipoprotein analyses were transported in dry-ice containers to the Oklahoma Medical Research Foundation. The electroimmunoassay of apolipoproteins was performed by previously described procedures. Plasma samples were measured for apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apolipoprotein C-III (apo C-III). Apo C-III was measured in whole serum (apo C-III-WS) and in heparin-precipitated (apo C-III-HP) and heparin-supernate (apo C-III-HS) lipoproteins. The ratio of apo C-III-HS to apo C-III-HP (apo C-III ratio) was calculated. Heparin precipitation of lipoproteins was by the procedure of Burstein et al. Apo C-III-HP approximates the quantity of apo C-III in HDL, whereas apo C-III-HP approximates that in VLDL plus LDL. All measurements were carried out in duplicate and repeated in duplicate if they disagreed by more than 5%; repeat measurements were accepted if agreement was within 5%.

**Angiographic Analysis**

Coronary angiogram procedures, described previously in detail, evaluated all lesions of more than 20% diameter stenosis in both native coronary arteries and grafts. Film pairs showing identical coronary artery views mounted side by side were viewed simultaneously by two expert angiographers who were blinded to the subject's demographic and clinical characteristics, treatment assignment, and temporal order of the angiograms. A global change score was assigned to include changes in both native arteries and bypass grafts and ranged from 0 (no change) to 3 (extreme change). After all film pairs had been evaluated, the code for film order was broken and lesions that were recorded in a later angiogram but not in a first were considered new lesions. The global change score ranged from −3 (regression) to +3 (progression). On average, 15 native coronary artery segments were evaluated per patient, and these contained an average of 10.6 lesions. The distribution of percent stenosis among lesions in native coronary artery segments at baseline was 20–49% (40% of lesions), 50–59% (35%), 90–99% (8%), and 100% (16%). On average, 2.6 bypass grafts per subject were
evaluated. There were no significant differences between treatment groups in the distribution of lesion severity in native coronary arteries and grafts or in the placement of grafts.

Statistical Analysis

Patients were classified as nonprogressors if their global change score was in the range of −3 to 0 (\(n=49\) in the drug-treated group; \(n=33\) in the placebo-treated group). Progressors, on the other hand, were patients who had a global change score from 1 to 3 (\(n=31\) in the drug-treated group, \(n=49\) in the placebo-treated group). Risk factors (independent variables) that were evaluated as possible predictors of progression included on-trial determinations of clinical status (blood pressure, pulse rate), lipids (total cholesterol, HDL-C, LDL-C, non-HDL-C, triglycerides, LDL-C/HDL-C, cholesterol/HDL-C), and apolipoproteins (A-I, B, C-III-WS, C-III-HS, C-III-HP, and C-III ratio). There were 15 independent variables (\(X_1, \ldots X_{15}\)) in all. On-trial averages were obtained from values weighted according to the scheduled interval (either 1 or 2 months) between treatment visits.

Initially, univariate logistic regression analyses were performed with each of the 15 independent variables as a single independent variable to determine which were significantly related to coronary progression. Logistic regression is a nonlinear analog of linear regression that relates the probability \(p\) of occurrence of a dichotomous outcome (in this case, coronary progression vs. nonprogression) to one or more independent variables. The logistic model is:

\[
\ln \left[ \frac{p}{1-p} \right] = b_0 + b_1 X_{i} \quad i = 1, \ldots 16
\]

The quantity \(\ln \left[ \frac{p}{1-p} \right]\) is the log of the odds of coronary progression, and \(b_i\), the coefficient of the independent variable \(X_i\), measures the effect of the variable on the probability of coronary progression. Analyses were performed separately within each treatment group and adjusted by patient age at entry and years since bypass because these covariates were found to be related to progression.

Next, stepwise multivariate logistic regression analyses were performed within each treatment group. The dependent variable again was the log odds of coronary progression. The independent variables chosen as candidates for the equation were those risk factors found to be significant from the univariate analyses. Variables were entered into the logistic equation in a stepwise fashion; the first variable to be entered was the variable that gave the best fit of the data (using a \(\chi^2\) goodness-of-fit test statistic). The next variable to be entered was the variable that significantly improved the fit, given that the first variable remained in the equation. The process stopped when no further variable could significantly improve the fit of the data. The purpose of the multivariate analyses was to reduce the set of risk factors to those that are statistically independent by deleting variables that are intercorrelated.

For each variable found to be predictive of progression, the relative risk, RR, of progression per 1 SD increase was estimated by the exponential of the product of the coefficient of the predictor variable with its SD. Thus, \(RR = e^{b_1}\). SDs for each predictor variable were estimated from baseline data for the combined treatment groups.

Results

The entry and on-trial determinations of fasting blood lipids and apolipoproteins are summarized in Table 1. There were no significant differences between the treatment groups at baseline in any of

### Table 1. Mean Baseline and On-Trial Fasting Lipid and Apolipoprotein Levels by Treatment Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline ((n=162))</th>
<th>Drug ((n=80))</th>
<th>Placebo ((n=82))</th>
<th>Between-treatment (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>244 (3)</td>
<td>180 (3)*</td>
<td>232 (4)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>200 (3)</td>
<td>120 (3)*</td>
<td>188 (4)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>153 (7)</td>
<td>110 (5)*</td>
<td>141 (9)*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (1)</td>
<td>61 (1)*</td>
<td>44 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>170 (2)</td>
<td>97 (3)*</td>
<td>160 (3)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>4.0 (0.1)</td>
<td>1.7 (0.1)*</td>
<td>3.8 (0.1)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol/HDL-C</td>
<td>5.8 (0.1)</td>
<td>3.1 (0.1)*</td>
<td>5.5 (0.1)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoproteins (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-I</td>
<td>118 (1)</td>
<td>141 (2)*</td>
<td>122 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B</td>
<td>125 (2)</td>
<td>83 (2)*</td>
<td>123 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-III-WS</td>
<td>11.8 (0.3)</td>
<td>11.2 (0.4)</td>
<td>11.5 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>C-III-HS</td>
<td>5.8 (0.1)</td>
<td>7.1 (0.2)*</td>
<td>5.5 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-III-HP</td>
<td>5.0 (0.2)</td>
<td>3.2 (0.2)*</td>
<td>4.9 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-III ratio</td>
<td>1.4 (0.1)</td>
<td>3.0 (0.2)*</td>
<td>1.5 (0.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Significant change from baseline (\(p<0.001\)).
TABLE 2. Univariate On-Trial Predictors of the Probability of Coronary Progression

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Progressor</th>
<th>Nonprogressor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group (n=49/33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>241 (5)</td>
<td>219 (5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>197 (6)</td>
<td>175 (5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>82 (1)</td>
<td>79 (1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Apo B</td>
<td>128 (3)</td>
<td>116 (4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Apo C-III-WS</td>
<td>12.4 (0.7)</td>
<td>10.3 (0.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Apo C-III-HS</td>
<td>5.9 (0.3)</td>
<td>4.9 (0.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Apo C-III-HP</td>
<td>5.5 (0.4)</td>
<td>4.1 (0.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>156 (13)</td>
<td>117 (8)</td>
<td>0.04</td>
</tr>
<tr>
<td>LDL-C</td>
<td>165 (4)</td>
<td>152 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Drug group (n=31/49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo C-III-HS</td>
<td>6.4 (0.3)*</td>
<td>7.5 (0.3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Mean±SEM.

Lipids and apolipoproteins measured in mg/dl; blood pressure measured in mm Hg.

the lipids or apolipoproteins. When comparing the on-trial values between the two treatment groups, large, significant differences were found for all lipids (p<0.001). In addition, large significant differences were found for apo A-I, apo B, apo C-III-HS, and apo C-III-HP (p<0.001) but not for apo C-III-WS. Within the drug-treated group, statistically significant percent decreases from baseline were found for total cholesterol (26%—the percents are not shown in Table 1), non-HDL-C (4%), triglycerides (22%), LDL-C (43%), LDL-C/HDL-C (57%), cholesterol/HDL-C (45%), apo B (34%), and apo C-III-HP (34%). In addition, the drug significantly increased HDL-C (37%), apo A-I (19%), apo C-III-HS (24%), and apo C-III ratio (142%). No change in apo C-III-WS was found. Within the placebo-treated group, modest yet statistically significant decreases were found for total cholesterol (4%), non-HDL-C (5%), triglycerides (5%), LDL-C (5%), LDL-C/HDL-C (6%), and cholesterol/HDL-C (5%). HDL-C, apo A-I, apo B, and apo C-III did not change significantly in the placebo-treated group. Placebo-treated group differences from baseline are attributed to the diet prescription for this group.

The results of univariate analysis of on-trial risk factors comparing progressors with nonprogressors are given in Table 2. All on-trial factors that were significantly different between progressors and nonprogressors are shown. In the placebo-treated group, progressors had significantly higher average levels of diastolic blood pressure, total cholesterol, non-HDL-C, triglycerides, LDL-C, apo B, and apo C-III (-WS, -HS, and -HP). In the drug-treated group, progressors showed significantly smaller values of apo C-III-HS.

When on-trial values of the significant factors summarized in Table 2 were compared with baseline, the following results were noted. In the placebo-treated group, both progressors and nonprogressors significantly decreased total cholesterol (−10±3 and −12±3 mg/dl, p<0.01) and LDL-C (−9±3 and −10±3 mg/dl, p<0.01) but made no changes in diastolic blood pressure, apo B, and apo C-III-WS, C-III-HS, and C-III-HP. Nonprogressors, on the other hand, significantly decreased their triglycerides (−20±7 mg/dl, p<0.01), whereas progressors did not (−9±4 mg/dl, p=NS). In the drug-treated group, both progressors and nonprogressors significantly increased apo C-III-HS (1.3±0.2 and 1.1±0.3 mg/dl, p<0.01), but average on-trial levels of C-III-HS were lower in progressors than in nonprogressors (6.4±0.3 vs. 7.5±0.3 mg/dl, Table 2).

Table 3 presents the results of the multivariate logistic regression analysis for each of the treatment groups. Shown in the table are the independent, significant predictors of progression and the relative risk of progression associated with a 1 SD increase in that risk factor. The significant independent predictor of the global change score in the placebo group was on-trial non-HDL-C; each 34-mg/dl (1 SD) increase in non-HDL-C was associated with an approximately twofold increase in risk of coronary progression. In the drug-treated group, apo C-III-HS was the significant risk factor for the global change score; each 1.9-mg/dl increase was associated with a decrease in the risk of developing new lesions by a factor equal to approximately 2.

**Discussion**

Coronary status was determined using a global change score as the primary end point. This score summarizes observed changes in three contributory end points: the appearance of new lesions in native coronary arteries, the appearance of new lesions in aortocoronary bypass grafts, and the change in the

<table>
<thead>
<tr>
<th>Group</th>
<th>Predictor</th>
<th>SD (mg/dl)</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Non-HDL-C</td>
<td>34</td>
<td>1.9 (1.2, 3.2)</td>
</tr>
<tr>
<td>Drug</td>
<td>Apo C-III-HS</td>
<td>1.9</td>
<td>0.6 (0.4, 0.9)</td>
</tr>
</tbody>
</table>

*RR, relative risk of increase of progression per SD increase of predictor with 95% confidence interval.
Table 4. Relation of Global Change Score With Alternate Endpoints of Coronary Progression

<table>
<thead>
<tr>
<th>Group</th>
<th>End point</th>
<th>Progressor</th>
<th>Nonprogressor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>New lesions, natives*</td>
<td>17 (35)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>New lesions, grafts</td>
<td>24 (49)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Stenosis change rate†</td>
<td>3.5 (0.6)</td>
<td>−0.2 (0.3)</td>
</tr>
<tr>
<td>Drug</td>
<td>New lesions, natives</td>
<td>6 (19)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>New lesions, grafts</td>
<td>11 (35)</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td>Stenosis change rate</td>
<td>1.9 (0.5)</td>
<td>−1.3 (0.4)</td>
</tr>
</tbody>
</table>

*Number of subjects (percent in parentheses).
†Mean (SEM).

The average degree of stenosis in existing coronary arteries. We have previously demonstrated a strongly significant relation between global change score and all of these measures in drug- and placebo-treated groups combined. The relation between each of these end points and global coronary change score for drug- and placebo-treated groups considered separately is summarized in Table 4. Progressors within both treatment groups showed substantial worsening of coronary disease for all of the three end points.

Separate risk factor analyses comparing subjects with global coronary progression and nonprogression were carried out within each treatment group, prompted by the fact that all on-trial risk factors but the apo C-III content of whole serum were significantly different on-trial (Table 1). Even with stratification by treatment, our study is the largest to date with risk factors measured prospectively between serial coronary angiograms.

**Placebo-Treated Group Findings**

Within the placebo-treated group, seven clinical and lipid risk factors (blood pressure, cholesterol, triglycerides, LDL-C, non-HDL-C, apo B, and apo C-III) had significant effects, and six of the seven findings confirm relations previously observed in cardiovascular epidemiology. The seventh risk factor, not heretofore reported, was apo C-III. On the average, progressors demonstrated larger apo C-III whole serum, heparin supernate, and heparin precipitate than did the nonprogressors. Although apo C-III-HS level was higher for the progressors than for the nonprogressors (contrary to findings in the drug-treated group discussed later), they also had higher levels of C-III-HP. Consequently, the progressors had a lower C-III ratio than the nonprogressors (1.2 ± 0.1 and 1.6 ± 0.1, p = NS). Further, the progressors made no change in their C-III ratio on trial (−0.1 ± 0.1, p = NS), whereas the nonprogressors significantly increased their C-III ratio (0.2 ± 0.1, p < 0.05).

**Drug-Treated Group Findings**

The paucity of significant risk factors in drug-treated subjects suggests that treatment overrode the effects of both pretreatment lipid and nonlipid coronary risk factors. The only significant on-trial risk factor was apo C-III-HS; nonprogressors had significantly higher apo C-III-HS levels than did progressors. The increase in level of apo C-III in HDL of nonprogressors was accompanied by a parallel reduction of apo C-III in VLDL and LDL. At the same time, average LDL-C had been reduced from 170 to less than 100 mg/dl by treatment. The combined effect of these changes was to reduce LDL and VLDL levels and increase the time HDL remained in the circulation, as discussed later.

Not all of the beneficial effects associated with HDL in nonprogressors can be attributed to drug therapy alone. On-trial apo C-III-HS levels of both progressors and nonprogressors increased significantly (1.3 and 1.1 mg/dl, respectively), but nonprogressors had significantly higher levels at baseline (6.4 vs. 5.1 mg/dl, p < 0.01). However, higher apo C-III-HS in the absence of drug therapy was not protective; progressors in the placebo-treated group had significantly higher baseline and on-trial levels of apo C-III-HS than did nonprogressors (Table 3).

**Multivariate Analysis**

The effect of the multivariate analysis was to substantially reduce in the placebo-treated group the number of significant predictors of progression. The univariate predictors of progression (Table 2) were “explained” by the single multivariate predictor, non-HDL-C (Table 3). The relative risk of progression increased by a factor of 1.9 per 1 SD increase in non-HDL-C. This result for non-HDL-C, which is the combination of LDL-C and VLDL-C, likely reflects the contributions of both LDL-C and triglycerides (as a surrogate for VLDL) to risk because both were univariately associated with progression in the placebo-treated group at about the same level of statistical significance. Apo C-III-HS was the sole significant risk factor of progression in the drug-treated group. The relative risk of progression decreased by approximately a factor of 2 per 1 SD increase in apo C-III-HS. The new information from both univariate and multivariate regression is the apparent importance of triglyceride-rich lipoproteins (chylomicron remnants and VLDL) in progression of atherosclerosis in both drug- and placebo-treated groups and the role of apo C-III as a controller of this process or marker of its effectiveness.

**Triglyceride-Rich Lipoproteins**

There is substantial evidence that triglyceride-rich chylomicron remnants and VLDL are atherogenic in animal models and humans with Type III hyperlipoproteinemia. Apo C consists of three polypeptides: apo C-I, which activates lecithin-cholesterol acyl transferase; apo C-II, which activates lipoprotein lipase; and apo C-III, which inhibits lipoprotein lipase and retards hepatic uptake of triglyceride-rich lipoproteins and their remnants. When triglyceride-rich lipoproteins, such as chylomicrons and VLDL, enter the circulation, they acquire apo C-I, apo C-II, apo C-III, and apo E from
circular HDL.\textsuperscript{26,27} During the lipolytic degradation of chylomicrons and VLDL, apo C-II–activated lipoprotein lipase catalyzes triglyceride hydrolysis, and apo E facilitates hepatic removal of the resulting remnants. It appears that all three apo C polypeptides may inhibit or modulate the apo E–mediated hepatic uptake of triglyceride-rich lipoproteins or their remnants, at least as long as they are integral components of these lipoprotein particles.\textsuperscript{28,29} As chylomicron and VLDL lipolysis proceeds, most of apo C-I, apo C-II, and apo C-III and a substantial part of apo E are transferred back to HDL.\textsuperscript{26,29,30}

**Apolipoprotein C-III**

Apo C-III can be used as a marker to estimate the distribution of apo C-peptides between HDL and VLDL. Eisenberg\textsuperscript{26} and others\textsuperscript{14} have suggested that larger amounts of apo C-III in HDL as compared with that in VLDL (a higher C-III ratio) are indicative of recent chylomicron and HDL clearance. In fact, a highly significant ($p<0.0001$) negative correlation between apo C-III ratios and concentrations of serum and VLDL-triglycerides and an equally significant positive correlation between apo C-III ratios and levels of HDL-C has been reported.\textsuperscript{14} These correlations also were seen in our data: the C-III ratio–triglyceride correlations were $-0.47$, $p<0.001$ (placebo) and $-0.58$, $p<0.001$ (drug); and the C-III ratio–HDL-C correlations were $0.69$, $p<0.001$ (placebo) and $0.66$, $p<0.001$ (drug).

Patients with a consistent increase in apo C-III ratios should have decreased concentrations of triglyceride-rich lipoproteins and, thus, reduced probability of contact between these lipoprotein particles and their arterial walls. Table 1 demonstrates that drug treatment produced no significant change in total apo C-III levels but made major alteration in the lipoprotein fractions in which apo C-III was transported, increasing the fraction transported in HDL and reducing the amount transported in VLDL and LDL. Results from several laboratories indicate that apo C-III in VLDL is associated with denser, smaller VLDL subclasses that are believed to be particularly atherogenic.\textsuperscript{31–33} Inhibition of lipoprotein lipase–activated lipolysis of VLDL by apo C-III transported in VLDL should prolong the circulation time of these particles. Transfer of apo C-III from VLDL to HDL could simultaneously increase the fractional catabolic rate of atherogenic VLDL and reduce the fractional catabolic rate of HDL by inhibition of the effects of hepatic lipase on HDL.\textsuperscript{33}

**Absence of HDL Cholesterol Effect**

One puzzling aspect of the CLAS data is the relative absence of significant associations between atherosclerosis change and HDL-C levels. HDL-C may be a better marker for end-stage coronary events than it is for predicting the earlier changes in coronary status reflected in the CLAS global change score. On the other hand, apo C-III-HS may be an early marker of change in coronary status in patients whose LDL-C is markedly reduced, as was the case in CLAS. In addition, it is noteworthy that the on-trial levels of HDL-C in the drug-treated group were less variable than that observed in C-III-HS. Therefore, our within-group analyses of a rather homogeneous group of patients with respect to HDL-C were more likely to demonstrate predictive effects due to C-III.

**Summary**

In summary, risk relations in CLAS on global change in coronary status of patients with coronary bypass surgery confirm relations previously observed by epidemiologic investigation of ischemic heart disease event rates in general populations. Further, new information regarding apo C-III in HDL point to the importance of triglyceride-rich lipoproteins in atherogenesis. In contrast to the lack of relations associated with HDL-C, a surprisingly large number of effects were associated with the distribution of apo C-III between HDL and VLDL plus LDL. Among the commonly measured lipoprotein fractions, non-HDL-C appeared the most useful in predicting overall events in the coronary circulation of nonsmoking men who have had coronary bypass surgery but are not on lipid-lowering therapy.

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