Plasma Triglycerides and Three Lipoprotein Cholesterol Fractions Are Independent Predictors of the Extent of Coronary Atherosclerosis

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Background The lipoprotein system has manifold links to atherosclerotic disease. LDL cholesterol is related to lesion formation and growth. The cholesterol of HDLs is indicative of protection against atherosclerosis. The status of triglycerides and of subfractions of high-density lipoproteins as risk factors is less certain. Also, the magnitude of the atherogenic/protective power of these factors is not known.

Methods and Results Five hundred patients (418 men and 82 women) were enrolled in an angiographic study. A total of 1006 coronary lesions with ≥50% narrowing were recorded as study end points. By extent of atherosclerosis, defined as the number of ≥50% lesions, the study subjects were allocated to one of four ordered categories with 0, 1 to 3, 4 to 6, or 7 to 10 lesions, respectively. Subfractions of HDL cholesterol were determined by a dual precipitation method. By a polychotomous logistic regression model, it was found that, besides age and sex, LDL cholesterol, HDL2 cholesterol, HDL3 cholesterol, and triglycerides were independently predictive (P<.05) of the extent of coronary atherosclerosis. An increase in age by 10 years was associated with an increase of the odds ratio for falling into a higher-extent category by a factor of 1.64, and the same increase of the odds ratio was obtained by increasing LDL cholesterol by 0.92 mmol/L or triglycerides by 1.01 mmol/L and by decreasing HDL2 cholesterol by 0.20 mmol/L or HDL3 cholesterol by 0.46 mmol/L. The less sensitive coronary end point, presence of atherosclerosis (ie, observation of ≥1 lesion of ≥50%) depended significantly on age, sex, LDL cholesterol, and HDL2 cholesterol, but not on HDL3 cholesterol or triglycerides.

Conclusions In addition to LDL, HDL2, and HDL3 cholesterol, triglycerides also proved independently predictive of the extent of coronary atherosclerosis. (Circulation. 1994;90: 2230-2235.)

Key Words • lipoproteins • heart diseases • lipids • atherosclerosis

The plasma concentrations of cholesterol and of its main component, LDL cholesterol, are established risk factors for the incidence of atherosclerotic vascular complications.1,2 Epidemiological studies have also consistently demonstrated that plasma concentrations of HDL cholesterol are inversely correlated with the incidence of coronary artery disease (CAD).3-6 Animal data suggest that this is a causal association: In transgenic mice, overexpression of the apolipoprotein A-I gene increased plasma HDL cholesterol and inhibited the development of early atherosclerotic ("fatty streak") lesions,7 and infusion of HDL induced regression of established fatty streaks in rabbits.8

Human HDL is a heterogeneous mixture of lipoprotein particles comprising two principal subfractions, HDL2 and HDL3.9 A widely held view is that the benefit of HDL is linked to HDL2.10,11 However, recent data from a case-control study12 and from the prospective Physicians' Health Study13 suggest that HDL3 confers equal if not superior protection against myocardial infarction.

A long-standing debate is to what extent triglycerides contribute to the risk of atherosclerosis. In cross-sectional studies, triglycerides show a univariate association with coronary artery disease, and this association persists after cholesterol or LDL cholesterol is taken into account.14 However, in prospective studies controlling also for HDL cholesterol concentration, triglycerides are eliminated as an independent risk factor in most studies.14

Myocardial infarction may be a suboptimal end point to assess atherogenicity because it represents the last step in a series of events triggered by atherogenic and thrombogenic factors; thrombogenic factors ultimately determine whether or not infarction occurs.15,16 Therefore, the incidence of myocardial infarctions is related to both thrombogenicity and atherosclerosis. Angiography preferentially assesses atherosclerosis. A relation of LDL cholesterol to angiographic characteristics of coronary atherosclerosis is well established.17,18 The few angiographic studies on HDL subfractions that have been published indicate a strong correlation between coronary atherosclerosis and decreased HDL2 levels, whereas the relation to HDL3 levels is less consistent.19,20 but these studies included fewer subjects than epidemiological studies on HDL subfractions.12,13 Also, the status of triglycerides as a risk factor independent of
LDL cholesterol and the two subfractions of HDL cholesterol has not been assessed by angiography. We therefore studied the independent relations of LDL cholesterol, HDL$_1$ cholesterol, HDL$_2$ cholesterol, and triglycerides to the presence and extent of coronary atherosclerosis in 500 patients who had angiography with a total of more than 1000 coronary lesions.

**Methods**

**Patient Selection**

The study group comprised consecutive patients undergoing elective coronary angiography for evaluation of established or suspected CAD. Indications for angiography were exercise-induced stable angina, silent ischemia, previous myocardial infarction, atypical chest pain, aortic stenosis, aortic regurgitation, and mitral regurgitation. Only patients who had adequate visualization of both the right and left coronary artery systems were included. Patients with idiopathic cardiomyopathy, unstable angina, myocardial infarction, cardiopulmonary resuscitation, or a major surgical intervention within the preceding 12 weeks were excluded. In addition, diabetes mellitus, weight loss, viral infections, immobilization, hospitalization, and any type of surgery during the preceding 4 weeks were exclusion criteria. Five hundred patients (418 men and 82 women) were enrolled in the study. Fifty-six patients taking lipid-lowering drugs (43 simvastatin or pravastatin, 13 gemfibrozil or fenofibrate) were excluded from the analysis. The total number of patients studied was 444.

**Coronary Angiography**

Selective coronary angiograms were obtained by the Judkins or Sones technique. Multiple views of the right and the left coronary arteries were recorded. For quantitative evaluation of atherosclerosis, the coronary circulation was divided into 12 segments: the left main coronary artery, the proximal left anterior descending artery (up to the first diagonal branch), the more distal left anterior descending artery, the major septal branch, the first and second diagonal branches, the circumflex artery, the first and second posterolateral (obtuse marginal) branches, the right coronary artery, the posterior descending artery, and the right posterolateral branch. The angiograms were independently reviewed and coded by two cardiologists (F.W.A. and R.C. or A.L.) without knowledge of the lipoprotein values. The presence and extent of CAD was determined by consensus. CAD was considered to be present if ≥1 lesion of ≥50% diameter stenosis was detected. CAD was then determined by extent, which was defined as the number of ≥50% stenoses. In 105 patients, no significant stenoses were found: 75 patients had completely normal coronary arteries, 4 had minimal lesions (<10% stenosis), 14 showed one 10% to 30% stenosis, and 12 had one 30% to 50% stenosis. This proportion of patients without angiographic lesions (75 of 444, or 17%) compares well with a large angiographic study on lipids. Of the 338 patients with significant stenoses (≥50%), 107 had one-vessel, 106 had two-vessel, and 125 had three-vessel disease. A total of 1006 significant lesions were documented; of these, 15 were located in the left main coronary artery, 394 in the tree of the left anterior descending artery, 301 in the tree of the circumflex artery, and 296 in the tree of the right coronary artery.

**Lipid and Lipoprotein Measurements**

After a supervised overnight fast of 12 to 13 hours and after complete abstinence from ethanol for at least 24 hours, venous blood was collected from an antecubital vein into EDTA-containing Vacutainer tubes (Becton Dickinson). During blood collection, the patient remained in a sitting position, and blood was drawn without a tourniquet. The blood sample was centrifuged immediately, and the plasma was frozen without delay to prevent in vitro lipid exchange between lipoproteins and stored at −20°C. Analytical procedures were performed within 3 days. Cholesterol and triglycerides were measured enzymatically using the Cholesterol CHOD-PAP and the Triglyceride GPO-PAP methods, respectively (Roche). These tests were adapted to a Cobas Mira random access analyzer (Roche). HDL, HDL$_1$, and HDL$_2$ cholesterol were determined with a stepwise precipitation procedure with dextran sulfate and the analytical method described above for total cholesterol. The results obtained by this stepwise HDL precipitation procedure were very close to those obtained by HDL subtraction analysis using rate zonal ultracentrifugation. Plasma concentrations of apolipoproteins A-1 and B were determined by turbidimetric immunoprecipitation assays (Uni Kit T, Roche) on a Cobas Mira. These methods have been shown to give excellent agreement with nephelometric assays. Non-HDL cholesterol was found by subtracting HDL cholesterol from total plasma cholesterol. LDL cholesterol and very-low-density lipoprotein (VLDL) cholesterol were calculated by Friedewald’s formula for plasma samples with triglyceride concentrations <400 mg/dL (4.52 mmol/L); in the six patients with triglyceride values >400 mg/dL (4.52 mmol/L), no attempt was made to estimate LDL cholesterol.

The following performance characteristics of the dual precipitation method were obtained in our laboratory: the first precipitation (HDL cholesterol) had a mean intra-assay coefficient of variation of 1.4% (mean, 49 mg/dL [1.26 mmol/L]) and an interassay variation coefficient of 1.6% (mean, 51 mg/dL [1.32 mmol/L]). The intra-assay variation coefficient of the second precipitation (HDL$_2$ cholesterol) was 1.7% (mean, 52 mg/dL [1.35 mmol/L]), and the interassay variation coefficient was 2.1% (mean, 53 mg/dL [1.37 mmol/L]). Further details have been described elsewhere.

**Statistics**

CAD was assessed angiographically with respect to presence (yes/no, based on whether there were lesions with ≥50% stenosis or not) and extent (number of lesions ≥50%). The extent varied between 0 and 10 lesions. To obtain statistically sensible results, we distinguished the following four categories: category 1, no lesions; category 2, 1 to 3 lesions; category 3, 4 to 6 lesions; and category 4, 7 to 10 lesions. Presence and extent of disease were investigated with respect to their associations with the factors total cholesterol, LDL cholesterol, HDL$_1$ cholesterol, HDL$_2$ cholesterol, and triglycerides, apolipoprotein B, age, and sex. To test the association of these risk factors with the presence of CAD, stepwise logistic regression was used. To test the association of risk factors with extent of CAD, stepwise ordinal polychotomous regression analysis was used. An ordinal polychotomous logistic regression is a generalization of standard logistic regression, allowing for more than two ordered categories in the response variable (30). The limits (P values) for entering or removing a factor were set to .1 and .15, respectively. All calculations were performed on a Sparc 10 work station using the statistical software package BMDP (BMDP Statistical Software, Inc.). The term HDL cholesterol was not included into stepwise regression models because HDL cholesterol represents the exact sum of HDL$_1$, HDL$_2$, and HDL$_3$ cholesterol and therefore contains all the variability of the two subfractions. For the same reason, apolipoprotein A-1, which is a main constituent of both HDL$_2$ and HDL$_3$, was not entered into the models.

**Results**

Of the 500 patients enrolled in the study, 56 were excluded from analysis because they were taking lipid-lowering drugs. Of the remaining 444 subjects, 339 had one or more significant (≥50%) coronary lesions (CAD+); 105 were free of such lesions (CAD−). Table 1 lists the demographic characteristics of these two
patient groups. As expected, the proportion of smokers was higher in CAD+ patients than in CAD− patients. By contrast, there were no significant differences with respect to age, body mass index, systolic or diastolic blood pressure, or alcohol intake.

Table 2 lists the lipoprotein values of patients with and without CAD. The results of the stepwise logistic regression analysis are depicted in Table 3. When only LDL cholesterol, HDL₁ cholesterol, HDL₂ cholesterol, age, and sex were included as explanatory variables for CAD presence, the method selected all five variables. With the exception of HDL₃ cholesterol, all of these variables had a significant independent influence (at the 5% level) on the occurrence of CAD. The P value of HDL₃ cholesterol was slightly greater (P=0.06). As expected, the factors LDL cholesterol, age, and male sex increased the probability of occurrence of CAD. HDL₁ and HDL₂ cholesterol had the opposite effect. The results remained identical when triglycerides, plasma cholesterol, VLDL cholesterol, and non-HDL cholesterol were also included: none of the latter variables were independently associated with CAD presence.

An increase in age by 10 years increased the risk for the presence of CAD by a factor of 1.3 (95% confidence interval, 1.02 to 1.69), provided that all other factors were kept constant. The same increase was obtained by increasing LDL cholesterol by about 0.87 mmol/L. The amounts of HDL₁ cholesterol and HDL₂ cholesterol by which this increase would be compensated were 0.11 and 0.24 mmol/L, respectively.

The quantity defined as “extent of CAD” gives a more refined measure of CAD than the dichotomized variable “presence of CAD.” The results of the stepwise polytomous logistic regression confirm the role of all three cholesterol subfractions, LDL, HDL₁, and HDL₂ cholesterol, but the stepwise procedure also included triglycerides and apolipoprotein B (Table 4). The contribution to the model was highly significant for triglycerides (P=0.005) but not for apolipoprotein B (P=0.78). An increase in age of 10 years increased the risk of falling into a higher category of CAD extent by a factor of 1.6 (95% confidence interval, 1.34 to 2.01), provided that all other factors were kept constant. The same increase was obtained by increasing LDL cholesterol by about 0.92 mmol/L or by increasing plasma triglycerides by about 1.01 mmol/L. The amounts of HDL₂ and HDL₃ cholesterol by which this increase would be compensated were 0.20 and 0.46 mmol/L, respectively.

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**Table 1. Demographic Characteristics of Patients With (CAD+) and Without (CAD−) Significant Coronary Lesions**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAD+</th>
<th>CAD−</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>339</td>
<td>105</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±0.5</td>
<td>58±1.0</td>
</tr>
<tr>
<td>Sex distribution, %, M/F</td>
<td>89/11</td>
<td>63/37</td>
</tr>
<tr>
<td>BMI, kg · m⁻²</td>
<td>25.9±0.2</td>
<td>25.3±0.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129±1</td>
<td>133±2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80±1</td>
<td>83±1</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>70</td>
<td>51</td>
</tr>
<tr>
<td>Ethanol intake ≥5 g/d, %</td>
<td>56</td>
<td>54</td>
</tr>
</tbody>
</table>

BMI indicates body mass index. Values are mean±SEM unless stated.

**Table 2. Lipid, Lipoprotein Lipid, and Apolipoprotein Levels in Patients With (CAD+) and Without (CAD−) Significant Coronary Lesions**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAD+</th>
<th>CAD−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cholesterol</td>
<td>5.86±0.06</td>
<td>5.60±0.10</td>
</tr>
<tr>
<td>Plasma triglycerides</td>
<td>1.80±0.06</td>
<td>1.51±0.10</td>
</tr>
<tr>
<td>HDL₁ cholesterol</td>
<td>1.18±0.02</td>
<td>1.41±0.04</td>
</tr>
<tr>
<td>HDL₂ cholesterol</td>
<td>0.18±0.01</td>
<td>0.29±0.02</td>
</tr>
<tr>
<td>HDL₃ cholesterol</td>
<td>1.00±0.01</td>
<td>1.13±0.02</td>
</tr>
<tr>
<td>Apolipoprotein A-1</td>
<td>1.35±0.01</td>
<td>1.49±0.02</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>1.22±0.02</td>
<td>1.11±0.03</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.89±0.05</td>
<td>3.55±0.09</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>5.26±0.09</td>
<td>4.26±0.13</td>
</tr>
<tr>
<td>LDL/HDL cholesterol</td>
<td>3.49±0.07</td>
<td>2.71±0.10</td>
</tr>
</tbody>
</table>

Plasma concentrations of lipids and lipoprotein lipids are given in mmol/L, apolipoproteins in g/L. Values are mean±SEM.

*Subjects taking lipid-lowering drugs were excluded from analysis.

**Table 3. Relation of Risk Factors to the Presence of Coronary Atherosclerosis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>β*</th>
<th>SD</th>
<th>β/SD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>0.132</td>
<td>0.139</td>
<td>2.24</td>
</tr>
<tr>
<td>HDL₁ cholesterol</td>
<td>-2.475</td>
<td>1.060</td>
<td>-2.34</td>
</tr>
<tr>
<td>HDL₂ cholesterol</td>
<td>-1.144</td>
<td>0.613</td>
<td>-1.86</td>
</tr>
<tr>
<td>Age</td>
<td>0.027</td>
<td>0.013</td>
<td>2.08</td>
</tr>
<tr>
<td>Sex</td>
<td>-1.292</td>
<td>0.302</td>
<td>-4.28</td>
</tr>
</tbody>
</table>

*A positive coefficient indicates that the corresponding factor tends to increase the probability of coronary atherosclerosis; a negative factor indicates that the factor tends to decrease the probability of coronary atherosclerosis.

†This column measures how strongly significant the corresponding effect is (if the term is ≥1.96 in absolute value, the effect is significant at the 5% level).

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**Table 4. Relation of Risk Factors to the Extent of Coronary Atherosclerosis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>β*</th>
<th>SD</th>
<th>β/SD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>0.5371</td>
<td>0.192</td>
<td>2.79</td>
</tr>
<tr>
<td>HDL₁ cholesterol</td>
<td>-2.432</td>
<td>0.958</td>
<td>-2.54</td>
</tr>
<tr>
<td>HDL₂ cholesterol</td>
<td>-1.067</td>
<td>0.506</td>
<td>-2.11</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.4899</td>
<td>0.176</td>
<td>2.79</td>
</tr>
<tr>
<td>Age</td>
<td>0.0493</td>
<td>0.010</td>
<td>4.76</td>
</tr>
<tr>
<td>Sex</td>
<td>-1.124</td>
<td>0.284</td>
<td>-3.96</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>1.190</td>
<td>0.675</td>
<td>1.76</td>
</tr>
</tbody>
</table>

*A positive coefficient indicates that the corresponding factor tends to increase the number of lesions.

†This column measures how strongly significant the corresponding effect is (if the term is ≥1.96, the effect is significant at the 5% level).

$\text{Male}=0$, $\text{female}=1$. 
Discussion

Extent is probably a better marker of coronary atherosclerosis than presence. It offers superior sensitivity because every stenosis represents a separate end point. This study documented 1006 end points, four to eight times more than reported from large prospective studies.\textsuperscript{13,31} Three fractions of blood cholesterol (LDL cholesterol, HDL\textsubscript{2} cholesterol, and HDL\textsubscript{3} cholesterol) as well as plasma triglycerides were strongly and independently related to the angiographic extent of coronary atherosclerosis. For the less sensitive end point, presence of coronary atherosclerosis, only HDL\textsubscript{2} cholesterol and LDL cholesterol were significant predictors.

Our finding of a strong independent predictive power of LDL cholesterol for presence and extent of coronary atherosclerosis fits well into the large body of evidence from animal studies, clinical trials, and observational epidemiological studies for a causal role of LDL cholesterol in atherosclerosis.\textsuperscript{1,2} This “LDL cholesterol” represents the non-HDL, non-VLDL fraction of plasma cholesterol and thus encompasses, besides the cholesterol of true LDL particles (density range, 1.019 to 1.063 g/mL), also that of intermediate-density lipoproteins (density range, 1.006 to 1.019 g/mL). The latter particles are considered particularly atherogenic because it was found that their plasma concentration is strongly predictive of the progression of coronary atherosclerosis.\textsuperscript{32,33} The predictive power of LDL cholesterol for disease extent as found in our study thus stands for the cholesterol that is carried by all particles in the density range of 1.006 to 1.063 g/mL and not exclusively for true LDL. Although this distinction is of major pathophysiological importance, it is less so for clinical strategies because the separation of intermediate-density lipoproteins from LDL is not feasible for the clinical laboratory.

In contrast to these problems with measurement of true LDL cholesterol, the two main subfractions of HDL cholesterol can be readily separated in the clinical laboratory. While the predictive power of HDL for the development of coronary atherosclerosis is well documented, it is less clear which of its subfractions is involved. We found that only HDL\textsubscript{2} is significantly related to the presence of coronary atherosclerosis but that both HDL\textsubscript{2} and HDL\textsubscript{3} are significantly predictive of disease extent.

These data clarify some of the controversy in the literature regarding the relation of HDL subfractions to CAD. Published studies differed by definition of CAD and by results: CAD presence was documented by myocardial infarction in prospective\textsuperscript{13,34,35} and retrospective studies\textsuperscript{12,36} and by angiographic evidence.\textsuperscript{22} Presence of CAD was inconsistently related to HDL subfractions, with one study demonstrating relations solely of HDL\textsubscript{2}\textsuperscript{35} and others more of HDL\textsubscript{2} than of HDL\textsubscript{3}\textsuperscript{22,24} more of HDL\textsubscript{3} than of HDL\textsubscript{2}\textsuperscript{13,36} or equally of HDL\textsubscript{2} and HDL\textsubscript{3}\textsuperscript{12}. However, those studies had one important limitation: none proved absence of significant CAD by angiography of control subjects. Thus, clinically silent but significant CAD may have been present in control subjects. In addition, in one study,\textsuperscript{13} only nonfasting plasma samples were available, and it has been argued\textsuperscript{37} that the postprandial state probably affected HDL subfraction distribution. In contrast to these previous studies, we demonstrated the absence of significant CAD angiographically in all individuals of the comparison group and used fasting plasma samples. We detected the larger difference (between the patients and the comparison group) in HDL\textsubscript{2} cholesterol (>30%) than in HDL\textsubscript{3} cholesterol (≈10%). These differences were remarkably similar to those reported in the prospective study by Gofman et al.,\textsuperscript{34} in which patients with CAD had 32% lower HDL\textsubscript{2} and 8% lower HDL\textsubscript{3} levels than control subjects.

The relation of HDL subfractions to the extent of CAD has been addressed in two studies.\textsuperscript{21,36} Brook et al.\textsuperscript{36} found no relation in 10 patients, whereas Miller et al.\textsuperscript{21} demonstrated a significant association with HDL\textsubscript{2} (but not of HDL\textsubscript{3}) in 104 patients. We found a significant association with CAD extent of both HDL\textsubscript{2} and HDL\textsubscript{3} cholesterol. Obviously, a large sample size is necessary to reveal the contributions of the two subfractions to CAD extent.

The mechanism by which HDL protects against atheroma is not fully understood. One concept is reversed cholesterol transport. Free cholesterol leaving cells is transferred to the surface of small so-called pre-β-HDL, where it is esterified to intensively hydrophobic cholesterol esters by lecithin:cholesterol acyl transferase to form a central lipid droplet. The levels of HDL cholesterol and particularly of the more cholesterol-enriched HDL\textsubscript{2} thus reflect the activity of this transport system. An alternative idea is that HDL impedes the oxidative modification of LDL\textsuperscript{38,39} that is believed necessary for its uptake into the arterial wall.\textsuperscript{40} Such HDL particles could hence protect from atherosclerosis by interfering with the atherogenicity of LDL.

Apart from age, sex, and cholesterol subfractions, triglycerides emerged as a significant and independent predictor for the extent of coronary atherosclerosis. It fits well into this notion that hypertriglyceridemia is frequently encountered in diabetic patients,\textsuperscript{14} in whom extent of coronary atherosclerosis is greater than in nondiabetic patients,\textsuperscript{41,42} and is related to triglyceride levels.\textsuperscript{41} However, a very sensitive tool is required to prove this association of triglycerides with disease extent also for nondiabetics who have a lower prevalence of hypertriglyceridemia. This is also demonstrated by our data: Triglycerides were not related to the less sensitive end point, presence of coronary atherosclerosis. From the three published angiographic studies in which triglyceride levels were adjusted for HDL cholesterol, the triglyceride association with disease extent remained significant in two\textsuperscript{43,44} but did not in one.\textsuperscript{45} However, none of them studied HDL subfraction cholesterol together with triglycerides.

Because of the correlation between HDL cholesterol and triglycerides, in most studies, triglycerides are eliminated as an independent risk factor when HDL cholesterol is included in multiple logistic regression models.\textsuperscript{14} A widely held view, therefore, is that high triglycerides are not directly atherogenic but act via decreased HDL levels. In contrast, our data point to a role for triglycerides to increase disease extent independently of HDL and LDL. The theoretical possibility that triglycerides are only an indicator of the atherogenicity residing in the cholesterol of triglyceride-rich particles can be excluded because VLDL cholesterol was not a significant variable in the statistical model.
One mechanism to explain an intrinsic atherogenicity of triglycerides is that high plasma triglyceride levels drive core lipid exchange between lipoproteins. Triglycerides are thereby transferred from triglyceride-rich lipoproteins to LDL in exchange with cholesterol esters. Subsequently, the triglyceride of LDL is hydrolyzed by lipoprotein lipase and/or hepatic lipase, which reduces size and increases density of these LDLs. Small, dense LDLs are the hallmark of the LDL subclass pattern B, also known as the "atherogenic lipoprotein phenotype." This pattern shows a dominant mode of inheritance, is present in about 30% of the population, and confers a high risk for myocardial infarction. Thus, LDL subclass pattern B appears to be a genetically influenced risk factor for CAD that is closely related to plasma triglyceride levels. In this context, triglycerides can be viewed as molecules that toxify LDL. This interpretation is consistent with the data from the PROCAM study, in which, among individuals with an LDL/HDL cholesterol ratio > 5.0, hypertriglyceridemia proved a powerful additional risk factor for atherosclerotic events.

The design of our study with its high number of end points also enabled us to compare reliably the power of the risk factors age, LDL cholesterol, and triglycerides and of the protective factors HDL2 cholesterol and HDL3 cholesterol. An increase of 10 years of age had the same effect on CAD extent as an increase of 0.92 mmol/L in LDL cholesterol or of 1.01 mmol/L in triglycerides and equaled the protective effect of 0.20 mmol/L HDL2 cholesterol or of 0.46 mmol/L HDL3 cholesterol. No such data on the relative power of these risk factors have been reported as yet, except that one study compared the effects of LDL cholesterol and HDL cholesterol (without subtraction analysis) on total cardiovascular mortality: an increase in LDL cholesterol of 30 mg/dL was found to be equivalent to a decrease in HDL cholesterol of 10 mg/dL in men. These numbers compare well to our risk ratios.

In summary, this large angiographic study demonstrates that a number of critical steps in lipid metabolism that have been recently elucidated are operative in vivo and contribute importantly to the extent of coronary atherosclerosis. Angiographic studies, however, have some limitations that can be dissected into three problem areas: First, inclusion of patients who recently had a myocardial infarction may alter risk factor levels. This problem was circumvented in our study in that patients who had an infarction within the previous 12 weeks were excluded from the study. Moreover, risk factors may be related to other causes of infarction than atherosclerosis, such as the clotting system or spasm. This limitation does not apply to our study because infarction per se was not an end point, and patients with old infarctions were classified simply according to their lesion number. The second problem area is that control subjects are not necessarily free of atherosclerosis. However, of our 105 subjects of the comparison group, only 12 had 30% to 50% stenoses, and 75 had none at all. Since absence of significant lesions was shown in all individuals of the comparison group and only a few patients with nonsignificant lesions were included, our comparison group appears better defined than "control subjects" defined simply by absence of clinical end points. A third concern is that arteriography series may have inherent selection bias because hyperlipidemic patients may be more readily referred to angiography than normolipidemic subjects. This was not the case in our cohort, because all referrals were based on clinical criteria and lipids were never considered for referral. Also, no acute coronary syndromes or disease states that alter lipid values were included. Thus, none of these three principal concerns substantially limited the validity of our data.

Acknowledgments

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