

## Editorial Comment

# Plasma Triglycerides and the Clinician: Time for Reassessment\*

RICHARD J. HAVEL, MD

San Francisco, California

Not many years ago, abnormally high values of plasma cholesterol were based on the upper fifth percentile of the population distribution. This is now an anachronism given the extensive body of evidence supporting the efficacy of cholesterol lowering and the recommendations of the National Cholesterol Education Program for primary and secondary prevention of coronary heart disease. As for plasma triglycerides, normal values are still based on the upper tail of the population distribution, despite the increasing body of evidence that increased triglyceride concentrations are at least as prevalent among patients with premature atherosclerotic vascular disease and predict risk of first and recurrent coronary events.

In 1993, a National Institutes of Health Consensus Panel (1) recommended consideration of triglyceride lowering in certain high risk situations associated with fasting plasma triglyceride concentrations >200 mg/dl, a value exceeding the upper fifth percentile of the population distribution in adult Americans (2,3). This recommendation was adopted in the second report on adults of the National Cholesterol Education Program (4). Other recent guidelines (5,6), perhaps influenced by European studies indicating an association of plasma triglycerides with coronary heart disease risk independent of high density lipoprotein (HDL) cholesterol, have taken a slightly more proactive stance, but likewise use a fasting triglyceride concentration of 200 mg/dl as the discriminant for treatment.

Additional data published in the past few years have added to the body of evidence that fasting plasma triglyceride concentrations are an independent risk factor for coronary heart disease in men and women (7). Moreover, fasting plasma triglycerides or measures related to increased concentrations of triglyceride-rich lipoprotein remnants have been found (8,9) to be independent predictors of increasing coronary artery stenosis and associated clinical events in patients with coronary heart disease. Finally, drug treatments that reduce the concentration of plasma triglycerides and triglyceride-rich lipoproteins and increase HDL cholesterol concentrations have low-

ered the rate of progression of coronary artery lesions and clinically related events (10-12). Although these outcomes have generally been independent of levels of low density lipoprotein (LDL) cholesterol, LDL particle size (another risk factor) may have been favorably affected, and it has not been possible in these studies to isolate the effect of changes in individual lipoprotein classes.

The mechanisms by which triglyceride-rich lipoproteins (for which fasting plasma triglycerides have been a useful surrogate) affect atherosclerotic lesions and clinical outcomes are uncertain, but effects on hemostasis and thrombosis as well as cholesterol accumulation in lesions may be involved (13). Clearly, less is known about the pathophysiologic consequences of hypertriglyceridemia than hypercholesterolemia.

In this issue of the Journal, Miller et al. (14) report on an 18-year follow-up of a study by the senior author, Thomas Pearson (15), on risk factors for angiographically documented coronary heart at The Johns Hopkins Hospital in the 1970s. A single measurement of fasting plasma triglycerides and total and HDL cholesterol was obtained on the morning of catheterization. It should be noted that the values obtained by Pearson (15) for these lipoprotein-bound lipids may have been 10% to 15% lower than those found in most studies because the patients were supine rather than sitting when the blood samples were taken. After certain exclusion criteria were applied, 535 patients were entered into the current study, of whom it was possible to contact 492. Of the 350 patients with angiographically gradable coronary stenosis, 39% had died from coronary heart disease-related events, and 18% had had a nonfatal coronary event or had undergone coronary artery revascularization. The investigators chose 100 mg/dl rather than 200 mg/dl as the fasting plasma triglyceride cutpoint in their analysis because it is close to the median value in American and Canadian men and women (2). Mean fasting triglyceride concentrations in the 199 cases were 160 mg/dl compared with 137 mg/dl in those patients free of a coronary-related event. Most notably, ~44% of patients with fasting plasma triglycerides <101 mg/dl remained free of an event during the 18-year follow-up period compared with ~20% of those with higher values. A multiple logistic regression analysis showed that plasma triglycerides (relative risk 1.5), HDL cholesterol (relative risk 1.5) and diabetes mellitus (relative risk 2.1) were independent predictors of coronary events. Thus, in this study, unexceptional fasting triglyceride concentrations (as low as 101 to 134 mg/dl in a quartile analysis) may have been deleterious to patients with established coronary heart disease. Given the variability of fasting plasma triglyceride concentrations and the close inverse relation of triglycerides and HDL cholesterol, the triglyceride-associated risk could well be greater.

Whether similar findings would apply to a coronary heart disease-free population is unclear. However, as pointed out by the authors of the current study, some large prospective population studies in this country and abroad also suggest that levels considerably <200 mg/dl may be deleterious.

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From the Cardiovascular Research Institute, University of California San Francisco, San Francisco, California.

Address for correspondence: Dr. Richard J. Havel, University of California San Francisco, Box 0130, M-1313, 505 Parnassus, San Francisco, California 94143. E-mail: havelr@itsa.ucsf.edu

#### Abbreviations and Acronyms

HDL = high density lipoprotein  
LDL = low density lipoprotein

Currently, many patients who survive a myocardial infarction are treated with lipid-lowering drugs that reduce plasma triglycerides as well as LDL cholesterol. Nicotinic acid, drugs of the fibrate class and atorvastatin can reduce triglyceride concentrations by 40% to 50%. Moreover, all these classes of drugs reduce the cholesterol content of triglyceride-rich lipoproteins disproportionately (16). Thus, many patients with coronary heart disease whose plasma triglyceride levels are well below 200 mg/dl are already being treated with plasma triglyceride and triglyceride-rich lipoprotein-lowering medications. The report of Miller et al. (14) focuses attention on the need for investigations of the basis for the common elevations of triglyceride-rich lipoproteins in patients with atherosclerotic cardiovascular disease and the potential specific benefit of triglyceride lowering. At the same time, their observations lend support to the use of non-HDL cholesterol (total plasma cholesterol minus HDL cholesterol) for atherosclerotic risk screening (17,18). This simple measurement, which includes triglyceride-rich lipoprotein cholesterol, as well as cholesterol in other atherogenic lipoproteins, can be obtained in nonfasting subjects, reserving triglyceride measurements for otherwise high risk situations. Non-HDL cholesterol may be a better guide than LDL cholesterol to the overall efficacy of lipid-lowering treatments once the lipoprotein abnormality has been established.

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