Editorial Comment

Joint Lipid Risk Factors and Coronary Heart Disease

Melissa A. Austin, PhD

The importance of lipid, lipoprotein, and apolipoprotein risk factors in the prediction, prevention, and regression of atherosclerosis is now well established. The role of elevated low density lipoprotein cholesterol (LDL C) in the development of coronary heart disease (CHD) is supported by evidence from numerous epidemiologic studies, clinical trials, and genetic studies.\(^1\)\(^-\)\(^3\) High density lipoprotein cholesterol (HDL C)\(^6\) and possibly apolipoprotein (apo) A-I are thought to have a protective role through reverse-cholesterol transport. Plasma levels of apo B, the primary protein on LDL particles, lipoprotein (a), selected apo E phenotypes, and subfractions of LDL and HDL particles have all been associated with increased risk as well.

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What has not often been appreciated are the interrelations between these risk factors and the possibility that they may have joint effects on risk of CHD. Instead, much attention has been focused on multivariate statistical analyses and the establishment of independent risk factors. The continuing controversy regarding elevated plasma triglyceride as a risk factor is probably one of the best examples.\(^5\) Most prospective epidemiological studies demonstrate a univariate association with CHD, without statistically adjusting for other risk factors. However, with few exceptions, levels of plasma triglyceride are inversely associated with levels of HDL C. Triglyceride levels also demonstrate considerably more variation than HDL C levels. Thus, in multivariate analyses in which triglyceride and HDL C are both included, triglyceride generally loses its statistical significance. The interpretation of the discrepancy between univariate and multivariate analyses has been problematic for nearly 30 years. Similar statistical concerns arise in evaluating the predictive value of other correlated lipid measures, for example, LDL C and plasma apo B levels.\(^6\)

In this issue of Circulation, Manninen et al\(^7\) present a further analysis of data from the Helsinki Heart Study that begins to shed light on these issues, at least in middle-aged men with dyslipidemia. The primary results from the Helsinki Heart Study, a randomized, double-blind clinical trial, previously demonstrated a 34% decrease in coronary heart disease in the gemfibrozil-treated group compared with the placebo group.\(^8\) Decreases in LDL C and increases in HDL C were both significantly associated with the lower event rate in the treated group.\(^9\) Despite a corresponding 35% lowering of plasma triglyceride levels, the association between decrease in risk and triglyceride lowering was not statistically significant. This perplexing result may reflect the relatively large variation of triglyceride levels: In the placebo group, the standard deviation was 120.5 mg/dl for triglyceride compared with 31.3 mg/dl for total cholesterol.\(^8\)

In the present analysis, the authors consider the joint effects of LDL C, HDL C, the LDL C–to–HDL C ratio, and triglyceride on the 5-year risk of cardiac events and on the reduction of risk with gemfibrozil treatment, using baseline fasting lipid values. Lipid variables were dichotomized using cutoff points of 5.0 mmol/l (193 mg/dl) for LDL C, 1.08 mmol/l (42 mg/dl) for HDL C, 5.0 for the ratio, and 2.3 mmol/l (200 mg/dl) for triglyceride, based on quintiles of the distributions and on the Nordic recommendations for drug treatment of hypertriglyceridemia. Univariate analysis demonstrated that HDL C and triglyceride were better predictors of CHD than total cholesterol or LDL C and that gemfibrozil treatment virtually eliminated the risk associated with low HDL C and high triglyceride. As has been reported in numerous other studies,\(^8\) triglyceride was a significant predictor in univariate analysis; but when HDL C was included in a multivariate statistical model, the triglyceride effect was no longer significant. Once again, however, triglyceride and HDL C were highly inversely correlated (\(r=-0.44\)). Manninen and coauthors performed further analyses “in an attempt to eliminate the effects of multicollinearity,” using a stratified approach to evaluate joint risk factors.

The results revealed a high-risk subgroup of subjects with LDL C–to–HDL C ratio greater than 5.0 and triglyceride of more than 2.3 mmol/l, consisting...
of approximately 12% of the study sample. In the placebo group, the relative risk in this subgroup over the 5 years of the study was 3.82 (95% confidence interval, 2.20–6.63), compared with the subgroup of subjects who had a ratio less than or equal to 5.0 and triglyceride less than or equal to 2.3 mmol/l. Relative risks were close to 1 in the remaining two placebo groups, those with only a high ratio or only high triglyceride. Among the treated subjects, the corresponding high-risk subgroup also received by far the most benefit from gemfibrozil treatment, with a remarkable 71% decrease in incidence of CHD. Much less benefit was seen in other groups. The authors conclude that “serum triglyceride concentration has prognostic value in combination with LDL C and HDL C levels.”

As convincing as these results appear, two important considerations must be kept in mind when interpreting these findings. First, the conclusions are based on a post hoc, subgroup analysis. The original study design, including the randomization procedure, was intended to compare CHD incidence and lipid changes only between the treated and the placebo groups. The subgroups considered in the present analysis were identified after the study was complete, being based on results that had already been evaluated. Thus, the reported p values may be spuriously low, and the results should be replicated to validate their statistical significance. In addition, whereas statistical models provide objective ways to evaluate associations between lipoprotein related risk factors and disease, by necessity they oversimplify the biological processes involved, and therefore must be interpreted with caution.

The second important consideration is the generalizability of the findings. As the authors note in the discussion of their article, the Helsinki Heart Study sample consisted of middle-aged (40–55 years old), Caucasian, hyperlipidemic (non–HDL C >200 mg/dl) men. Whether the results also apply to women and to other ethnic groups cannot be concluded with any certainty. In addition, this sample of men in the Helsinki Heart Study appears to be somewhat unusual compared with those of other clinical trials. Although two thirds of the subjects in both the treated and the placebo groups were classified as type IIA, only 42% of men had LDL C levels above the 5.0 mmol/l (193 mg/dl) cutpoint used in the present analysis. Because non–HDL C consists primarily of LDL C and very low density cholesterol (VLDL C), the eligible subjects with normal LDL C levels must have had elevated VLDL C and were therefore likely to have increased triglyceride levels. This is in contrast to other studies, in which hyperlipidemic subjects are selected primarily for elevated total cholesterol or LDL C. Thus, the sampling procedure may have provided an opportunity to detect a triglyceride–disease association not seen in other studies. Similarly, epidemiological studies conducted in Scandinavia have often found triglyceride to be an independent risk factor.

What cannot be determined from these data is the frequency of the occurrence of a high LDL C–HDL C ratio in combination with hypertriglyceridemia among Caucasian populations in general. Therefore, although the data clearly show this subgroup to have both higher risk and increased benefit from treatment, the potential for disease prevention will depend on the prevalence of this syndrome in clinical populations. As more investigators consider this joint approach to lipid risk factors, the overall impact of the treatment used in the Helsinki Heart Study will become more apparent.

The relation of the syndrome of high LDL C–HDL C ratio and hypertriglyceridemia to other lipid and lipoprotein-related disorders and risk factors will now be of considerable interest. For example, these lipid characteristics resemble those seen among subjects with LDL subclass phenotype B (a predominance of small dense LDL). This phenotype appears to be a common genetically influenced trait in the general population and has been associated with both increased risk of myocardial infarction and an atherogenic lipoprotein profile consisting of increases in plasma triglyceride and apo B and decreases in HDL C and apo A-I. In addition, it is possible that familial combined hyperlipidemia or hyperapolipoproteinemia is present in the families of some subjects in the high-risk subgroup defined in the present study.

The insights provided by this study clearly demonstrate the complexity of the relations between lipoproteins and atherosclerosis. In one sense, this should not be surprising considering the intricacies of both lipid metabolism and arterial wall pathophysiology. The simultaneous use of multiple lipid measures and the assessment of their joint effect provides a valuable approach to identifying high-risk individuals and developing effective targeted interventions for specific subgroups of patients.

References


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M A Austin

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