Reducing Cardiovascular Risk by Targeting High-density Lipoprotein Cholesterol

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Although lowering low-density lipoprotein (LDL) cholesterol with statins can substantially reduce cardiovascular morbidity and mortality, many treated patients retain a residual risk for cardiovascular events. Low levels of high-density lipoprotein (HDL) cholesterol may underpin this residual risk and may represent an additional target for intervention. Several new therapies for substantially increasing HDL cholesterol levels are under investigation, including cholesteryl ester transfer protein (CETP) inhibitors, apolipoprotein A-I mimetics and recombinant HDL, liver X receptor (LXR) agonists, and peroxisome proliferator–activated receptor (PPAR) agonists. Combining new HDL cholesterol–elevating agents with existing LDL cholesterol–lowering agents may improve the cardiovascular risk reductions currently attainable.

HDL Cholesterol and Protection Against Atherosclerosis

Epidemiologic evidence that HDL cholesterol is antiatherogenic

Large-scale epidemiologic studies such as the Framingham Heart Study [13,14], the Atherosclerosis Risk in Communities (ARIC) study [15], and the Prospective CV Münster (PROCAM) study [16,17] have demonstrated a strong inverse correlation between baseline HDL cholesterol levels and the incidence of CHD. For example, results from almost 3000 individuals aged 49 years or older in the Framingham Heart Study showed that after 4 years of follow-up there was a clear inverse relationship between baseline HDL cholesterol and CHD risk, such that baseline HDL cholesterol levels less than 35 mg/dL were associated with an eightfold increase in the incidence of CHD compared with baseline HDL cholesterol levels of 65 mg/dL or more [13]; this was a relationship that persisted through 12 years of follow-up [14]. Indeed, a meta-analysis of four prospective studies in the United States found that for every 1-mg/dL increase in serum HDL cholesterol concentration there was a 2% to 3% reduction in the risk of CHD [18]. This relationship remained significant after adjustment for other cardiovascular risk factors, including LDL cholesterol or total.
cholesterol levels [13–17], implying that HDL cholesterol was an important risk factor even in patients with low LDL cholesterol. In fact, HDL cholesterol was the strongest individual lipid predictor of CHD risk in both the Framingham and PROCAM Studies [13,14,16].

Benefits of HDL cholesterol elevation
Emerging evidence from preclinical and clinical studies shows that therapeutic elevation of HDL cholesterol is associated with cardiovascular benefit. Experiments in rabbit and mouse models of atherosclerosis demonstrate that HDL elevation can protect against, or even reverse, progression of atherosclerosis [19–21].

Clinical trial data show that modest elevations of HDL cholesterol, attainable by treatment with fibrates, niacin, and statins, may reduce the risk of cardiovascular events and CHD. The Helsinki Heart Study [22], the Diabetes Atherosclerosis Intervention Study (DAIS) [23], and the Veterans Affairs HDL-C Intervention Trial (VA-HIT) [24] all demonstrated that fibrate treatment (either fenofibrate or gemfibrozil) significantly elevated HDL cholesterol and reduced progression of atherosclerosis or the risk of CHD, and that HDL cholesterol levels were significantly associated with CHD outcomes [23,25–27]. HDL cholesterol levels were also increased by bezafibrate in the Bezafibrate Infarction Prevention trial [28], although reductions in the frequency of the primary endpoint (nonfatal and fatal myocardial infarction and sudden death) were not significant relative to placebo (13.6% on bezafibrate and 15.0% on placebo; P = 0.26). Further analysis, however, indicated that a subgroup of study subjects with triglyceride levels of 200 mg/dL or higher and HDL levels less than 35 mg/dL experienced a significant reduction of 42% (P = 0.02) in the frequency of the primary endpoint [28]. In accordance with epidemiologic studies, HDL cholesterol level at study entry was the most important risk factor for CHD in the placebo group in the Helsinki Heart Study [25,26], with combined results from the Helsinki Heart Study and the VA-HIT study suggesting that a 1% increase in HDL cholesterol with fibrate therapy is associated with a reduction in CHD of up to 3% [29]. This finding is supported by a recent meta-analysis of 53 clinical trials that showed that fibrates elevate HDL cholesterol by approximately 10% relative to baseline (P < 0.00001) and reduce the risk for first major coronary events by 25% [30].

Niacin is the most effective HDL cholesterol–raising agent available, with a recent meta-analysis of 30 clinical trials showing an average increase in HDL cholesterol of 16% following niacin treatment [30]. In the largest niacin trial to measure changes in HDL cholesterol levels—the Arterial Disease Multiple Intervention Trial (ADMIT)—HDL cholesterol levels were observed to increase by up to 30% in 468 patients with peripheral arterial disease [31]. Among the 1119 men randomized to the niacin treatment arm of the Coronary Drug Project, risk for myocardial infarction and stroke was reduced by 27% and 26%, respectively (both P < 0.05), relative to placebo over 5 years of follow-up. Risk for either all-cause or cardiovascular mortality was not reduced during the course of the trial [32]. However, after 15 years of follow-up, there was an 11% decrease in cardiovascular mortality (P = 0.0004) [33]. Although, to date, no large-scale trials with niacin have correlated changes in HDL cholesterol levels with cardiovascular endpoints, the reductions in cardiovascular risk associated with niacin therapy are believed to be at least partially attributable to increases in HDL cholesterol [12,34,35]. In the smaller Familial Atherosclerosis Treatment Study (FATS), the effects of lovastatin/colestipol or niacin/colestipol combinations were evaluated in 120 men with CHD [36]. The levels of LDL cholesterol and HDL cholesterol changed only slightly in patients who received placebo or colestipol monotherapy (-7% and +5%, respectively), but more substantially among patients treated with lovastatin/colestipol (-46% and +15%) or niacin/colestipol (-32% and +43%). Compared with patients who received placebo or colestipol monotherapy, both the lovastatin/colestipol and niacin/colestipol regimens were associated with a reduced frequency of coronary lesion progression (46%, 21%, and 25% of patients, respectively) and increased frequency of lesion regression (11%, 32%, and 39% of patients, respectively).

Clinical trials have shown that statins markedly reduce the risk of CHD in at-risk patients, primarily due to a reduction in LDL cholesterol levels [6–10,37–40], although HDL cholesterol increases of up to 8% with statin therapy may also contribute to reductions in cardiovascular risk [41,42]. However, an important observation is that, after statin treatment, patients with low baseline HDL cholesterol levels typically experience a greater number of CHD events during follow-up than patients with higher baseline HDL cholesterol levels [8,43–45]. This suggests that statin therapy alone may be insufficient to ameliorate the CHD risk associated with low HDL cholesterol levels and supports a strategy of elevating HDL cholesterol levels concomitantly with statin therapy.

Antiatherogenic properties of HDL cholesterol
Multiple mechanisms underlie the atheroprotective effects of HDL cholesterol, the most important of which may be the pivotal role played by HDL cholesterol in reverse cholesterol transport, the process by which excess cholesterol is transported from blood vessels and peripheral tissues to the liver for excretion (Fig. 1) [46]. Peripheral tissues transfer excess free cholesterol to lipid-poor apolipoprotein A-I (apoA-I) via the adenosine triphosphate binding cassette A1 (ABCA1) receptor, forming nascent pre-β HDL [47]. Free cholesterol in nascent HDL is then converted to cholesteryl ester and internalized to form the mature α-HDL particle [47]. Peripheral cells may also efflux free cholesterol directly to mature HDL particles via the scavenger receptor-B1 (SR-B1) receptor [48] or via the recently discovered ABCG1 and ABCG4 receptors [49••].