Reduced plasma levels of high-density lipoproteins (HDL) were found to be associated with increased risk of atherosclerosis more than 50 years ago. Diverse methodologies including electrophoresis, ultracentrifugation, and biochemical characterization were used even at that time to examine the association between the cholesterol, phospholipid, and protein composition of HDL, also known as α-lipoproteins, and atherosclerosis.1-4 Within 25 years of these seminal observations, the model was proposed in which atherosclerosis is driven by an excess of atherogenic lipoproteins (primarily low-density lipoprotein), which are deposited in the vessel wall, and a deficiency of protective HDL particles, which control cholesterol efflux from the vessel wall.5

See page 2185

In our current models of atherosclerosis, the major mechanism for the atheroprotective properties of HDL is thought to be reverse cholesterol transport, a process by which lipid-poor nascent HDL particles accept cholesterol from peripheral cells through the interaction of apolipoprotein A-I (apoA-I), the major protein of HDL, with ATP-binding cassette protein A1. After esterification of the cholesterol by (apoA-I), the major protein of HDL, the lipid-poor nascent HDL particle transfers the cholesteryl esters to the liver via scavenger receptor B1 or to the apoB-containing particles (in exchange for triglycerides) through the action of cholesteryl ester transfer protein.

The cholesterol content in HDL (HDL-C) has been inversely related to risk for coronary heart disease (CHD) in numerous epidemiological studies, with each 1-mg/dL increase in HDL-C associated with an ∼2% to 3% decrease in risk for CHD.6 Measurement of HDL-C is recommended for all adults to assess the risk for CHD, and the HDL-C level is to be considered in the development of treatment strategies. Although measurement of HDL-C has proven clinical utility, we know that HDL includes a diverse group of particles with variations in apolipoprotein composition, size, charge, and function. Therefore, one would postulate that more sophisticated methods to subclassify HDL (Figure) would lead to tests that provide better clinical utility to assess risk of cardiovascular disease and response to therapy.7 Density gradient ultracentrifugation has been used to classify HDL on the basis of flotation characteristics: HDL2 is a large, lipid-rich, lower-density particle, and HDL3 is a smaller denser particle. Although many studies comparing HDL subclasses defined by density gradient ultracentrifugation have found the larger HDL2 particles to be more atheroprotective than the smaller HDL3 particles,8-9 in some large prospective epidemiological studies, HDL2 and HDL3 measurements did not provide any additional predictive value beyond that of HDL-C.10

ApoA-I is the major apoprotein in HDL, and measurement of apoA-I, rather than HDL-C, has been proposed as a better method to assess protective levels of HDL. Although some studies have shown that apoA-I is superior to HDL-C, other large prospective studies have shown no additional benefit of apoA-I over HDL-C.10,11 HDL can be classified on the basis of the apolipoprotein composition: some HDL particles contain only apoA-I (LpA1), whereas others contain both apoA-I and apoA-II (LpA1:AII). A number of studies comparing LpA1 and LpA1:AII have suggested that LpA1 may be more atheroprotective than LpA1:AII, but other studies did not show this distinction.12 Characterization of HDL by electrophoretic mobility or gradient gel electrophoresis has also not consistently shown superiority over measurement of HDL-C. A more sophisticated approach has been developed by Asztalos and colleagues to assess the apoA-I levels in various subclasses of HDL by using native 2-dimensional gel electrophoresis that separates HDL by electrophoresis into pre–α and pre–α-3, and apoA-II (LpA1:AII). A number of studies comparing LpA1 and LpA1:AII determined by 2-dimensional gel electrophoresis to predict risk of new cardiovascular events in a study of the Veterans Affairs HDL Intervention Trial (VA-HIT).14 In VA-HIT, 2531 men with CHD and HDL-C of 40 mg/dL or less, and low-density lipoprotein cholesterol of 140 mg/dL or less were randomized to therapy with gemfibrozil or placebo.15 In the current study, 398 patients with cardiovascular events (CHD death, stroke, or myocardial infarction) and 1097 subjects without cardiovascular events were included. In addition, the authors analyzed 431 patients

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See page 2185


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without cardiovascular disease from the Framingham Offspring Study.16

Subjects from VA-HIT who developed new cardiovascular events were found to have more apoA-I in the poorly lipidated, small α-3, and pre-β-1 HDL particles (3% and 9%, respectively) and less apoA-I in the better lipidated and larger α-1 and α-2 particles (12% and 7%, respectively) compared with subjects without new cardiovascular events. For every SD increase in α-1 and HDL-C, the hazard for new events decreased by 18% (P=0.002) and 15% (P=0.015), respectively. The results were similar in the placebo arm (ie, no gemfibrozil therapy) of VA-HIT, which had a 12% decrease in new cardiovascular events for each 1-SD increase in α-1 levels. Among HDL-related variables, the α-1 apoA-I level was the most significant risk factor measured for development of a new cardiovascular event.

These results add to a growing body of evidence in different populations and circumstances for the importance of HDL subfractions, in particular α-1, for predicting CHD risk. The same group has shown that simvastatin–niacin combination therapy significantly increased apoA-I–containing α-1 HDL concentration in 123 subjects with CHD in the HDL-Atherosclerosis Treatment Study (HATS) and in turn was associated with less progression of coronary stenosis.17 Similarly, a severe depletion in α-1 and pre-α species of apoA-I–containing HDL subpopulations was noted in CHD cases compared with controls even after stratifying by HDL-C <35 mg/dL and >35 mg/dL.18

The question that needs to be given further consideration is how best to use this observation: should HDL subclasses be used primarily for research, only in high-risk patients, or in routine clinical practice? Researchers like Ridker19 and Manolio20 have suggested a useful framework when considering the clinical utility of a new risk marker, including answering certain questions: (1) is there consensus as to the best way to measure the risk marker, (2) are the results of series of prospective epidemiological studies consistent with each other, (3) is the marker able to add to our ability to predict risk over and above existing tools, (4) is the marker able to account for a large proportion of risk associated with the disease, (5) is the assay reproducible (ie, low coefficient of variation), (6) what are the sensitivity and specificity of the marker in predicting disease, and (7) what are the cost, availability, and ease of performance of the test?

This study adds more support to a growing body of epidemiological data that have demonstrated that large cholesterol-rich HDL subspecies such as α-1 are cardioprotective. Although the inter- and intraassay coefficients of variation in this study were reported to be <10%, it is not clear whether this method could be implemented in routine clinical chemistry labs with coefficients of variation remaining <10%. In contrast, because of extensive standardization and automation, measurement of HDL-C routinely has coefficients of variation ≤5% and is relatively inexpensive.

In addition to helping with risk assessment, measurement of HDL subspecies may help to determine the efficacy of therapies (ie, α-1 apoA-I may be an improved surrogate marker for efficacy of lipid-modifying drugs). Statins (albeit in varying degrees) have been shown to modify and significantly increase α-containing and pre–α-1-containing HDL subpopulations.21,22 Although statins have been shown to increase α-1 apoA-I, we do not know whether the increased levels of α-1 apoA-I on statin therapy are associated with a reduction in events. In contrast, we do have data that the change in apoA-I on statin therapy was associated with event reduction.23 Prior attempts that have used HDL subspecies to predict risk have yielded mixed results. In an earlier report from VA-HIT, HDL₃ and not HDL₂₃ was found to be predictive of CHD events.24 The current study reports only baseline values and does not provide information as to whether changes in HDL subpopulations were associated with the event reduction with gemfibrozil. Clearly, future studies that examine the association between change in α-1 apoA-I level with statins, fibrates, or other agents and reduction in cardiovascular events are needed.

Treatment of patients with low HDL-C levels is now the focus of major efforts in the development of new therapies,
and new therapies such as cholesteryl ester transfer protein inhibitors and apoA-I infusions will provide further key information on HDL and atherosclerosis. Identifying and understanding the various steps in HDL metabolism and quantitative assessment of HDL subspecies will continue to be an important research area and may provide improved risk assessment and better surrogates for monitoring therapy.

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Fat, Fit, and Leading the Charge: The Evolution of Measuring High-Density Lipoprotein Subpopulations
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