High-Density Lipoprotein and Cardiovascular Risk

Peter P. Toth, MD, PhD

Low serum levels of high-density lipoprotein (HDL) are commonly encountered in patients with coronary artery disease (CAD). An example of this type of patient is a 42-year-old white man with a history of sudden-onset angina secondary to a 90% obstructive lesion along the proximal left anterior descending coronary artery. The family history was significant for his father, who died of a myocardial infarction (MI) at age 44 years. The patient underwent percutaneous transluminal angioplasty with stenting but developed in-stent restenosis. He underwent cutting balloon angioplasty and brachytherapy and was asymptomatic for approximately 6 months. The stent then developed a high-grade occlusion with recurrence of angina, and the patient required single-vessel bypass surgery.

The patient’s baseline serum lipid profile revealed low-density lipoprotein (LDL) 128 mg/dL, HDL 27 mg/dL, and triglycerides 92 mg/dL. His lipoprotein(a), C-reactive protein, and homocysteine levels were normal. He was not hypertensive, had no impairment of glycemic control, and did not smoke. With a combination of simvastatin 40 mg and niacin (Niaspan; Kos Pharmaceuticals) 1000 mg daily, the patient’s lipid profile improved, with LDL 78 mg/dL, HDL 43 mg/dL, and triglycerides 60 mg/dL. Follow-up stress testing demonstrated normal myocardial perfusion, and the patient has been asymptomatic for 2 years.

HDL as an Independent Risk Factor for CAD

With few exceptions, low HDL is an independent risk factor for CAD in case-control and prospective observational studies. In contrast, high HDL levels are associated with longevity and are protective against the development of atherosclerotic disease. In the Framingham Study, risk for CAD increases sharply as HDL levels fall progressively below 40 mg/dL.1 In the Quebec Cardiovascular Study, for every 10% reduction in HDL, risk for CAD increased 13%.2 Many clinicians believe that low HDL is associated with increased CAD risk because it is a marker for hypertriglyceridemia and elevated remnant particle concentrations. The Prospective Cardiovascular Münster Study, however, demonstrated that the increased risk associated with low HDL is independent of serum triglyceride levels.3

In the United States, low HDL is present in 35% of men and 15% of women.4 Given the evolving epidemic of obesity, diabetes mellitus, and metabolic syndrome, the prevalence of low HDL will continue to rise. In one study, low HDL occurred in approximately 63% of patients with CAD.5 Low HDL is associated with increased risk for MI, stroke, sudden death, restenosis after angioplasty, and severe premature atherosclerotic disease in the proximal left main coronary artery.6–9 In one autopsy series, the average total cholesterol:HDL ratio and HDL level in men who died suddenly during exertion were 8.2 and 36 mg/dL, respectively.10

Antiatherogenic Effects of HDL

HDLs are a heterogeneous class of lipoproteins with diverse functions and antiatherogenic effects. The most important antiatherogenic function of HDL is believed to be its ability to drive reverse cholesterol transport, a series of reactions by which HDL is able to interact with cells in the systemic vasculature and deliver excess cholesterol back to the liver for disposal as bile salts.11

There is considerable controversy about whether one HDL subfraction is more antiatherogenic than others. At the present time, the preponderance of evidence favors increasing total HDL mass, rather than any one subfraction of this lipoprotein.

HDL reverses endothelial cell dysfunction, stimulates prostacyclin pro-
duction (which is both vasodilatory and antithrombotic), inhibits endothelial cell apoptosis, decreases platelet aggregability, and inhibits LDL oxidation, among other functions. The intravenous infusion of HDL in animal models prevents atherogenesis and can stimulate some degree of plaque reversion. In one study, the weekly injection of a bioengineered HDL into patients with CAD resulted in a 4.3% average reduction in atheromatous plaque volume after 5 weeks of therapy.

**HDL Targets**

The National Cholesterol Education Program (NCEP) defines an HDL level <40 mg/dL as a categorical risk factor for CAD. Virtually all cardiologists can point to patients in their practices whose only risk factor for CAD is a low HDL. Despite this, relatively few physicians target it for therapeutic elevation. There are 3 important reasons for this. First, raising HDL can be challenging and frequently requires multiple medications and significant lifestyle modification to be successful. Second, because there are currently no pharmacological interventions available that specifically raise HDL and leave other lipid levels unchanged, it is unclear to many physicians whether raising HDL reduces risk for cardiovascular morbidity and mortality. Third, although the NCEP clearly articulated goals for LDL and non-HDL cholesterol based on global cardiovascular risk evaluation, similar targets for HDL are as yet undefined.

In an effort to address some of this uncertainty, guidance in high-risk groups has been offered. The American Diabetes Association recognizes that an HDL level ≥40 mg/dL is optimal in diabetic patients. Among diabetic patients, a multivariate risk model for macrovascular disease prevention demonstrates that the second most important risk factor to manage after LDL reduction is HDL elevation. After extensive evaluation of the available data, an Expert Group on HDL Cholesterol has recommended that HDL be raised to ≥40 mg/dL in patients with cardiovascular disease, metabolic syndrome, or CAD risk equivalents.

**Pharmacological Intervention**

1. **Statin Therapy**

   Statins typically raise HDL 6% to 14% by stimulating hepatic apolipoprotein A-I expression and weakly inhibiting cholesteryl ester transfer protein (CETP). The Air Force/Texas Coronary Atherosclerosis Prevention Study was a primary prevention trial that compared lovastatin to placebo in men and women with “average” risk for CAD (mean LDL 150 mg/dL; HDL 37 mg/dL). The patients whose baseline HDL level was <40 mg/dL experienced a 3-fold (45% versus 15%) greater reduction in risk for first-time CAD-related events compared with patients whose HDL level was ≥40 mg/dL. One interpretation of this observation is that statin therapy significantly reduces the risk associated with low HDL.

   In the Prospective Study of Pravastatin in the Elderly at Risk trial, among patients aged 70 to 82 years, the only group with a statistically significant reduction in the primary end point (coronary death, nonfatal MI, or stroke) when treated with pravastatin was the one with baseline HDL level <43 mg/dL. Consistent with these findings, the Heart Protection Study demonstrated a trend toward increasing benefit with simvastatin therapy as baseline HDL progressively decreased. In an angiographic subgroup analysis of data from the Lipoprotein Coronary Atherosclerosis Study, fluvastatin reduced rates of CAD progression significantly more in patients with baseline HDL <35 mg/dL than in those patients with HDL ≥35 mg/dL. In one study of Japanese patients with CAD, the ability of pravastatin to raise HDL was highly correlated with reductions in atheromatous plaque volume, whereas reductions in LDL and total cholesterol were not.

   Statin therapy appears to disproportionately benefit patients with low HDL. This observation may be partly explained by the fact that many of the pleiotropic effects exerted by statins (reversing endothelial cell dysfunction, augmenting nitric oxide and prostacyclin production, decreasing inflammation) are also mediated by HDL. Statins should be the drug of choice in patients with a combination of low HDL and an LDL level above NCEP targets.

2. **Fibrate Therapy**

   Fibric acid derivatives are beneficial to patients with a combination of hypertriglyceridemia and low HDL. Fibrates stimulate HDL biosynthesis 6% to 20% by stimulating hepatic apolipoprotein A-I expression and lipoprotein lipase activity. The activation of lipoprotein lipase allows for the catabolism of very-low-density lipoprotein and chylomicra. As these large lipoproteins are hydrolyzed, they release surface coat constituents that can be used to form HDL in serum. Patients with insulin resistance states are particularly prone to low lipoprotein lipase activity.

   The Helsinki Heart Study and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) both demonstrated that gemfibrozil therapy was associated with reductions in cardiovascular morbidity and mortality in patients with hypertriglyceridemia and low HDL. VA-HIT also demonstrated: (1) a reduction in cardiovascular morbidity and mortality occurred, independent of changes in LDL, and (2) the patients with the lowest HDL derived the greatest benefit.

   Fibrates should be first-line therapy in patients with hypertriglyceridemia, LDL <130 mg/dL, and low HDL (Figure). These patients should also be evaluated for metabolic syndrome and type 2 diabetes mellitus. Relieving insulin resistance with weight loss, exercise, and thiazolidinedione (pioglitazone or rosiglitazone) therapy help to raise serum HDL. Standard dosing regimens for fibrates include: (1) gemfibrozil 600 mg twice daily or (2) fenofibrate 54 or 160 mg once daily.
Fibrate therapy can be associated with a rise in LDL because these drugs stimulate the conversion of very-low-density lipoprotein to LDL in serum. If the LDL rises above NCEP targets, then the addition of a statin or ezetimibe to the fibrate may be indicated. Gemfibrozil can block the glucuronidation of statins and lead to increased risk for hepatic and skeletal muscle toxicity. Fenofibrate is a safer choice when considering combination therapy because it does not interfere with statin metabolism. No outcome trials using the combination of a fibrate and statin have yet been completed. Fibrates can be used to raise HDL in the absence of hypertriglyceridemia.

3. Niacin
Niacin raises serum HDL up to 35% by blocking its hepatic uptake and catabolism and can be used as adjuvant therapy with statins and fibrates. In the Coronary Drug Project, crystalline niacin (3000 mg daily versus placebo) given as monotherapy to men with established CAD reduced the risk for stroke and nonfatal MI by 24% and 27%, respectively. An outcomes-based primary prevention trial with niacin monotherapy is not yet available. The combination of niacin and a statin can markedly decrease CAD event rates and rates of coronary plaque progression. Niacin as adjuvant therapy should be used as tolerated (crystalline niacin up to 3000 mg/d and sustained-release Niaspan [Kos Pharmaceuticals] up to 2000 mg/d) to raise HDL, particularly when statin or fibrate monotherapy does not raise HDL above 40 mg/dL in high-risk patients.

Lifestyle Modification
The NCEP emphasizes lifestyle modification for anyone with lipid levels outside target range. HDL is modestly increased by smoking cessation (up to 20%), weight loss (1 mg/dL per 3 kg), and aerobic exercise. Moderate alcohol ingestion can significantly raise serum HDL and is associated with reduced risk for acute cardiovascular events. Obese patients with insulin resistance may particularly benefit from weight loss and aerobic exercise when trying to raise HDL.

Conclusion
There is clear, clinical trial–based support for treating patients with low HDL, especially in the presence of CAD. In the primary and secondary prevention settings, the statin trials demonstrate significant risk reduction when treating patients with low HDL and average or elevated LDL levels (≥ 130 mg/dL). The fibrate trials support treating patients with hypertriglyceridemia and low HDL. Patients with low HDL, normal triglycerides, and low LDL (<100 mg/dL) constitute a somewhat equivocal group. There are no clinical trial data to guide clinical decision-making. Additional investigation will have to be done to determine which LDL thresholds constitute high risk for CAD at specific levels of HDL. If the patient has no risk factors other than a low HDL but has a strong family history for premature CAD, then consideration should be given to lifestyle modification and treatment with a statin and niacin as indicated (Figure). In other cases, when a patient presents with low HDL and has other risk factors but no evidence for CAD or a CAD risk equivalent, then calculation of the Framingham risk score is recommended. If the 10-year risk exceeds 20%, then the patient is at high risk for CAD and should be treated in conjunction with lifestyle modification.

Exciting new means of raising HDL and treating CAD in patients with low HDL are in development. CETP inhibitors, a vaccine against CETP, and bioengineered HDLs will be entering clinical trials. These studies will help to further clarify the role of HDL in the treatment and prevention of atherosclerotic disease. In the meantime, the treatment of patients with low HDL with currently available antilipidemic medication provides substantial reductions in risk for, and progression of, cardiovascular disease.

References


High-Density Lipoprotein and Cardiovascular Risk

Peter P. Toth

Circulation. 2004;109:1809-1812
doi: 10.1161/01.CIR.0000126889.97626.B8

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/109/15/1809