Triglyceride- and Cholesterol-Rich Lipoproteins Have a Differential Effect on Mild/Moderate and Severe Lesion Progression as Assessed by Quantitative Coronary Angiography in a Controlled Trial of Lovastatin

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Background The Monitorod Atherosclerosis Regression Study, a randomized, double-blind, placebo-controlled, 2-year trial of lovastatin monotherapy, found that coronary lesions <50% diameter stenosis (%) and coronary lesions ≥50% at baseline had different responses to therapy. We now report on clinical, lipid, and nonlipid risk factors of treatment response in these lesion subsets.

Methods and Results Two hundred seventy subjects, 37 to 67 years old, with plasma total cholesterol (TC) 190 to 295 mg/dL (4.91 to 7.63 mmol/L) and total triglyceride <500 mg/dL (5.65 mmol/L) were randomized to low-fat, low-cholesterol diet and either lovastatin 80 mg/d or placebo. Logistic regression was used to model the association between risk factors and coronary lesion progression in mild/moderate (<50%) and severe (≥50%) lesions in 220 angiogram pairs analyzed by computer quantitative coronary angiography. In the placebo group, risk factors (P<.05) for the progression of mild/moderate lesions were triglycerides and TC/high-density lipoprotein cholesterol (HDL-C). Risk factors for the progression of severe lesions were HDL-C (negative), low-density lipoprotein cholesterol (LDL-C)/HDL-C, and TC/HDL-C. TC/HDL-C was the predominant risk factor for both mild/moderate and severe lesions in the multivariate analysis. In the lovastatin group, with aggressive lowering of LDL-C and TC below 85 mg/dL and 156 mg/dL, respectively, risk factors for mild/moderate lesions included triglycerides and very-low-density lipoprotein-LDL-associated apolipoprotein C-III (apo C-III–heparin precipitate), a marker of triglyceride-rich lipoprotein particles. Apo C-III–heparin precipitate was the predominant risk factor in the multivariate analysis. Risk factors for severe lesions were LDL-C, LDL-C/HDL-C, TC/HDL-C, and apo B; LDL-C/HDL-C was the predominant risk factor.

Conclusions These results indicate that triglyceride-rich lipoproteins and cholesterol-rich lipoproteins have a differential effect on mild/moderate and severe lesion progression, respectively. These results add to the growing evidence of the importance of triglyceride-rich lipoproteins as a risk factor for coronary artery disease and the need for treatment in the progression of atherosclerosis. (Circulation. 1994;90:42–49.)

Key Words • apolipoproteins • risk factors • coronary disease

The Monitorod Atherosclerosis Regression Study (MARS) was a double-blind, 2-year, placebo-controlled, randomized coronary angiographic trial that tested reduction of low-density lipoprotein cholesterol (LDL-C) using lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. The two angiographic outcomes in MARS were the per-subject change in percent diameter stenosis (%) as measured by quantitative coronary angiography (QCA) (primary end point) and the global change score, a consensus opinion of angiographic change as determined by panels of blinded expert human readers (secondary end point). The mean global change score was +0.9 (indicating progression) in the placebo group and +0.4 in the lovastatin group (P<.01); 13 placebo versus 28 lovastatin subjects had global change scores indicating regression (P=.02). Conversely, no statistical differences were found in the overall change in %S between treatment groups as measured by QCA: %S increase of +2.2% for the placebo group versus +1.6% for the lovastatin group (P=NS). However, benefit due to lovastatin was seen for severe (≥50%) lesions at baseline (%S increase of +0.9% for the placebo group versus %S decrease of −4.1% for the lovastatin group, P<.01) but not for mild/moderate lesions (<50%) at baseline (%S increase of +3.0% in the placebo group versus +2.6% in the lovastatin group, NS). An external Data and Safety Monitoring Committee recommended against further continuation of an optional 2-year extension of MARS, primarily on the basis of the observed treatment benefit in the global change score end point and the QCA end point for lesions ≥50%.

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Although evidence for greater treatment effects on more advanced lesions versus new/early lesions has previously been seen in four cholesterol-lowering angiographic trials, the risk factors that might account for these findings remain unknown. We have reported in 63 MARS subjects on a selective effect of lovastatin on cholesterol ester–rich lipoprotein B particles (LpB) and lack of effect on apolipoprotein (apo) A-I and apo A-I:A-II-containing lipoprotein particles. Lovastatin treatment was also accompanied by a heterogeneous response of triglyceride-rich lipoproteins. Further, in the Cholesterol Lowering Atherosclerosis Study, we reported that the predominant risk factor for progression of coronary artery lesions was elevated levels of non–high-density lipoprotein (HDL) cholesterol in placebo subjects and reduced levels of apo C-III content in HDLs in colestipol/niacin subjects. Both of these findings pointed to the important role for triglyceride-rich lipoproteins in the progression of coronary artery lesions. The Cholesterol Lowering Atherosclerosis Study used identical methodologies to those of MARS for panel-read and image-processed end points of change in coronary artery lesions, as well as identical methodologies for clinical and lipid and apolipoprotein determinations.

Because of the differential effect of lovastatin on mild/moderate versus severe lesions in MARS, we carried out a within-group analysis of clinical, lipid, and nonlipid risk factors as predictors of treatment response in lesions <50%S and ≥50%S at baseline. Since the global change score is a single (per-patient) number representing overall angiographic change, we used the QCA measures of percent diameter stenosis to carry out these analyses stratified by lesion size. Our hypothesis was that with aggressive reduction of LDL-C, different risk factors for mild/moderate versus severe lesion progression would emerge.

Methods

MARS Design

The MARS design has been described in detail. In brief, 270 subjects (91% men) 37 to 67 years old (average, 58 years) with plasma total cholesterol 190 to 295 mg/dL (4.91 to 7.63 mmol/L) and angiographically defined coronary artery disease (in at least two segments with at least one segment narrowed by at least 50% and unaltered by percutaneous transluminal coronary angioplasty) were randomized to cholesterol-lowering diet and either lovastatin 80 mg/d or placebo. Treatment groups had identical dietary targets for cholesterol and fat intake (daily cholesterol intake ≤250 mg; ≤27% of calories as fat, with saturated fat constituting ≤7% of total calories; and monounsaturated and polyunsaturated fats ≤10% of calories each).

Baseline and 2-year follow-up coronary angiograms were completed by 247 subjects (23 subjects did not have a second angiogram for medical or personal reasons). The percutaneous femoral technique was used, and sufficient right and left anterior oblique views were obtained to demonstrate all lesions clearly. QCA analyses were performed blinded to treatment but not to temporal order. Film pairs were processed in tandem with dual projectors to match frames for orientation and degree of contrast filling, and arterial segments were defined from branch to branch. Twenty-three film pairs with nitroglycerin mismatches (eg, nitroglycerin administered at one but not the other angiogram) and 4 film pairs not evaluable by QCA were excluded from QCA analyses, resulting in 230 evaluable angiogram pairs. Three sequential frames exposed during end diastole were digitized when possible; if not, three sequential frames from other phases of the cardiac cycle were digitized. %S was measured and averaged over three sequential frames. The primary end point in MARS, also used in this article, was the average per-patient change in %S measured by QCA. This end point was analyzed for lesions <50%S (mild/moderate lesions) at baseline and for lesions ≥50%S (severe lesions) at baseline.

Lipids, Lipoproteins, and Apolipoproteins

Fasting blood total cholesterol (TC) and triglyceride levels were determined by an enzymatic method standardized against reference materials supplied by the Standardization Program of the National Centers for Disease Control. HDL cholesterol (HDL-C) was measured after precipitation of apo B containing very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) in whole plasma by heparin-manganese chloride. VLDL cholesterol (VLDL-C) was assumed to equal one fifth of the serum triglyceride concentration. LDL-C was obtained by the Friedewald equation, which was shown not to be statistically different from that obtained with an ultracentrifugation method.

For the apolipoprotein analyses, plasma samples were stored at −20°C and transported on dry ice to the Oklahoma Medical Research Foundation. Electroimmunoassays of apolipoproteins were performed by previously described procedures for apo A-I, apo B, apo C-III, and apo E. Apo C-III was measured in whole serum as well as heparin-Mn++ supernatants and heparin-Mn++ precipitates as previously described. Apo C-III–heparin supernatant approximates the quantity of apo C-III in HDL, and apo C-III–heparin precipitate approximates that in VLDL plus LDL. All measurements were carried out in duplicate and repeated if they disagreed by >5%.

Statistical Analysis

The two dependent variables were the average per-patient change in %S in mild/moderate lesions (<50%S) at baseline and the average per-patient change in %S in severe lesions (≥50%S) at baseline. Each dependent variable was dichotomized to represent nonprogression (average change in %S ≤0) or progression (average change in %S >0). Independent variables included on-trial values and changes from baseline in clinical factors (age, smoking status, fasting glucose, systolic and diastolic blood pressures, pulse rate, and percent ideal body weight); lipids (TC, HDL-C, LDL-C, triglycerides, and the ratios TC/HDL-C and LDL-C/HDL-C); and apolipoproteins (A-I, B, C-III–heparin serum, C-III–heparin supernatant, C-III–heparin precipitate, and the ratio of C-III–heparin supernatant to C-III–heparin precipitate). On-trial values were calculated as the average over all visits weighted by the interval between visits; changes were computed as the on-trial weighted average minus the baseline average.

All analyses were carried out within each treatment group. Associations between independent and dependent variables were assessed by univariate and stepwise multiple logistic regression. For the univariate analysis, the relative risk (RR) and 95% confidence intervals were expressed per SD for clinical, lipid, and lipoprotein factors and per unit for ratios of these factors. Variables that were univariately significant at the P < .05 level were candidates for the stepwise multiple logistic regression analyses. For variables that were found to be independently significant in the stepwise analysis, an RR and a 95% confidence interval were calculated for each quartile of the distribution; the first quartile was the referent category (ie, RR = 1).

Results

Baseline Lipid and Clinical Characteristics and On-Trial Changes

The two treatment groups were not significantly different at baseline for any of the lipids, lipoproteins,
TABLE 1. Clinical Characteristics and Baseline Levels and On-Trial Changes in Lipids, Lipoproteins, and Apolipoproteins

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Baseline (n=220)</th>
<th>On-Trial Change</th>
<th>P</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>L (n=114)</td>
<td>P (n=106)</td>
<td></td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125.3 (1.0)†</td>
<td>-2.5 (0.9)</td>
<td>-1.3 (1.1)</td>
<td>.39</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80.0 (0.6)</td>
<td>-2.2 (0.6)</td>
<td>-0.3 (0.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>60.7 (0.6)</td>
<td>1.0 (0.5)</td>
<td>-0.2 (0.6)</td>
<td>.08</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>94.1 (0.8)</td>
<td>2.3 (0.9)</td>
<td>0.8 (0.8)</td>
<td>.23</td>
</tr>
<tr>
<td>Percent ideal body weight</td>
<td>121.9 (1.0)</td>
<td>0.0 (0.4)</td>
<td>-0.8 (0.4)</td>
<td>.18</td>
</tr>
<tr>
<td>Lipids, mg/dL, and ratios‡±</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>230.1 (1.6)</td>
<td>-74.3 (1.9)</td>
<td>-4.0 (1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>156.0 (1.6)</td>
<td>-70.2 (1.9)</td>
<td>-5.1 (1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>42.3 (0.7)</td>
<td>3.2 (0.4)</td>
<td>0.6 (0.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>5.7 (0.1)</td>
<td>-2.1 (0.1)</td>
<td>-0.1 (0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>3.8 (0.1)</td>
<td>-1.9 (0.1)</td>
<td>-0.1 (0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TG</td>
<td>160.4 (5.1)</td>
<td>-38.6 (4.5)</td>
<td>4.0 (5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Apolipoproteins, mg/dL, and ratios‡±</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-I</td>
<td>131.3 (2.1)</td>
<td>-0.5 (2.6)</td>
<td>-1.9 (2.4)</td>
<td>.75</td>
</tr>
<tr>
<td>B</td>
<td>109.0 (1.7)</td>
<td>-32.1 (2.3)</td>
<td>8.0 (2.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>E</td>
<td>13.4 (0.2)</td>
<td>-1.6 (0.4)</td>
<td>1.2 (0.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>C-III-WS</td>
<td>12.7 (0.4)</td>
<td>-1.4 (0.2)</td>
<td>0.1 (0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>C-III-HS</td>
<td>6.5 (0.2)</td>
<td>-0.3 (0.2)</td>
<td>-0.2 (0.3)</td>
<td>.86</td>
</tr>
<tr>
<td>C-III-HP</td>
<td>4.9 (0.2)</td>
<td>-0.9 (0.2)</td>
<td>0.8 (0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>C-III-HS/C-III-HP</td>
<td>1.7 (0.1)</td>
<td>0.4 (0.1)</td>
<td>-0.4 (0.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

L indicates lovastin; P, placebo; BP, blood pressure; bpm, beats per minute; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; WS, whole serum; HS, heparin supernatant; and HP, heparin precipitate.

* t test (two-tailed).
† Mean (SEM).
‡ ± To convert cholesterol values to mmol/L multiply by 0.02586; to convert triglyceride values to mmol/L multiply by 0.01129.

Compared with the placebo group, the lovastatin-treated group showed significantly greater on-trial decreases in diastolic blood pressure (P<.03), TC, LDL-C, TC/HDL-C, LDL-C/HDL-C, triglycerides, apo B, apo E, and apo C-III (whole serum and heparin precipitate), all P<.001. The lovastatin group also showed significantly greater increases in HDL-C and the ratio of apo C-III–heparin supernatant to C-III–heparin precipitate (P<.001). There were no treatment differences in apo A-I. Although triglyceride levels decreased on average by 22% in the lovastatin-treated group, triglyceride and apo C-III levels increased in 14% and 31% of the lovastatin subjects, respectively.

Baseline Angiographic Characteristics and On-Trial Changes

Baseline–2-year film pairs were evaluable by QCA for 1893 lesions in 220 subjects. There were no significant treatment group differences at baseline either in the distribution of mild/moderate or severe lesions or in the average %S. The majority (n=1569, 83%) of lesions were <50%S at baseline. The correlation in average per-patient change in %S between mild/moderate and moderate/severe lesions was 0.09 overall, 0.11 for subjects treated with lovastatin, and 0.06 for subjects treated with placebo (NS). For lesions <50%S, 67 of 112 subjects (60%) showed progression (ie, average change in %S >0) in the lovastatin group versus 65 of 105 subjects (62%) in the placebo group. For lesions ≥50%S, 23 of 77 subjects (30%) showed progression in the lovastatin group versus 34 of 79 subjects (43%) in the placebo group.

Risk Factors for Progression

Univariate results of logistic regression analyses are presented by treatment group for mild/moderate and moderate/severe lesions in Table 2. RR estimates >1 indicate that high levels of the independent variable are associated with coronary progression, while RR estimates <1 indicate that high levels of the independent variable are associated with coronary nonprogression. Multivariate logistic regression models are presented in Table 3.

Placebo Group

In the placebo group, univariate risk factors for progression of mild/moderate baseline lesions were
absolute increases from baseline in TC/HDL-C and triglycerides (Table 2). Univariate risk factors for progression of severe baseline lesions were absolute increases from baseline in LDL-C/HDL-C and TC/HDL-C and absolute decreases from baseline in HDL-C. No clinical factor, including age, smoking, fasting glucose, blood pressure, pulse rate, and percent ideal body weight, was found to be predictive of progression for either class of lesions. In the multivariate models, absolute increase of TC/HDL-C was the single risk factor associated with progression for both mild/moderate and severe lesions (Table 3). The greatest risk of progression was found for the fourth quartile of the distribution of TC/HDL-C (RR=3.6; 95% confidence limits, 1.0 to 12.7) for mild/moderate lesions and 8.7 (95% confidence limits, 2.0 to 38.3) for severe lesions.

**Lovastatin Group**

In the lovastatin group, univariate risk factors for progression of mild/moderate lesions (Table 2) were absolute increases in systolic blood pressure, apo C-III-heparin precipitate, and on-trial triglyceride and apo C-III (both whole serum and heparin precipitate). In the multivariate model, the on-trial level of apo C-III—
heparin precipitate was the single risk factor associated with progression of mild/moderate lesions (Table 3). Univariate risk factors for progression of severe lesions were on-trial values of LDL-C, apo B, LDL-C/HDL-C, and TC/HDL-C (Table 2). No clinical factor, including age and smoking status, was found to be predictive of progression for severe lesions. In the multivariate model, the on-trial level of LDL-C/HDL-C was the single risk factor associated with progression (Table 3). The greatest risk of progression was found for the fourth quartile of the distributions of apo C-III-heparin precipitate for mild/moderate lesions (RR = 5.0; 95% confidence limits, 1.4 to 17.1) and LDL-C/HDL-C for moderate/severe lesions (RR = 6.4; 95% confidence limits, 1.5 to 27.9).

**Discussion**

Observational coronary angiographic studies have shown a clear relation between coronary artery disease progression and cholesterol-rich lipoproteins, primarily high LDL-C and low HDL-C levels. Serial coronary angiographic randomized clinical trials offer further opportunities to study risk factors for progression of coronary artery lesions. To date, the only serial coronary angiographic clinical trial to report within-group analyses describing risk factors for lesion progression in drug-treated and placebo-treated groups has been the Cholesterol Lowering Atherosclerosis Study. Within-group analyses can yield important information if the sample size and risk factor relations are sufficiently large. From the placebo group, assessment of risk factors for lesion progression determined by sequential coronary angiography verifies observational findings that certain risk factors are related to lesion progression in untreated subjects. Examination of the drug-treated group by sequential coronary angiography permits assessment of risk factors for lesion progression after one major risk factor for lesion progression, LDL-C, is
aggressively lowered and its overall contribution to lesion progression reduced. This latter point has important implications, since all coronary angiographic trials to date demonstrate continued lesion progression in 25% to 60% of subjects even with the most aggressive LDL-C lowering. This implies that reduction of LDL-C can slow but not completely inhibit lesion progression. Clearly, other risk factors contribute to continued lesion progression once LDL-C is lowered. Within-group analysis of the treated group in which LDL-C is aggressively lowered affords us the opportunity to determine what some of these additional risk factors for lesion progression may be. In practical terms, identification of these risk factors may improve our ability to reduce coronary artery lesion progression beyond LDL-C lowering.

MARS, as well as the NHLBI Type II Coronary Intervention Study,2 the Familial Atherosclerosis Treatment Study (FATS),3 the Lifestyle Heart Study,4 and the St Thomas’ Atherosclerosis Regression Study (STARS)5 have all reported a differential effect of therapy on lesions <50%S and ≥50%S at baseline. Taken together, these studies suggest that risk factors for progression of coronary artery lesions may vary by lesion size. Determination of risk factors for lesion progression according to baseline size has been relatively unexplored, and it is unknown whether different risk factors determine lesion progression according to lesion size. MARS, one of the five sequential coronary angiographic trials published to date reporting a differential response to therapy according to lesion size, offers a unique opportunity to determine whether different risk factor relations exist between different baseline lesion sizes, since the study sample size (n=220) and treatment effect (LDL-C <85 mg/dL) are large relative to other trials.

Within-group analyses from MARS demonstrate that for mild/moderate lesions <50%S at baseline, both triglyceride-rich and cholesterol-rich lipoproteins or their markers (triglyceride and TC/HDL-C) were significant univariate risk factors for progression in the placebo group (Table 2). In contrast, with aggressive lowering of LDL-C <85 mg/dL (2.20 mmol/L) and TC <156 mg/dL (4.03 mmol/L), the influence of cholesterol-rich lipoproteins and their markers was reduced, and triglyceride-rich lipoproteins or their markers (triglyceride and apo C-III) became the predominant predictors of progression in the lovastatin group. This was further evidenced in the multivariate analysis by the presence of apo C-III-heparin precipitate, a normal constituent of intact or partially delipidized triglyceride-rich lipoproteins (which also includes the apo B triglyceride-rich lipoprotein particles,20 LpB.C, LpB.C.E, and LpA-II:B.C:D:E), as the single significant risk factor for progression of lesions <50%S (Table 3). For severe lesions ≥50%S at baseline, only cholesterol-rich lipoproteins or their markers (HDL-C, LDL-C/HDL-C, and TC/HDL-C) were significant univariate risk factors for progression in the placebo group (Table 2). Unlike the situation with lesions <50%S, aggressive LDL-C and TC lowering did not alter cholesterol-rich lipoproteins or their markers (LDL-C, apo B, LDL-C/HDL-C, and TC/HDL-C) as the predictors of progression of lesions ≥50%S in the lovastatin group.

In the multivariate analyses, TC/HDL-C emerged as the single risk factor for both mild/moderate and severe lesion progression in the placebo group; LDL-C/HDL-C was the single significant risk factor for progression of severe lesions in the lovastatin group (Table 3). These findings are consistent with the NHLBI Type II Coronary Intervention Study, which, with placebo and treatment groups combined, demonstrated TC/HDL-C and LDL-C/HDL-C ratios as the predominant risk factors for progression of lesions ≥50%S. Risk factor relations to lesions <50%S were not reported.2 The St Thomas’ Atherosclerosis Regression Study (STARS)5 and the Leiden Intervention Trial21 also reported the TC/HDL-C ratio as the predominant risk factor for lesion progression. However, risk factor relations were not determined within treatment groups or by lesion size. The Framingham observational study has additionally demonstrated the importance of the TC/HDL-C ratio as a risk factor for the development of coronary heart disease.22 As shown in Table 3, the risk of progression in either group was greatest for the upper quartile of the distributions of TC/HDL-C (placebo group, mild/moderate, or severe lesions) and LDL-C/HDL-C (lovastatin group, severe lesions).

Multivariate analysis demonstrated apo C-III-heparin precipitate to be the predominant risk factor driving lesions <50%S toward progression once LDL-C was aggressively reduced. As shown in Table 3, the risk of progression was greatest for the upper quartile of distribution for this marker of triglyceride-rich lipoproteins. These findings of a differential effect of triglyceride-rich and cholesterol-rich lipoproteins on mild/moderate lesion and severe lesion progression, respectively, adds to the growing evidence of the importance of triglyceride-rich lipoproteins as a risk factor for coronary artery disease and suggests that different risk factors may act early versus late in the atherosclerotic process.

Although most lipid-lowering coronary angiographic intervention trials have demonstrated a reduction in triglyceride levels, the Cholesterol Lowering Atherosclerosis Study (CLAS) is the only trial to show a relation between triglyceride-rich lipoproteins and coronary artery lesion progression.8 Furthermore, only a few observational studies of patients undergoing coronary angiography have demonstrated an association between triglycerides and coronary artery disease after adjustment for HDL-C.23 Two well-recognized problems with the assessment of triglycerides as a coronary risk factor that may account for these findings are (1) the heterogeneity of the lipoproteins that contain triglycerides and (2) postprandial changes in triglyceride levels. Two additional and perhaps unrecognized problems for failing to consistently find a relation between triglyceride-rich lipoproteins and coronary artery disease are demonstrated by the present analyses: (1) cholesterol-rich lipoproteins are the predominant risk factor driving coronary artery lesion progression and thus masking the importance of triglyceride-rich lipoproteins and (2) triglyceride-rich lipoproteins appear to be most important as a risk factor for progression of mild/moderate coronary artery lesions <50%S.

It has been found useful to augment analyses of the effects of TC with separate analyses of LDL-C and HDL-C, lipoproteins that each have different transport functions. Similarly, analyses of the effects of triglycerides have been augmented with studies of chylomicron
remnant, intermediate-density lipoprotein, VLDL, and postprandial fat tolerance levels. In CLAS and MARS, we used apo C-III, the distribution of apo C-III in HDL, and a combined LDL-VLDL--apo C-III precipitate as markers of triglyceride-rich lipoprotein metabolism. Increased amounts of apo C-III in HDL relative to apo C-III in LDL-VLDL (an increased apo C-III--heparin supernatant to apo C-III--heparin precipitate ratio) are indicative of recent chylomicron and VLDL clearance.

Furthermore, apo C-III in VLDL is associated with denser smaller VLDL subclasses believed to be particularly atherogenic. Inhibition of lipoprotein lipase--activated lipolysis of VLDL by apo C-III transported in VLDL could prolong the circulation time of these particles, thereby increasing their atherogenic potential. These measures are well suited for controlled clinical trials because they have significantly smaller within-subject variation than do triglycerides. For example, in MARS the total triglyceride within-subject coefficient of variation was 61%, compared with 20% for apo C-III--heparin precipitate.

Recent work on plaque fissuring has indicated the need to specifically evaluate risk from lesions <50% S, in which plaque fissuring, lesion disruption, and rapid lesion growth can be catastrophic. Current theories about plaque fissuring involve the central lipid core, which can be influenced by triglyceride-rich lipoproteins as well as by LDL-C. As a substrate for free radical reactions, triglyceride-rich lipoprotein peroxidative products within the lipid core could participate in plaque fissuring and lesion disruption. Additionally, linked to the coagulation and fibrinolytic cascades, triglyceride-rich lipoproteins could lead to thrombus formation and rapid lesion growth. A recent report from FATS indicates that progression of mild/moderate lesions in a placebo/usual care group of subjects leads to clinical coronary events, whereas their stabilization in subjects treated with clofibrate/niacin or clofibrate/lovastatin reduces the risk of events from this class of lesions. Our results, along with those of others, indicate the need for further research in the pathophysiological mechanisms associated with a differential lesion response according to lipoprotein type.

Our risk factor analyses from MARS, which extend previous findings of CLAS, indicate that triglyceride-rich lipoproteins play an important role in progression of lesions <50% S in subjects treated with aggressive LDL-C lowering. These results are the first to indicate that lipoproteins have an important differential effect on lesion progression according to lesion size. Since triglyceride-rich lipoproteins are a significant risk factor for driving lesions <50% S toward progression, they need attention in addition to LDL-C in the treatment of atherosclerosis.

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References


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