Lipoprotein predictors of the severity of coronary artery disease in men and women

MICHAEL F. REARDON, PH.D., † PAUL J. NESTEL, M.D., IAN H. CRAIG, M.D., and RICHARD W. HARPER, M.D.

ABSTRACT In this study we examined the relationships between levels of several components of plasma lipoproteins and severity of coronary artery disease in 65 men and 42 women who underwent coronary arteriography for suspected coronary disease. Severity of coronary atherosclerosis was scored as the extent of disease seen at arteriography. Univariate analyses of the relationships between the plasma lipoprotein parameters and score for severity of atherosclerosis revealed a marked difference between men and women. In men, the score for severity of atherosclerosis was strongly related to the low-density lipoprotein (LDL) cholesterol and apolipoprotein B concentrations, whereas in women it was related to the triglyceride concentrations in plasma intermediate-density lipoprotein (IDL) and LDL and to the cholesterol and apolipoprotein B concentrations in IDL. The significance of these correlations was not negated by possible confounding factors such as alcohol intake, diabetes, and treatment with thiazides and β-adrenergic blockers. Stepwise regression analyses of data adjusted for weight and age indicated that 22% of the variation in the score for severity of atherosclerosis could be accounted for by levels of LDL cholesterol in men. No other lipoprotein parameter could account for any further variation. In contrast, cholesterol did not account for any variation in the score for severity of atherosclerosis in women, whereas plasma triglyceride accounted for 16% of the observed variation in this group. No relationships were found between score for severity of atherosclerosis and high-density lipoprotein cholesterol or plasma apolipoprotein A-I concentrations in either group. This study indicates the importance of the triglyceride-rich lipoproteins in the development of coronary atherosclerosis in women.


EPIEMIOLOGIC STUDIES have clearly established that a high plasma cholesterol level is associated with an increased risk of coronary artery disease (CAD). This risk is associated primarily with the cholesterol level of the low-density lipoprotein (LDL) fraction. † In contrast, the cholesterol level in the high-density lipoprotein (HDL) fraction is an important determinant of reduced risk. ‡ Of the lipid-related indexes, the ratio of plasma cholesterol to HDL cholesterol has been suggested to be the most powerful predictor of premature development of CAD. §

In 1978, a report from this laboratory was among the first to relate lipoprotein lipid concentrations to the severity of CAD, as determined from the extent of disease in eight major segments of the coronary circu-

lation. ‡ The major finding was that, on multivariate analysis, levels of three lipoprotein lipids correlated independently with the severity of CAD: those of HDL cholesterol inversely and those of plasma cholesterol and LDL triglyceride directly. Subsequent reports of similar estimates of CAD in large numbers of subjects undergoing coronary arteriography have demonstrated a variety of independent correlates with lipoprotein lipid and apolipoprotein concentrations. † † † † However, only plasma concentrations of cholesterol and LDL cholesterol have been uniformly found to predict the extent of CAD. In several, † † † † but importantly not all, studies † † † the level of HDL cholesterol (or more specifically HDL₂ cholesterol) † † † was found to be inversely correlated with the severity of disease. Other parameters that showed independent predictive capacity were the plasma concentration of apolipoprotein B † † † and the concentration of intermediate-density lipoprotein (IDL) cholesterol. ‡

The relevance of levels of lipoprotein triglycerides in predicting CAD has been less obvious. In only one prospective study has hypertriglyceridemia emerged as
a strong independent risk factor. Nevertheless, there is ample evidence to suggest that some triglyceride-rich lipoproteins, particularly very low-density lipoprotein (VLDL) remnants, have a high potential for causing atherosclerosis. VLDL remnant concentrations are elevated in a number of disease states associated with the rapid and premature development of atherosclerosis. These include type III hyperlipoproteinemia, renal disease, hypothyroidism, and diabetes. VLDL remnants have a high capacity for interacting with cells such as skin fibroblasts and arterial smooth muscle cells. It is possible that the failure to show an independent association between hypertriglyceridemia and CAD in most epidemiologic studies has been caused by heterogeneity in the triglyceride-rich lipoproteins, particularly in relation to their atherogenic potential.

We have examined the association between levels of a number of components of lipoproteins and severity of CAD, but have paid particular attention to the lipoproteins derived primarily through triglyceride metabolism. These we subdivided into VLDL and VLDL remnant fractions (termed IDL). The hepatic recognition and subsequent metabolism of VLDL remnants are largely dependent on the presence of the E3 or E4 isomers of apolipoprotein E. The quantitative importance of a "partial deficiency" of E3 or E4 (i.e., in patients heterozygous for E3 or E4) to the catabolism of VLDL remnants may therefore have some relevance to development of CAD. In this study we have measured the concentrations of triglyceride, cholesterol, and apolipoprotein B in whole plasma, VLDL, IDL, LDL, and HDL in patients with suspected clinical CAD and in whom an index of severity of disease could be obtained. Each patient’s phenotype with respect to apolipoprotein E isomers was also determined.

**Methods**

**Patient group.** Sixty-five male and 42 female consecutive patients who presented for coronary arteriographic assessment were studied. All patients were undergoing testing because of chest pain and all were under 65 years of age. At the time of the arteriographic examination and after an overnight fast, 30 ml blood was collected from each into tubes containing EDTA (1 mg/ml) and aprotinin (1000 IU/ml). The plasma obtained was used for the lipoprotein determinations described below. Each patient’s clinical history was examined and the presence of factors such as overweight, hypertension, diabetes, cigarette smoking, alcohol intake, and family history of CAD were noted. Treatment received before the investigation was recorded.

**Interpretation and scoring of coronary angiograms.** Coronary arteriography was performed by the Judkins technique. Angiograms were recorded at 50 frames/sec on 35 mm Kodak CFS film with the use of a General Electric Fluoricon 300 image intensifier. Multiple transverse projections of the right and left coronary arteries were recorded in posteroanterior and axial views, with either 6 or 4½ inch screen magnifications. Cineangiograms were recorded on videotape and reviewed for adequacy before completion of each study. All cineangiograms were reviewed by two of us (I. H. C. and R. W. H.) who had no knowledge of the patient’s clinical history or lipid profile.

Scoring of severity of coronary artery disease was performed with a modification of the coronary atherosclerosis scoring system described previously. For analysis the coronary circulation was divided into eight proximal segments (figure 1). Disease in the distal segments was not considered because of difficulty in quantitating the severity of lesions in these areas. The eight proximal segments scored included the left main coronary artery, the left anterior descending artery (LAD) up to the junction of the middle and distal third of the vessel, the proximal third of the major septal branch of the LAD, the proximal third of the major diagonal branch of the LAD, the circumflex coronary artery (CFX) up to the junction of the middle and distal thirds of the vessel, the proximal third of the major obtuse marginal branch of the CFX, the right coronary artery (RCA) up to and including the origin of the posterior descending coronary artery (PDA), and the proximal third of the PDA. In cases in which the PDA was supplied by the CFX vessel (CFX dominance), lesions in the CFX up to the origin of the PDA were included, as were lesions of the RCA up to the origin of the middle and distal thirds of the vessel. The PDA was scored identically for RCA- and CFX-dominant circulations.

The percentage by which each lesion in the proximal coro-

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**FIGURE 1.** Proximal segments of the coronary circulation used in assessing the score for severity of coronary atherosclerosis score. LMCA = left main coronary artery. Lesions in shaded portions were not scored.

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nary circulation narrowed the artery was assessed according to the maximal narrowing of the diameter of the artery in all projections. The extent and severity of the proximal coronary disease was assessed by assigning points to each lesion as follows: less than 50% stenosis of the luminal diameter, 1 point; 50% to 74% stenosis, 2 points; 75% to 99% stenosis, 3 points; total obstruction, 4 points. The points for each lesion in the proximal coronary circulation were summed and a score for severity of coronary atherosclerosis was obtained. In our previous study, the coefficient of variation between two angiograms analyzed several months apart without knowledge of the previous score was 4.9%. 5

Lipoprotein determinations. Initially, 8 ml of plasma was overlaid with 0.15M NaCl and 0.001M EDTA, pH 7.4, and ultracentrifuged in a SW-41 rotor at 100,000 g for 2 hr at 18° C to obtain a supernatant fraction of 60 or more Svedberg flotation units (Sf) (termd VLDL). The infranate was adjusted to a salt density of 1.019 g/ml with potassium bromide and ultracentrifuged at 110,000 g for 18 hr at 4° C in a Beckman 50.1 Ti rotor. The supernatant obtained (Sf 12 to 60) was termed IDL. From the infranate, LDL was isolated by further ultracentrifugation at salt density of 1.063 g/ml for 20 hr at 110,000 g. HDL lipids were measured in plasma after the precipitation of other lipoproteins with heparin-manganese. 23 Recovery of total lipoprotein triglyceride, cholesterol, and apolipoprotein B was routinely determined and at all times exceeded 96%. Concentrations of cholesterol and triglyceride were measured with a Technicon Autoanalyzer II modified for enzymatic techniques. Apolipoprotein B values in plasma, VLDL, IDL, and LDL were determined by electroimmunoassay with a technique specifically designed for application to triglyceride-rich lipoproteins. 24 Plasma levels of apolipoprotein A-I were determined by electroimmunoassay. Apolipoprotein E isoforms (E1, E2, E3) in Sf 12 to 400 lipoproteins were scanned densitometrically after isoelectric focusing on polyacrylamide gels. The presence of E4 was determined visually. Patients were then classified as phenotypes E4/E3, E4/E2, E3/E2, or E2/E2, as described previously. 25

Statistical analyses. For all statistical analyses, triglyceride concentrations were treated as logarithmic concentrations because of their skewed distribution. Univariate correlations and multivariate correlations were carried out with the statistical computer package GLIM (Royal Statistical Society, London, U.K.). Stepwise multiple regression analyses were performed as described by Draper and Smith, 26 with the data adjusted first with age and weight as covariates.

Results

Clinical data are listed in table 1 and lipoprotein profiles are shown in table 2. There were no significant differences between men and women with respect to any of the mean lipid values, but scores for severity of coronary atherosclerosis in women were significantly lower than those in men (p < .01). Results of univariate analyses of lipid and apolipoprotein parameters that were significantly related to the score for severity of atherosclerosis are shown in table 3. Although mean lipid values were not significantly dissimilar in men and women (table 2), marked differences between the sexes were seen for the parameters that were related to severity of disease. In men plasma levels of cholesterol, LDL cholesterol, plasma apolipoprotein B, and LDL apolipoprotein B were significantly correlated

### Table 1: Clinical details

<table>
<thead>
<tr>
<th></th>
<th>Men and women (n = 107)</th>
<th>Men (n = 65)</th>
<th>Women (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, ± SD)</td>
<td>52±8</td>
<td>51±9</td>
<td>53±7</td>
</tr>
<tr>
<td>Body weight (kg, ± SD)</td>
<td>72±12</td>
<td>76±10</td>
<td>66±12</td>
</tr>
<tr>
<td>Plasma cholesterol (mg/dl)</td>
<td>240±51</td>
<td>235±51</td>
<td>246±49</td>
</tr>
<tr>
<td>Plasma triglyceride (mg/dl)</td>
<td>188±81</td>
<td>206±216</td>
<td>152±101</td>
</tr>
<tr>
<td>Positive family history (%)</td>
<td>57.4</td>
<td>51.6</td>
<td>66.7</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>60.4</td>
<td>71.9</td>
<td>42.9</td>
</tr>
<tr>
<td>Hypertensive (%)</td>
<td>35.9</td>
<td>28.1</td>
<td>47.6</td>
</tr>
<tr>
<td>Diabetics (%)</td>
<td>9.3</td>
<td>7.8</td>
<td>11.9</td>
</tr>
<tr>
<td>Heavy drinking* (%)</td>
<td>15.9</td>
<td>26.1</td>
<td>0</td>
</tr>
<tr>
<td>Score for severity of coronary atherosclerosis</td>
<td>11.9±10.1</td>
<td>13.8±9.3</td>
<td>8.9±10.6</td>
</tr>
</tbody>
</table>

*More than six drinks/day.

with score for severity of atherosclerosis. In marked contrast, parameters that correlated with the score in women were related to concentrations of the remnant lipoproteins (plasma IDL and LDL triglyceride, IDL cholesterol, and IDL apolipoprotein B). Severity of disease was positively correlated with age in women. No relationship was found between the score for severity of atherosclerosis and levels of the triglyceride-rich lipoproteins in men or between score and levels of cholesterol-rich lipoproteins in women.

The data were further analyzed by stepwise multiple regression and multivariate analysis. On multivariate analysis, the relationship between score for severity of atherosclerosis and levels of LDL apolipoprotein B in men was found to be dependent on LDL cholesterol. The relationship between the score and levels of LDL cholesterol was independent of body weight, age, and levels of LDL apolipoprotein B and plasma triglyceride (r = .32, p < .01). On multivariate analysis no single parameter emerged as independently related to

### Table 2: Lipoprotein profiles (apolipoprotein B, cholesterol, and triglyceride concentrations)

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Sex</th>
<th>Apolipoprotein B</th>
<th>Cholesterol</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>M</td>
<td>6±6</td>
<td>10±12</td>
<td>41±44</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>5±3</td>
<td>9±7</td>
<td>35±35</td>
</tr>
<tr>
<td>IDL</td>
<td>M</td>
<td>19±12</td>
<td>27±18</td>
<td>93±77</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>16±9</td>
<td>26±16</td>
<td>74±46</td>
</tr>
<tr>
<td>LDL</td>
<td>M</td>
<td>104±29</td>
<td>155±45</td>
<td>57±96</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>95±20</td>
<td>160±41</td>
<td>39±26</td>
</tr>
<tr>
<td>HDL</td>
<td>M</td>
<td>—</td>
<td>45±10</td>
<td>15±11</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>—</td>
<td>50±11</td>
<td>15±11</td>
</tr>
</tbody>
</table>

Values are mean ± SD mg/dl.
the score for severity of atherosclerosis in women because triglyceride concentrations were so highly intercorrelated among lipoproteins (VLDL with IDL, r = .63; VLDL with LDL, r = .55; IDL with LDL, r = .77). However, on stepwise regression analysis total plasma triglyceride did independently predict the score for severity of atherosclerosis in women. The IDL concentrations of cholesterol and apolipoprotein B were not independently related to score for severity of atherosclerosis on multivariate analysis. The relationship between score for severity of atherosclerosis and triglycerides in the women was not significantly altered by removing data from diabetic subjects from the statistical analysis. Of particular interest was the absence of a strong relationship between score for severity of atherosclerosis and HDL cholesterol level: in the women, and in the group of men and women combined, the observed negative relationships had a p value of > .05 < .1. Similarly, no relationships were found between the score and plasma concentrations of apolipoprotein A-I, the observed correlation coefficients being even lower than those for HDL cholesterol.

In men stepwise regression analysis showed that 22% of the variability in score for severity of atherosclerosis could be accounted for by changes in LDL cholesterol ($r^2 = .218$), which had been previously adjusted for weight and age. In women, 16% of the variability in the score for severity of atherosclerosis could be accounted for by changes in plasma triglyceride ($r^2 = .163$), similarly adjusted for weight and age. No other lipoprotein parameter was found to account significantly for any variation in the score in either group.

The importance of several potential confounding factors was analyzed in a univariate correlation matrix. The factors included the high ethanol intake of 17 men, diabetes mellitus in five women, thiazide treatment in 11 women, and treatment with β-adrenergic–blocking drugs in over half the patients (tables 4A and 4B). Although each of these factors modified the correlations obtained for the total population, they did not alter the conclusions. Specifically, in men the exclusion of data from the heavy alcohol drinkers or those treated with β-blockers did not negate the significant correlations between the score for severity of atherosclerosis and cholesterol and apolipoprotein B in plasma and LDL. Similarly, in women the exclusion of data from diabetics or of findings in those treated with thiazides or β-blockers did not negate the significant correlations between the severity score and triglyceride concentrations in plasma and in some lipoproteins. Because of the smaller numbers in the subgroups the correlations were in some instances weaker, although in others (e.g., in the case of thiazide treatment) the correlations for the untreated group were strengthened. The absence of a significant negative correlation between the score for severity of atherosclerosis and level of HDL cholesterol was not altered by excluding the above factors.

The distribution of plasma levels of triglyceride and LDL cholesterol in men and women are illustrated in figure 2. An almost identical distribution was found for LDL cholesterol concentrations in the two groups, even though LDL cholesterol was related to the score for severity of atherosclerosis in men only. The distribution of plasma levels of triglyceride differed in the two groups, with women having a lower mean plasma triglyceride level than men. Nevertheless, plasma triglyceride was found to contribute significantly to the observed variability in the score for severity of atherosclerosis in women.

No significant differences in the score for severity of atherosclerosis were found among any of the apolipoprotein E phenotypic classes (table 5). Somewhat lower severity scores were observed in women in associ-
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TABLE 4A
Effects of heavy ethanol consumption (HE), thiazides, and \( \beta \)-blockers on severity score in men

<table>
<thead>
<tr>
<th></th>
<th>Plasma choI</th>
<th>LDL choI</th>
<th>Plasma apo B</th>
<th>LDL apo B</th>
<th>HDL choI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HE (n = 17)</td>
<td>.58(^{A})</td>
<td>.65(^{B})</td>
<td>.50(^{A})</td>
<td>.50(^{A})</td>
<td>-.11</td>
</tr>
<tr>
<td>No HE (n = 48)</td>
<td>.29(^{A})</td>
<td>.38(^{B})</td>
<td>.22</td>
<td>.29(^{A})</td>
<td>-.04</td>
</tr>
<tr>
<td>On ( \beta )-blockers (n = 41)</td>
<td>.24</td>
<td>.32(^{A})</td>
<td>.21</td>
<td>.24</td>
<td>—</td>
</tr>
<tr>
<td>Not on ( \beta )-blockers (n = 24)</td>
<td>.48(^{A})</td>
<td>.60(^{B})</td>
<td>.36(^{A})</td>
<td>.39(^{A})</td>
<td>—</td>
</tr>
<tr>
<td>Total (n = 65)</td>
<td>.31(^{B})</td>
<td>.43(^{C})</td>
<td>.27(^{B})</td>
<td>.33(^{B})</td>
<td>-.05</td>
</tr>
</tbody>
</table>

Results are \( r \) values for correlations between severity score and levels of the various lipoproteins.
choI = cholesterol; apo = apolipoprotein.
\(^{A}\) \( p \leq .05; \(^{B}\) \( p \leq .01; \(^{C}\) \( p \leq .001.

Discussion

In this study we examined, in a patient population suspected of having coronary heart disease, levels of a number of components of lipoproteins to determine which may be related to severity of coronary artery disease and therefore have a possible causal role in the disease process. The major finding was that different lipoprotein lipids were related to severity of disease in men and women, even though the two groups did not differ significantly with respect to mean lipid concentrations. LDL cholesterol accounted for 22% of the observed variation in the score for severity of coronary atherosclerosis in men in whom no other lipoprotein parameter was found to contribute further. In contrast, parameters involving cholesterol did not account for any variation in the score in women, whereas plasma triglyceride accounted for 16% of the observed variability.

Few of the many studies examining the relationships between plasma lipid levels and cardiovascular disease have made specific comparisons between findings in men and women. In one of those that has done so, the Framingham study,\(^{27}\) it was shown by univariate analysis that the plasma triglyceride concentration had much higher predictive power for clinical CAD in women than in men. Furthermore, in women, but not in men, the predictive power of plasma levels of triglyceride was greater than that of levels of plasma cholesterol or LDL cholesterol. A large study from the Mayo Clinic\(^{6}\) that resembled our study in design noted that in women severity score was correlated with level of HDL cholesterol, total cholesterol ratio, relative weight, and smoking; in men only age and LDL cholesterol emerged as significantly related to the score for severity of atherosclerosis on multivariate analysis.

An inverse relationship between VLDL and HDL concentrations has often been observed.\(^{28}\) It may be that HDL cholesterol provides a more stable index of triglyceride metabolism than estimates of concentrations of triglyceride-rich lipoproteins, which vary considerably during the day in response to hormonal and dietary factors. In our studies, HDL cholesterol was found to make no significant contribution to score for severity of atherosclerosis. However, as shown in table 3, negative relationships between HDL cholesterol and the severity score were found to be almost significant in the total group and in women (\( p < .1 \)). Thus, in our studies it is possible that the failure to find a relationship with HDL cholesterol may have been due to

TABLE 4B
Effects of diabetes, thiazides, and \( \beta \)-blockers on severity score in women

<table>
<thead>
<tr>
<th></th>
<th>Log plasma TG</th>
<th>Log VLDL TG</th>
<th>Log IDL TG</th>
<th>Log LDL TG</th>
<th>IDL choI</th>
<th>IDL apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (n = 5)</td>
<td>.85(^{A})</td>
<td>.48</td>
<td>.87(^{A})</td>
<td>.91(^{A})</td>
<td>.94(^{B})</td>
<td>.62</td>
</tr>
<tr>
<td>No diabetes (n = 37)</td>
<td>.47(^{B})</td>
<td>.25</td>
<td>.38(^{A})</td>
<td>.44(^{B})</td>
<td>.33(^{A})</td>
<td>.38(^{A})</td>
</tr>
<tr>
<td>On thiazides (n = 11)</td>
<td>.07</td>
<td>-.42</td>
<td>.05</td>
<td>.45</td>
<td>.01</td>
<td>.04</td>
</tr>
<tr>
<td>Not on thiazides (n = 31)</td>
<td>.56(^{A})</td>
<td>.38(^{A})</td>
<td>.49(^{B})</td>
<td>.47(^{B})</td>
<td>.37(^{A})</td>
<td>.39(^{A})</td>
</tr>
<tr>
<td>On ( \beta )-blockers (n = 23)</td>
<td>.47(^{A})</td>
<td>.21</td>
<td>.46(^{A})</td>
<td>.41(^{A})</td>
<td>.43(^{A})</td>
<td>.33</td>
</tr>
<tr>
<td>Not on ( \beta )-blockers (n = 19)</td>
<td>.45(^{A})</td>
<td>.30</td>
<td>.33</td>
<td>.51(^{A})</td>
<td>.10</td>
<td>.32</td>
</tr>
<tr>
<td>Total (n = 42)</td>
<td>.47(^{B})</td>
<td>.26</td>
<td>.40(^{B})</td>
<td>.42(^{B})</td>
<td>.31(^{A})</td>
<td>.33(^{A})</td>
</tr>
</tbody>
</table>

Results are \( r \) values for correlations between severity score and levels of the various lipoproteins.
TG = triglyceride; other abbreviations as in table 4A.
\(^{A}\) \( p < .05; \(^{B}\) \( p < .01; \(^{C}\) \( p < .001.

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the attempt to demonstrate a direct relationship with concentrations of triglyceride-rich lipoproteins. There is an apparent discrepancy between the consistent findings of diminished HDL cholesterol in subjects with clinical CAD in epidemiologic surveys and the inconsistent findings when HDL is related to the severity of atherosclerosis. Noma et al., in a survey of 100 Japanese men, emphasized this point when they found that while the presence of clinical CAD was related to both increased LDL cholesterol and decreased HDL cholesterol concentrations, the severity of coronary atherosclerosis correlated significantly with the LDL cholesterol concentration only. This may explain our previous finding of an inverse correlation between HDL cholesterol and the score for severity of atherosclerosis, which was not confirmed in the present study. The scoring of severity was expanded in the present survey to quantify all lesions observed in the designated arterial segments, thereby leading to a more accurate estimate of the overall severity of the existing disease.

Although triglyceride concentration is frequently neglected as a potential risk factor, mainly because of the lack of sufficient evidence from the prospective American studies, there is a considerable body of evidence that favors triglyceride as an independent risk factor. Major studies from Sweden and Finland have demonstrated a closer link between myocardial infarction and the plasma concentration of triglyceride than between infarction and plasma cholesterol. Similar findings have been reported from Japan where, in one study, increased concentrations of triglyceride (and reduced HDL cholesterol) were found to be stronger predictors of CAD than the plasma cholesterol concentration. Another study from Japan demonstrated the significance of IDL and VLDL cholesterol as indicators of severity of coronary atherosclerosis. The severity of coronary atherosclerosis determined at autopsy has also been shown to correlate better with the antemortem plasma concentration of triglyceride than of cholesterol. Atherosclerosis in the large arteries of the legs is generally associated with hypertriglyceridemia. In our previous study, conducted in a manner similar to the present investigation, LDL triglyceride was one of the three independent predictors of severity score. The association of triglyceride (whether in plasma or in specific lipoproteins) with the score for severity of atherosclerosis is therefore not necessarily a reflection of a reduced HDL concentration. In fact, the converse might apply in some situations and it is noteworthy that several of the above studies, as well as the work presented here, have failed to demonstrate an independent role for HDL cholesterol in atherosclerosis.

Although our results in this study established in the women a correlation between remnants of triglyceride-rich lipoproteins and the score for severity of atherosclerosis, we were not able to define precisely the specific lipoprotein fraction that might have been responsible for the relationship found. Triglyceride concentrations in VLDL, IDL, LDL, and HDL were highly intercorrelated. On univariate analysis the strongest correlations were found between IDL and LDL triglyceride (IDL cholesterol and apolipoprotein B were also significantly related), suggesting that IDL and triglyceride-rich LDL may have the highest “atherogenic potential,” as reported in the previously mentioned Japanese study. Nevertheless, in terms of predictive

![Figure 2](http://circ.ahajournals.org/)

**FIGURE 2.** The distribution of plasma concentrations of triglyceride (top) and cholesterol (bottom) in the men (––) and women (––•) studied.

<table>
<thead>
<tr>
<th>E phenotype</th>
<th>Severity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/3 (n = 17 for men, 7 for women)</td>
<td>15.2 ± 9.5</td>
</tr>
<tr>
<td>4/2 (n = 20 for men, 1 for women)</td>
<td>20</td>
</tr>
<tr>
<td>3/3 (n = 38 for men, 29 for women)</td>
<td>12.9 ± 8.6</td>
</tr>
<tr>
<td>3/2 (n = 8 for men, 5 for women)</td>
<td>14.7 ± 12.6</td>
</tr>
</tbody>
</table>

**TABLE 5**

Score for severity of coronary atherosclerosis related to various phenotypes for apolipoprotein E isomorphs

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power, plasma triglyceride was found to account for more variability in the score for severity of atherosclerosis than did concentrations of IDL or LDL triglyceride.

Our previous finding, confirmed in the present study, of a correlation between LDL triglyceride and severity score may be related to the nature of the LDL particle found in patients with hyperapobetalipoproteinemia. Since a raised plasma concentration of apolipoprotein B may be as atherogenic as an elevated LDL cholesterol concentration, it is relevant that the predominant LDL particle found in hyperapobetalipoproteinemia is a particle enriched in triglyceride and depleted in cholesterol. In fact, hypertriglyceridemia associated with an increased concentration of LDL apolipoprotein B, a variant of combined hyperlipoproteinemia, is highly atherogenic. Since this finding characterizes the female group investigated in the present study, it is possible that combined hyperlipoproteinemia or multiple lipoprotein disorder is the most common lipoprotein abnormality in women with CAD in this age range, whereas hypercholesterolemia is the predominant disorder in men.

Triglyceride concentrations are frequently associated with obesity, glucose intolerance or diabetes, and cigarette smoking. It is interesting that diabetes, obesity, low concentrations of HDL cholesterol, and increased plasma triglyceride collectively constituted a risk for CAD only in women in the Framingham study. In the present study, triglyceride concentration remained statistically independent correlated with the score for severity of atherosclerosis even when body weight and diabetes were considered, although the small number of diabetic subjects in the analyses should be noted. However, we have not excluded the possibility of an undetected higher prevalence of diminished glucose tolerance in the female group studied.

With respect to the correlation between the severity score and specific apolipoproteins, we have not found that for apolipoprotein B to be superior to that for LDL cholesterol or plasma cholesterol, as suggested by Klodetsky et al. and Sniderman et al. The absence of significant differences in the scores among the patients with the various E phenotypes or with the E3/E2 ratio confirms the observations of Menzel et al. We have failed to find a correlation between the score for severity of atherosclerosis and plasma apolipoprotein A-I levels, which may be expected in view of an absence of any significant relationship of the score to HDL cholesterol. Whereas Maciejko et al. found that the concentration of apolipoprotein A-I correlated more strongly with the score for severity of atherosclerosis than did that of HDL cholesterol, Miller et al. did not find apolipoprotein A-I concentration to be a useful predictor of risk among subjects in whom HDL cholesterol was significantly related to the severity score.

The wide use of \( \beta \)-adrenergic–blocking drugs was not surprising and must be considered as a factor in the lipoprotein lipid profile of the subjects. Diuretics, mainly of the thiazide variety, were taken by proportionately more women than men, reflecting the higher prevalence of hypertension among the women. Diuretics are known to induce small increases in plasma triglyceride levels and, to a lesser extent, in plasma cholesterol levels. \( \beta \)-Adrenergic–blocking drugs, especially those used most frequently by subjects in this study, tend to reduce the HDL cholesterol concentration. However, as shown in tables 4A and 4B, the use of thiazides or of \( \beta \)-adrenergic blockers did not invalidate the significant correlations between severity of coronary atherosclerosis and triglyceride level in women and between severity and LDL cholesterol level in men. An additional factor was the high prevalence of heavy alcohol consumption, defined as more than six alcoholic drinks daily, in the men in the study (the drink was invariably beer in the 17 men so identified). However, the exclusion of data from these 17 men from the analysis did not improve the correlation between HDL cholesterol level and coronary atherosclerosis.

In our study population the relationship between severity of disease and plasma lipoprotein concentrations varied markedly between men and women. None of the subjects was hyperlipidemic, indicating the importance of plasma lipid variability even at concentrations considered normal.

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