The Yin and Yang of High-Density Lipoprotein Cholesterol*

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High-density lipoproteins (HDL) are fairly complex macromolecules consisting of a core of hydrophobic lipids (cholesterol esters and triglycerides), an envelope of phospholipids and some unesterified (free) cholesterol, and apolipoproteins (apo) that ensure structural integrity, serve as ligands for protein (and possibly lipid) receptors, can act as coactivators of enzymatic reactions, and are involved in the cellular secretion of the lipoprotein. When the clinical laboratory gives a report, it refers to the mass of cholesterol within the specific particle (i.e., the HDL-C level). Relatively little used is the measurement of serum apoA-I levels, the major protein moiety of HDL particles, which may reflect the number of circulating HDL particles. Given the extraordinary biological diversity of HDL particles, these measurements, HDL-C and apoA-I levels, do not provide much functional information.

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Decades of research on the function of HDL have yielded considerable insights and confusion. The cardioprotective effects of HDL seem to be multiple: prevention of low-density lipoprotein oxidation and of vascular wall inflammation and of thrombosis (1); preservation of endothelial vasomotor, proliferative, and survival functions (2); possible prevention of macrophage apoptosis (3); increase in endothelial progenitor cells (4); and the well-characterized role in reverse cholesterol transport. It is this latter mechanism (i.e., removal of macrophage cholesterol from the plaque) that is considered to be the most potent antiatherosclerotic mechanism of HDL.

Three decades ago, the first reports linking a low HDL-C level with the presence of coronary artery disease were reported (5) and subsequently confirmed in multiple epidemiologic studies. On the basis of these studies, the HDL-C level became a categorical cardiovascular risk factor in the National Cholesterol Education Program guidelines (6), but not a therapeutic target. This epidemiologic association was thought to work in reverse: raising HDL should prevent coronary artery disease. This simple paradigm remains unproven to date.

With the molecular characterization of the major proteins involved in HDL metabolism, the investigation of genetic disorders of HDL identified 2 mutations challenging the once firmly held belief that with HDL-C, more was better. ApoA-I Milano, a naturally occurring variant of apoA-I Arg173Cys causes very low HDL-C levels without an increase in coronary heart disease events (7); carriers of the mutation seem to enjoy a healthy life. Mutations that impair the function of cholesteryl ester transfer protein (CETP) are associated with marked elevations in HDL-C levels but not necessarily with protection against coronary heart disease (8). The CETP inhibitors became the focus of a large drug discovery program in several pharmaceutical companies. The first CETP inhibitor (compound JTT705) used in clinical trials produced elevations in HDL-C on the order of 35% at the highest (900-mg) dose. The second such compound, torcetrapib, proved toxic despite causing a large increase in HDL-C levels and was withdrawn from clinical use.

The study by van der Steeg et al. (9) in this issue of the Journal combines data from a clinical study (the IDEAL [Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering] trial) and the epidemiologic longitudinal study EPIC Norfolk. The investigators examined the risk of cardiovascular events at extreme levels of HDL-C, corrected (or not) for levels of apoA-I and apoB (as well as other covariates).

The significant and consistent finding is that in both studies (which differed in scope, intent, and populations), elevated levels of HDL-C are no longer cardioprotective and may confer additional risk once corrected for apoA-I and apoB levels. Interestingly, quartile analysis of the data did not show this relationship of potential harm in high HDL-C levels; a similar finding was reported in the TNT (Treating to New Targets) study (10). This apparently counterintuitive finding may have important clinical implications: first, naturally occurring high levels of HDL-C may not protect against heart disease, and second, and herein lies the most important and provocative finding, HDL-C as a therapeutic goal may be fraught with potential dangers. This was the case in the torcetrapib trials (Illuminate, Illustrate, Radiance 1 and 2) (11,12). One potential explanation may be that large cholesterol-enriched HDL particles lose some of their biological functions (cellular cholesterol efflux via the adenosine binding cassette transporters ABCA1, ABCAG1; vascular endothelial vasomotor function modulation via SR-B1; antioxidant, antithrombotic,

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and anti-inflammatory properties). The finding that apoA-I, even when corrected for HDL-C and apoB, remains cardioprotective suggests that the means by which HDL particles are increased may be far more important than the cholesterol mass in HDL particles.

These provocative findings must now be replicated in other large clinical and epidemiologic studies, there should be an attempt to explain these findings in the laboratory, and finally, the development of HDL biomarkers (13) should be explored to assess clinically, rapidly, and reliably, the many biological functions of HDL. This study raises several important issues.

Is raising HDL beneficial in terms of cardiovascular health? Clinical trials aimed at modifying lipids and lipoprotein lipids have shown the unequivocal benefits of reducing low-density lipoprotein-C levels to reduce cardiovascular events. Commonly used drugs (statins and fibrates) have a modest (5% to 10%) effect on HDL-C, and this effect is of uncertain clinical significance. Niacin increases HDL-C by 25% to 35% but has been used in combination therapy with other lipid-lowering drugs in most trials, and evidence of unequivocal reduction in hard cardiovascular end points remains elusive. Presently, there are no data showing unequivocally that raising HDL-C pharmacologically reduces cardiovascular risk.

Does the means by which this increase is achieved matter? Given the multiple potentially beneficial effects of HDL on cardiovascular biology, there is scientific support for the concept that raising small HDL particles (often referred to as “nascent” HDL particles) may be more important than generating large, cholesterol-rich HDL particles. Drugs that modulate HDL-C levels can be conceptually seen as those that decrease catabolism (CETP inhibitors, possibly niacin) and those that increase the production rate (fibrates and possibly small molecules that increase apoA-I production, and agonists of the liver-specific receptor LxR to increase ABCA1-mediated cholesterol efflux from cells). The latter category is presently under pre-clinical development. Although there are many theoretical considerations to favor an increase in apoA-I (and nascent HDL) production as a therapeutic target, clinical trials will determine the appropriateness of this approach.

Is HDL-C or apoA-I the appropriate measurement for therapeutic goals? The HDL-C level is a time-honored measurement, and subfractions (HDL$_3$, HDL$_2$) or apoA-I have not markedly increased, in large-population-based studies, our ability to discriminate between cases and controls. Novel analytical techniques reveal that HDL particles contain over 50 different proteins (15). There is an increasing need for the development of better analytical techniques of HDL function and biomarkers of HDL particles. Based on the study by van der Steeg et al. (9), the measurement of apoA-I will be an absolute necessity in clinical trials.

Is HDL-C (simply) a marker of cardiovascular health? Proper life-style that includes no smoking, physical activity, and normal body weight are all associated with higher HDL-C levels and stand on their own merits with respect to cardiovascular health.

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