High-Density Lipoproteins:
The Neglected Stepchildren Whose
Importance as a Risk Factor
Continues to Be Defined

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Featured Article: Warnick GR, Benderson J, Albers JJ. Dextran Sulfate-Mg2+ Precipitation Procedure for Quantitation of High-Density-Lipoprotein Cholesterol. Clin Chem 1982;28:1379–88.[2]

The inverse association of HDL-cholesterol (HDL-C) with coronary artery disease (CAD) risk was rediscovered in the mid-1970s, coinciding with diagnostics companies seeking a revenue replacement for lipoprotein electrophoresis, the use of which was fading because lipoprotein phenotyping had been discredited. As a result, HDL-C measurements rapidly transitioned from specialty lipid research laboratories into general clinical practice, igniting interest in measurement methods. Our group at the Northwest Lipid Research Clinic at the University of Washington in Seattle had considerable interest in and experience with lipoproteins, especially HDLs, and we began publishing our observations in a series of methodological papers. As an indication of both the intense interest in HDL-C and the methodologic challenges of achieving reliable measurements, beginning in 1976 we and various collaborators published at least one HDL paper in *Clinical Chemistry* each and every year for a total of 12 years as well as 15 HDL papers in other journals. The 1982 paper listed above described a precipitation reagent with dextran sulfate-Mg2+, compatible with enzymic assays, that became a "Selected Method" and during the 1980s eventually became the most common HDL reagent, until it was gradually replaced in the 1990s by automated homogeneous methods.

To put this work into proper context, I must point out that our early research on HDL-C was facilitated by visionaries at the National Heart Lung and Blood Institute, especially Donald Fredrickson and Robert Levy, who recognized the critical role of the laboratory in supporting clinical studies and, when organizing the Lipid Research Clinics Program, provided funding as well as encouragement for methodological improvements and innovations and for standardization of the lipid/lipoprotein analytes. Also, at the University of Washington, Ed Bierman had organized an internationally recognized CAD/lipoprotein research program including Bill Hazzard, the LRC Clinic Director, an exceptional clinician and manager; John Albers, who had already in graduate school recognized the future importance of the lipoproteins in characterizing CAD; and Marian Cheung, a superb bench scientist, as well as Joan Benderson and many other talented technologists. We were surrounded at the University of Washington by other luminaries: Russell Ross, a pathologist, who first characterized atherosclerosis as a response to vascular injury; John Glomset, who conceptualized reverse cholesterol transport, a major protective effect of HDL; John Brunzell, a leading expert on triglyceride metabolism; Alan Chait, who pioneered studies of lipoprotein modifications; and Greg Brown, who laid the groundwork for the current understanding of vulnerable plaque etiology of myocardial infarction. In 1973 I joined this talented group of scientists to develop the core lipoprotein laboratory, in the process gaining a compulsion to improve the lipid and lipoprotein measurement technologies, an interest that has consumed me for more than 3 decades.

A historical review of this work is timely, because views of the relevance and utility of HDL-C are changing dramatically. HDL-C has been a neglected "stepchild" to the major cholesterol carrier, LDL, readily accepted as the "bad" lipoprotein because the atherogenic contribution of cholesterol had been known for more than a century. Thus, LDL-C became the focus of treatment guidelines and interventions. A protective role for HDL-C was less readily accepted, although HDL-C subclasses and their inverse association with CAD had been clearly demonstrated in the early 1950s by John Gofman's seminal studies *(1)* using the technically challenging analytical ultracentrifuge at the Donner Laboratory of the University of California at Berkeley. Because other established researchers were
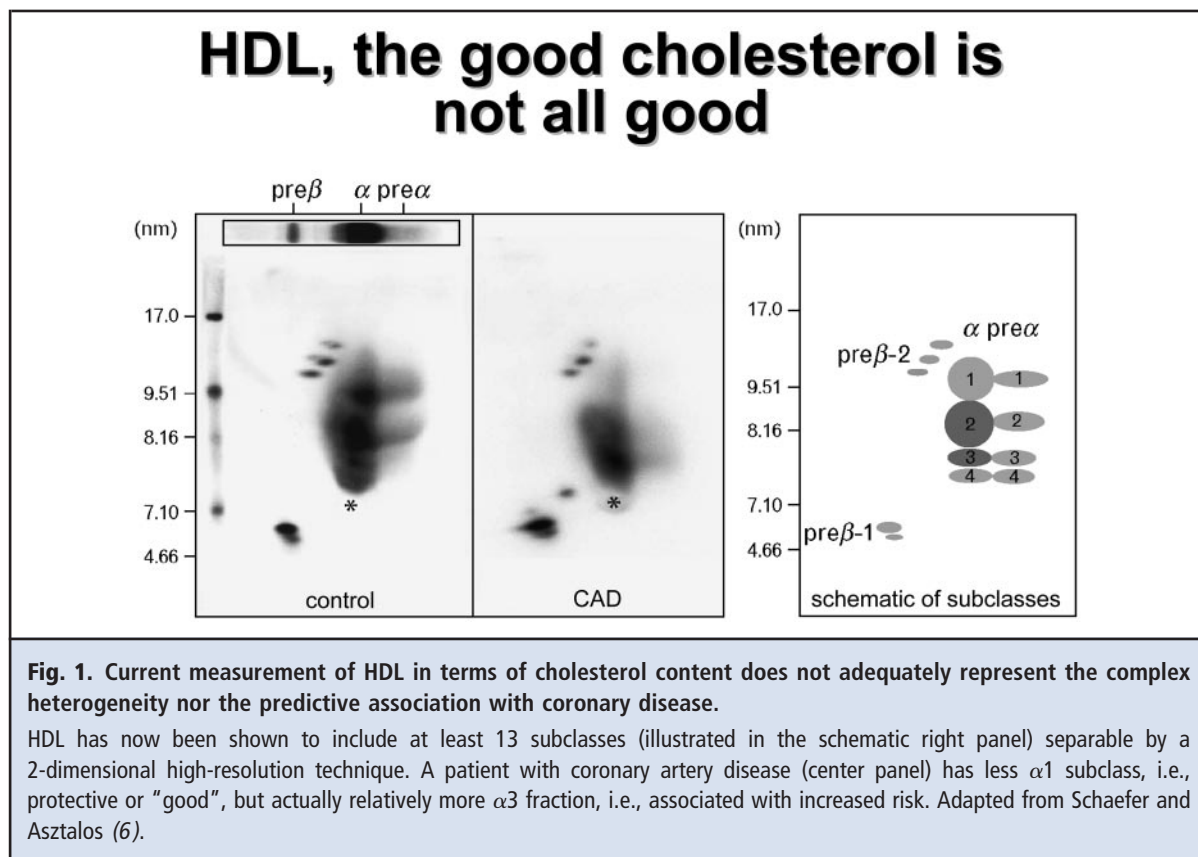
Fig. 1. Current measurement of HDL in terms of cholesterol content does not adequately represent the complex heterogeneity nor the predictive association with coronary disease.

HDL has now been shown to include at least 13 subclasses (illustrated in the schematic right panel) separable by a 2-dimensional high-resolution technique. A patient with coronary artery disease (center panel) has less α1 subclass, i.e., protective or "good", but actually relatively more α3 fraction, i.e., associated with increased risk. Adapted from Schaefer and Asztalos (6).

unable to replicate Gofman's findings and therefore rejected them, total cholesterol and LDL took center stage. Thus, "good" HDL-C received little attention until the mid-1970s, when Framingham and other studies confirmed that HDL-C was important and even a stronger contributor to CAD than LDL-C (2). Nevertheless, intervention studies and consequent national guidelines continued to target LDL-C, resulting in the statins becoming among the most common drugs prescribed. Only recently is awareness developing that LDL-C lowering by statin monotherapy only slows atherosclerosis, and to achieve regression HDL-C must be enhanced as well (3).

HDL has turned out to be highly complex, much more so than LDL. High-resolution separation methods reveal at least 12 or 13 different particle subclasses, and suggest that although some are protective others may be atherogenic (4). Other studies suggest that even "good," i.e., usually antiinflammatory, HDL particles can be chemically modified to become proinflammatory and atherogenic (5). HDL-C is unquestionably important in atherogenesis and CAD, but the conventional measurement of HDL-C may not be adequate, and new measures of HDL structure, composition, and function will likely be necessary to fully characterize the CAD risk associations.

References

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