The Relation of Documented Coronary Artery Disease to Levels of Total Cholesterol and High-Density Lipoprotein Cholesterol

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Abstract:

Recommendations for identifying persons at high risk for coronary heart disease are based primarily on levels of total and low-density lipoprotein cholesterol. We examined whether, given knowledge of these levels, information on the high-density lipoprotein cholesterol level would improve the prediction of arteriographically documented coronary artery disease among 591 men. We found that even at levels of total and low-density lipoprotein cholesterol considered desirable, high-density lipoprotein cholesterol was inversely related to disease severity. For example, among the 112 men with a total cholesterol level <180 mg per dl, the mean occlusion score (representing the overall severity of disease) was 107 among men with a high-density lipoprotein cholesterol level ≤30 mg per dl *vs* a mean score of 52 among men with levels ≥45 mg per dl. Furthermore, men with low levels of both low-density lipoprotein cholesterol (<110 mg per dl) and high-density lipoprotein cholesterol (≤30 mg per dl) had as much occlusive disease as did men with high levels of both lipoprotein fractions. Given information on the ratio of high-density lipoprotein cholesterol to total cholesterol, the actual levels of the lipoprotein fractions did not improve disease prediction. Our results emphasize the importance of considering high-density lipoprotein cholesterol when assessing coronary heart disease risk.
Keywords: cholesterol levels, HDL lipoproteins, LDL lipoproteins, coronary artery disease, lipids.

Article:

The 1988 guidelines from the National Cholesterol Education Program suggest that all adults have a non-fasting determination of total cholesterol at least once every 5 years.[1] A lipoprotein analysis is recommended for persons with a total cholesterol level ≥240 mg per dl, as well as for those with levels between 200 and 239 mg per dl if either coronary heart disease or two additional risk factors are present. Persons with a total cholesterol level <200 mg per dl (considered desirable) would be advised to have another measurement within 5 years. Although the guidelines recognize that the risk of coronary heart disease is increased if the high-density lipoprotein (HDL) cholesterol level is low, recommendations for identification and treatment are based on levels of total and low-density lipoprotein (LDL) cholesterol.

Because the inverse association between HDL cholesterol and disease incidence is independent of total cholesterol,[2,3] persons with a low level of HDL cholesterol may be at increased risk for coronary heart disease even if total cholesterol is in the desirable range.[4-7] Among patients with documented occlusive disease, a large proportion have a relatively low total cholesterol level,[8,9] and the HDL cholesterol level is predictive of subsequent cardiovascular events.[10] A recent consensus conference panel recommended that HDL cholesterol be measured, in conjunction with total cholesterol, when evaluating coronary heart disease risk among healthy adults and persons with prevalent disease.[11]

Because of the opposing associations of LDL cholesterol and HDL cholesterol levels with coronary heart disease, several ratios (HDL cholesterol ÷ total cholesterol, HDL cholesterol ÷ LDL cholesterol, and their reciprocals[6,9,12-15]) have been used to summarize the atherogenicity of a lipoprotein profile. Only one

study,[14] however, has compared the accuracy of these ratios in predicting disease with that achieved by using the actual levels of the lipoprotein cholesterol fractions. Our objective, in this cross-sectional study of 591 men who underwent coronary arteriography, is to assess the joint relation of total cholesterol and HDL cholesterol to disease severity; we were particularly interested in the severity of occlusive disease among men with low levels of both total cholesterol and HDL cholesterol. Furthermore, we examine whether simple ratios can adequately summarize the information contained in the specific levels of total cholesterol, LDL cholesterol, and HDL cholesterol.

Methods

POPULATION AND DISEASE STATUS

The Milwaukee Cardiovascular Data Registry, established in 1972, contains data on patients referred for diagnostic coronary angiography because of angina pectoris, previous myocardial infarction, or recurrent chest pain of unknown origin. Between 1977 and 1986, HDL cholesterol determinations were performed for about 1,000 white men, and the current analyses are restricted to this race-sex group. (Other races represented less than 5% of all patients.) Patients were excluded from this study if they reported having a previous myocardial infarction, either hypothyroidism or hyperthyroidism, or if they used cholesterol-lowering drugs, thyroid medications, or adrenocorticosteroids during the 3 previous months. Because levels of LDL cholesterol were calculated according to the Friedewald equation,[16] three men with a triglyceride level ≥400 mg per dl were also excluded. The analytic sample comprised 591 men who ranged in age from 34 to 84 years (mean = 59 years).

The extent of occlusive disease was evaluated by a radiologist and cardiologist without knowledge of risk factor data. Reductions in lumen diameter due to the most serious stenosis in the left anterior descending, circumflex, and right coronary arteries were incorporated into an overall occlusion score.[17] The scale, however, was inverted, so that a score of 0 indicates no occlusion of any artery, and a score of 300 represents total occlusion of all vessels. The mean occlusion score was 112, and 22% (131 of 591) had a score of 0. In addition to this overall score, in some analyses we considered the extent of coronary artery disease to be clinically important if the lumen diameter of any vessel was decreased by >50%.

RISK FACTOR INFORMATION

We used medical records and questionnaires to obtain data on race, age, weight, height, alcohol consumption, smoking history, history of hypertension, previous myocardial infarction, angina, diabetes mellitus, and medication use. The frequency and duration of smoking were summarized using a five-point scale (for example, 1 = never smoked; 5 = smoked two or more packs daily for 20 years); consumption of beer, wine, and mixed drinks was converted to ounces of alcohol per week.[18,19] Height and weight were used to compute Quetelet index (kg per m^2); because of missing data, Quetelet index could not be calculated for 30 men. Because (1) there was no association between overweight and disease severity in either bivariate or multivariable analyses, and (2) Quetelet index did not confound the cholesterol-disease association, overweight was not included in the current analyses.

Fasting blood samples were collected before angiography. Plasma levels of total cholesterol were measured using automated procedures[20,21] in a laboratory that was standardized by the Centers for Disease Control and monitored by its surveillance program. HDL cholesterol was measured using procedures employed by the Lipid Research Clinics,[21] and LDL cholesterol was calculated as total cholesterol — HDL cholesterol —(triglycerides ÷ 5).[16] Mean levels were 216 mg per dl (total cholesterol), 167 mg per dl (triglycerides), 143 mg per dl (LDL cholesterol), and 39 mg per dl (HDL cholesterol).

STATISTICAL METHODS

We assessed associations among disease severity and various characteristics using Spearman and Pearson correlations. (The results of analyses using logarithmic and square root transformations were very similar to those using the untransformed data.) We calculated 95% confidence intervals for these correlation coefficients following a z-transformation.[22]

Multiple linear regression was used to examine the independent relation of cholesterol and the lipoproteins to disease severity after controlling for age (four dummy variables for five categories), year of lipid analysis (five dummy variables), diabetes mellitus, hypertension, cigarette smoking, alcohol consumption, and use of beta-blockers. Complete information on the lipoproteins and covariates was available for 95% (562 of 591) of the patients. Because of the difference in the measurement scales of the lipoproteins and ratios, we examined the relative importance of each by calculating the predicted change in the occlusion score associated with a change of 1 standard deviation. Effect modification of the relation of levels of total cholesterol and the lipoproteins to disease severity was examined by stratification and regression analyses.[23] We also examined the extent of occlusive disease after cross-classifying categories of HDL cholesterol with those of total cholesterol or LDL cholesterol.

We used regression analyses to assess the improvement in disease prediction obtained with various characteristics. Changes in the multiple R^2 due to the additional information on lipoprotein cholesterol levels or ratios were compared with the R^2 of baseline models containing the (1) covariates only, (2) covariates and total cholesterol, (3) covariates and HDL cholesterol, or (4) covariates and HDL cholesterol ÷ total cholesterol. A large ΔR^2 would indicate that the added information improved the prediction of disease severity beyond that obtained with the baseline model.

TABLE 1. Pearson Correlation Coefficients among the Occlusion Score, Lipoproteins, and Other Characteristics

		Cholesterol						
	Occlusion Score*	Total	LDL	HDL	HDL ÷ Total	HDL ÷ LDL	Age	Smoking†
Total cholesterol	0.17 (0.10, 0.25)							
LDL cholesterol	0.19 (0.11, 0.27)	0.95						
HDL cholesterol	−0.25 (−0.17, −0.32)	0.14	0.04					
HDL cholesterol ÷ total cholesterol	−0.34 (−0.27, −0.41)	−0.49	−0.53	0.76				
HDL cholesterol ÷ LDL cholesterol	−0.34 (−0.26, −0.41)	−0.52	−0.62	0.65	0.94			
Age	0.13 (0.05, 0.21)	−0.07	−0.03	−0.07	−0.01	−0.01		
Cigarette smoking†	0.07 (−0.01, 0.15)	0	−0.03	0.01	0	0	−0.02	
Alcohol consumption‡	−0.08 (0, −0.16)	0.05	−0.03	0.21	0.15	0.18	−0.07	0.11

* Ninety-five per cent confidence limits are given in parentheses.
† Based on a 5-point scale: 0 = nonsmoker; 5 = heavy smoker.
‡ Ounces per week.

Results

The occlusion score was related positively to levels of total cholesterol and LDL cholesterol (r = 0.17 and r = 0.19, respectively) and inversely with HDL cholesterol (r = -0.25), but associations were stronger with the lipoprotein ratios (Table 1). Disease severity was related similarly to levels of both HDL cholesterol ÷ total cholesterol and HDL cholesterol ÷ LDL cholesterol (r = -0.34). We found weaker associations between the occlusion score and age (r = 0.13), alcohol consumption (r = -0.08), and cigarette smoking (r = 0.07). Alcohol consumption was also moderately associated (r = 0.21) with levels of HDL cholesterol. Diabetics, persons with a history of hypertension, and those using beta-blockers had a higher mean occlusion score, along with a lower HDL cholesterol level than did other persons (data not shown).

An examination of mean occlusion scores within deciles of total cholesterol or HDL cholesterol ÷ total cholesterol indicated that the associations were fairly linear (Figure 1). Only 3% (total cholesterol) or 12% (HDL cholesterol ÷ total cholesterol) of the variability in disease severity, however, could be explained by these characteristics. In these bivariate analyses, each standard deviation increase in total cholesterol (≈45 mg per dl) was associated with a 14-point increase in the occlusion score, whereas each standard deviation increase in HDL cholesterol ÷ total cholesterol (≈0.06 unit) was associated with a 28-point decrease.

Mean lipid levels according to the number of diseased vessels are shown in Table 2. Mean levels of total cholesterol differed by about 8% between men with no significant disease (207 mg per dl) and those with three-vessel disease (226 mg per dl); comparable differences between mean levels of HDL cholesterol and HDL cholesterol ÷ total cholesterol were 18% and 28%, respectively. We also examined the predicted change in the occlusion score associated with a 1-standard deviation change in each characteristic after controlling for the

covariates (final column). These changes ranged from +17 points (total and LDL cholesterol) to -25 points (HDL cholesterol ÷ LDL cholesterol).

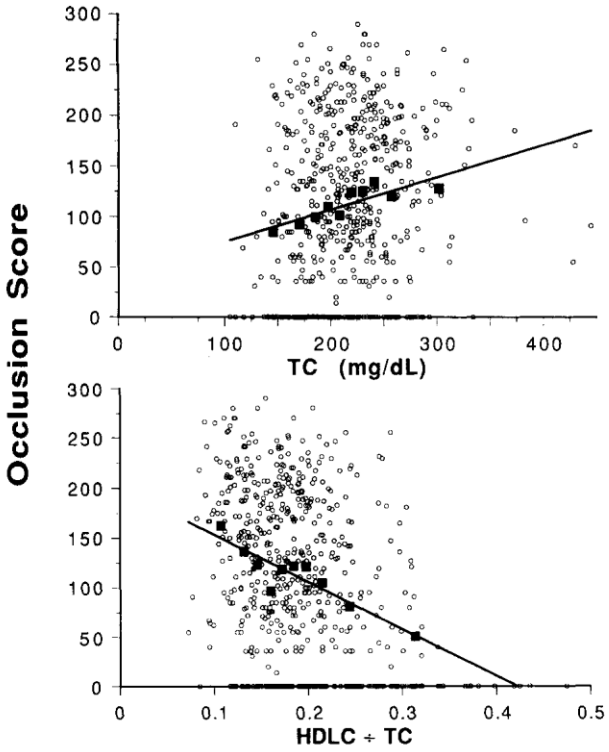

FIGURE 1. **Relation of coronary artery disease severity to levels of total cholesterol (*upper panel*) and HDL cholesterol ÷ total cholesterol (*lower panel*). *Open circles* represent individual men (N = 591); ■ = the mean occlusion score within deciles of each predictor variable. The estimated regression line is also shown in each panel. Regression equations for the occlusion score are 43 + 0.32 × total cholesterol, and 201 − 476 × (HDL cholesterol ÷ total cholesterol).**

TABLE 2. **Relation of Lipid and Lipoprotein Levels to the Severity of Coronary Artery Disease, as Measured by the Occlusion Score**

Characteristic	Number of Diseased Vessels* 0 (N = 216)	1 (N = 124)	2 (N = 122)	3 (N = 129)	Δ† (%)	Predicted Change in Occlusion Score‡
Total cholesterol (mg/dl)	207	217	221	226	8	17 (11, 23)
LDL cholesterol (mg/dl)	134	145	150	152	12	17 (11, 24)
HDL cholesterol (mg/dl)	42	39	37	36	−18	−14 (−7, −20)
HDL cholesterol ÷ total cholesterol	0.21	0.18	0.17	0.16	−23	−24 (−18, −31)
HDL cholesterol ÷ LDL cholesterol	0.35	0.28	0.26	0.25	−28	−25 (−18, −31)

* Based on a >50% reduction in lumen diameter.
† Calculated as (mean level of characteristic among men with three-vessel disease − mean level among men with no disease) ÷ (mean level among men with no disease).
‡ Change (as predicted from multiple linear regression) in the occlusion score associated with a one-standard deviation unit increase in each characteristic. Covariates included in regression models are age, year of examination, diabetes mellitus, hypertension, cigarette smoking, alcohol consumption, and use of beta-blockers. Ninety-five per cent confidence limits are given in parentheses.

We then examined disease severity, as assessed by both the occlusion score and the presence a >50% stenosis, after cross-classifying levels of HDL cholesterol with total cholesterol or LDL cholesterol (Table 3). (Overall, the mean occlusion score was 112, with 63% of the men having clinically important disease.) HDL cholesterol

was inversely related to disease severity at all levels of total and LDL cholesterol, even at values considered desirable. For example, at a total cholesterol <180 mg per dl, there was a twofold difference in the mean occlusion score (52 *vs* 107) and in the proportion of men with significant disease (28% *vs* 60%) over the three HDL cholesterol strata. Furthermore, the severity of disease among men with total cholesterol <180 mg per dl and HDL cholesterol ≤30 mg per dl was almost identical to that among men with levels of total cholesterol ≥240 and HDL cholesterol ≥45 (a mean occlusion score of 107 in both cells). A similar pattern was seen for LDL cholesterol: the proportion of men with clinically important disease in the low-LDL cholesterol, low-HDL cholesterol group (67%) was similar to that for the high-LDL cholesterol, high-HDL cholesterol group (62%).

TABLE 3. Mean Levels of the Occlusion Score and the Proportion of Men with Clinically Important Disease by Levels of Total Cholesterol, LDL Cholesterol, and HDL Cholesterol*

	HDL Cholesterol (mg/dl)			
	≤30 (N = 109)	31–44 (N = 312)	≥45 (N = 141)	Correlation Coefficient†
Total cholesterol (mg/dl)				
<180 (N = 112)	107 (60)‡	76 (39)	52 (28)§	−0.28 (−0.10, −0.42)
180–199 (N = 92)	101 (65)§	117 (67)	66 (50)	−0.32 (−0.12, −0.49)
200–219 (N = 92)	165 (90)	113 (66)	99 (53)	−0.27 (−0.07, −0.45)
220–239 (N = 112)	148 (91)	114 (63)	121 (83)	−0.25 (−0.07, −0.41)
≥240 (N = 154)	149 (91)	138 (82)	107 (61)	−0.30 (−0.15, −0.43)
LDL cholesterol (mg/dl)				
<110 (N = 109)	113 (67)	80 (41)	40 (22)	−0.35 (−0.17, −0.50)
110–129 (N = 114)	124 (72)	105 (60)	80 (57)	−0.31 (−0.13, −0.47)
130–159 (N = 155)	127 (87)	119 (66)	120 (72)	−0.10 (0.06, −0.25)
≥160 (N = 184)	153 (86)	133 (79)	105 (62)	−0.33 (−0.19, −0.45)

* Analyses are restricted to the 562 men with complete information on all covariates.
† Pearson correlation between the HDL cholesterol level and the occlusion score. Ninety-five per cent confidence limits are given in parentheses.
‡ Mean occlusion score; value in parentheses represents the percentage of men with at least one >50% stenosis. All values have been adjusted for age, year of examination, diabetes mellitus, cigarette smoking, alcohol consumption, and use of beta-blockers and antihypertensive medications. All values are based on ≥20 observations except where noted.
§ N < 20.

We then examined the multiple R^2 values for the prediction of the occlusion score in several linear regression models, as well as the increases in R^2 achieved by using additional information on levels of total cholesterol or the lipoprotein cholesterol fractions. As shown in the first column of Table 4, about 17% of the variability of the occlusion score could be statistically explained by the covariates alone, but using information on total cholesterol or the cholesterol fractions improved the prediction of disease severity. The maximum R^2 increase (+8.4%) was seen following the addition to the model of levels of HDL cholesterol ÷ total cholesterol or HDL cholesterol ÷ LDL cholesterol. Furthermore, a model containing both total cholesterol and HDL cholesterol (as separate predictors) did not account for more of the variability in the occlusion score than did a model containing HDL cholesterol ÷ total cholesterol (+7.8% vs +8.4%).

TABLE 4. Additional Information (ΔR^2) Provided by Lipids and Lipoproteins in Predicting the Occlusion Score

	Variables in Baseline Regression Model			
Additional Predictors	Covariates*	Covariates, Total Cholesterol	Covariates, HDL Cholesterol	Covariates, HDL Cholesterol ÷ Total Cholesterol
None	17.0†	20.9	19.8	25.3
Total cholesterol	+4.0		+4.9	+0.4
LDL cholesterol	+4.2	+0.2	+4.5	+0.4
HDL cholesterol	+2.8	+3.8		+0.7
Total cholesterol and HDL cholesterol	+7.8			+0.8
LDL cholesterol and HDL cholesterol	+7.3	+3.8		+0.7
HDL cholesterol ÷ total cholesterol	+8.4	+4.8	+6.2	
HDL cholesterol ÷ LDL cholesterol	+8.4	+4.8	+5.7	+0.3

* The covariates (age, year of examination, diabetes mellitus, hypertension, cigarette smoking, alcohol consumption, and use of beta-blockers) are included as independent variables in all models.
† Values represent the multiple R^2 of the baseline model (first row) or the increase in R^2 associated with the addition of various characteristics to the baseline model. The R^2 is the percentage of the variation in the occlusion score that can be statistically "explained" by the variability of the predictor variables.

The results of other models are also shown in Table 4. Given knowledge of the covariates and the total cholesterol level (column 2), the prediction of disease severity was improved by using information on HDL cholesterol and the lipoprotein ratios. Furthermore, levels of total cholesterol, LDL cholesterol, and the ratios each improved the prediction of the occlusion score beyond that obtained with HDL cholesterol and the covariates (third column). In contrast, given information on the covariates and HDL cholesterol ÷ total cholesterol (final column; baseline $R^2 = 0.253$), the largest ΔR^2 was only 0.8%. Therefore, the actual level of total, LDL, or HDL cholesterol provides little additional information on disease severity if the HDL cholesterol ÷ total cholesterol level is already known.

Discussion

Although the 1988 guidelines from the National Cholesterol Education Program based therapeutic decisions solely on the LDL cholesterol level,[1] a recent consensus conference panel recommended that HDL cholesterol should also be measured when evaluating the risk for coronary heart disease.[11] Our results suggest that this additional information will substantially improve disease prediction. We found that levels of HDL cholesterol were inversely related to the disease severity at all levels of total cholesterol and LDL cholesterol, even those considered "desirable." Furthermore, the extent of occlusion among men with low levels of both total cholesterol and HDL cholesterol was almost identical to that among men with high levels of LDL cholesterol and HDL cholesterol. Despite these similar disease patterns, based on the 1988 National Cholesterol Education Program guidelines, persons in the former group (low total cholesterol) would be retested within 5 years, whereas persons in the latter group (high LDL cholesterol) would receive dietary, and possibly pharmacologic, therapy. Knowledge of the HDL cholesterol level among persons with high LDL cholesterol may also help to distinguish subgroups that differ in risk.

Although coronary arteriography has several advantages in studying associations with atherosclerotic disease,[24] and several of the first studies to report a beneficial effect for HDL cholesterol were based upon patients undergoing coronary arteriography,[19,25] limitations of our cross-sectional study design should be considered. We did not have a normal control group, and we were unable to study either men with asymptomatic coronary atherosclerosis or those who died suddenly from a myocardial infarction. Furthermore, coronary arteriography patients undergo several selection processes, and it is possible that some subjects had already taken steps to lower their cholesterol level. Nevertheless, we excluded men who reported using cholesterol-lowering drugs and those who reported a myocardial infarction; men in the latter group may have made behavioral changes (for example, weight reduction, smoking cessation, reduced alcohol consumption) that could influence levels of LDL cholesterol and HDL cholesterol. Although it is still possible that life-style changes may have affected levels of total and HDL cholesterol in our study, any nondifferential misclassification would have biased our results toward the null hypothesis.

Our results concerning the joint effects of total cholesterol and HDL cholesterol agree well with those from cohort studies that have cross-classified levels of total cholesterol and HDL cholesterol. In the Framingham Heart Study, for example, the 12-year incidence of myocardial infarction among men with low levels of both total cholesterol and HDL cholesterol (<25th percentile) was higher (17 per 100) than the incidence (11 per 100) among men with high levels of both (total cholesterol ≥245 mg per dl, HDL cholesterol a ≥54 mg per dl).[4] An elevated risk among persons with a low HDL cholesterol level, even in combination with a relatively low level of total cholesterol or LDL cholesterol, has also been seen in other cohorts.[6,7,12] Because HDL cholesterol and total cholesterol are only weakly correlated,[26] a substantial number of adults with a desirable total cholesterol level will likely have a low HDL cholesterol level.[27]

Although various ratios have been used to summarize the atherogenicity of the lipoprotein profile,[6,9,12-15] few investigators have examined whether these ratios adequately convey the joint information contained in the lipoprotein cholesterol fractions. The HDL cholesterol ÷ total cholesterol ratio, for example, could be considered insufficient if knowledge of the actual level of total cholesterol, LDL cholesterol, or HDL cholesterol improved disease prediction. We found, as did Castelli et a1,[14] that knowledge of the actual levels of total cholesterol and HDL cholesterol did not greatly improve disease prediction if the HDL cholesterol ÷ total

cholesterol level was known. Because HDL cholesterol ÷ total cholesterol can be assessed in nonfasting persons and is easily interpreted, representing the proportion of cholesterol in the HDL fraction, it might be preferred to ratios that incorporate LDL cholesterol. It is possible, however, that a simple ratio may not always provide sufficient information, particularly if levels of both LDL cholesterol and HDL cholesterol are very low, as in Tangier disease.[28] Knowledge of the actual level of each lipoprotein cholesterol fraction would also be necessary for intervention.

The benefits of raising the HDL cholesterol level need further clarification. Although it has been suggested that HDL cholesterol mediates the reverse transport of cholesterol from tissues,[29] it is possible that its association with disease may be secondary to other mechanisms. Apolipoprotein A-I, the major protein component of HDL particles, is involved in the stabilization of prostacyclin,[30] and persons with low levels of HDL cholesterol have extensive postprandial lipemia.[31] Evidence for a direct role of HDL cholesterol in atherosclerosis, however, comes from animal studies in which infusion of the plasma HDL fraction led to regression of fatty streaks in cholesterol-fed rabbits.[32] Furthermore, reductions in risk among gemfibrozil-treated men in the Helsinki Heart Study were more strongly related to changes in HDL cholesterol than to LDL cholesterol.[33] No clinical trial, however, has focused exclusively on raising levels of HDL cholesterol.

Knowledge of the HDL cholesterol level may also help in identifying subgroups for whom different therapies might be appropriate. For persons with a low HDL cholesterol level, nonpharmacologic methods to raise HDL cholesterol could include weight reduction, smoking cessation, increased aerobic exercise, and the substitution of monounsaturated fats for saturated fats (which would increase the HDL cholesterol ÷ total cholesterol ratio). (Although *moderate* alcohol consumption could also increase HDL cholesterol levels, its use has not been recommended because of possible increases in triglycerides and the detrimental effects of heavy consumption.) Whereas treatment with cholestyramine might be appropriate for most persons with an elevated LDL cholesterol level, if HDL cholesterol is low, it might be reasonable to consider normalizing both lipoprotein fractions.[34] Our findings provide additional support for the recent recommendations from the consensus conference on levels of triglycerides and HDL cholesterol[11]: an HDL cholesterol determination should accompany a total cholesterol measurement when assessing the risk of coronary heart disease.

Note Added in Proof

The recently released Second Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults recognizes the importance of HDL cholesterol levels in the initial assessment of coronary heart disease risk status (see JAMA 1993;269:3015-3023). The new recommendations include HDL cholesterol measurement at the time of initial serum total cholesterol testing, designate HDL cholesterol levels above 59 mg/ dl as a negative risk factor, and prescribe that HDL cholesterol levels be considered in the selection of drug therapy to lower persistently high LDL cholesterol levels.

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