

# CardiologyRounds™

AS PRESENTED IN THE ROUNDS OF THE CARDIOVASCULAR DIVISION  
OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

## High-density lipoprotein metabolism as a therapeutic target for atherosclerosis

BY DANIEL J. RADER, M.D.

There is a strong inverse association between plasma HDL cholesterol (HDL-C) levels and incidence of coronary heart disease (CHD) that is independent of other known risk factors.<sup>1</sup> Even when LDL cholesterol (LDL-C) levels are low, HDL-C is still a major and independent predictor of cardiovascular risk (Figure 1). Low levels of HDL-C are frequently found in patients with premature CHD,<sup>2</sup> whereas genetic syndromes of high HDL-C are often associated with decreased risk of CHD. These observations led to the recommendation for the inclusion of HDL-C in routine screening of all adults<sup>3</sup> and as an independent risk factor in the assessment of cardiovascular risk.<sup>4</sup> Recent attention has focused on HDL metabolism as a potential target for therapeutic intervention.

### HDL metabolism and relationship to atherosclerosis

HDL is a lipoprotein composed of lipids (primarily phospholipids and cholesterol) as well as apolipoproteins (the major one is apolipoprotein A-I or apoA-I). The metabolism of HDL is depicted in Figure 2. HDL is thought to protect against atherosclerosis, at least in part, by promoting efflux of excess cholesterol from cells in the arterial wall and transporting it to the liver for excretion into the bile, a process known as "reverse cholesterol transport."<sup>5</sup> The discovery that persons with defective cellular cholesterol efflux and low levels of HDL-C are at increased risk for atherosclerosis has provided support for this concept.<sup>6,7</sup> HDL has other properties that may also partly explain its atheroprotective effects. *In vitro*, HDL has been shown to protect LDL from oxidation, reduce endothelial cell adhesion molecule expression, and inhibit platelet aggregation. However, there are not yet convincing *in vivo* data demonstrating that these mechanisms are operative. There remains much to be learned about HDL metabolism and its relationship to atherosclerosis.

Animal studies have provided substantial support for the principle that intervention targeted toward HDL reduces atherosclerosis. Transgenic hepatic overexpression of human apoA-I in transgenic mice and rabbits reduced the initiation and progression of atherosclerosis.<sup>8</sup> Regular infusions of HDL into cholesterol-fed rabbits<sup>9</sup> and hepatic gene transfer of human apoA-I in hypercholesterolemic mice<sup>10</sup> induced significant regression of atherosclerotic lesions. Based on studies in animals, intervention targeted toward HDL metabolism in humans might be expected to reduce the risk of atherosclerotic vascular disease.

### Causes of low HDL cholesterol levels in humans

Low HDL-C levels are often, in part, secondary to other factors. Cigarette smoking, obesity, and physical inactivity all contribute to a low HDL-C. Type II diabetes mellitus, end-stage renal disease, and hypertriglyceridemia from any cause are all associated with low HDL-C. Beta-blockers, thiazide diuretics, androgens, and progestins, as well as a very low fat diet can lower HDL-C, although the clinical significance of this is uncertain. The most common form of low HDL-C is probably in association with a metabolic syndrome that includes visceral obesity and insulin resistance (Table 1).<sup>11</sup> Therefore,



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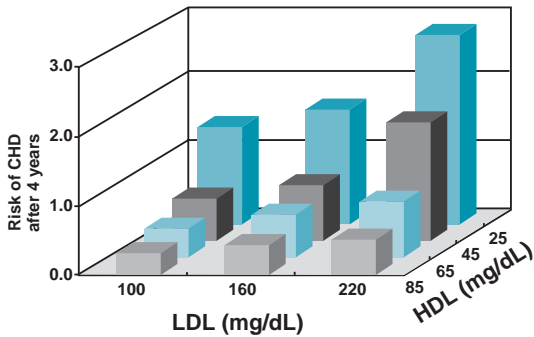
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**Figure 1: HDL-C levels are independently predictive of cardiovascular risk even when LDL-C levels are normal or low.**



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low HDL-C is in part a marker for the presence of other cardiovascular risk factors.

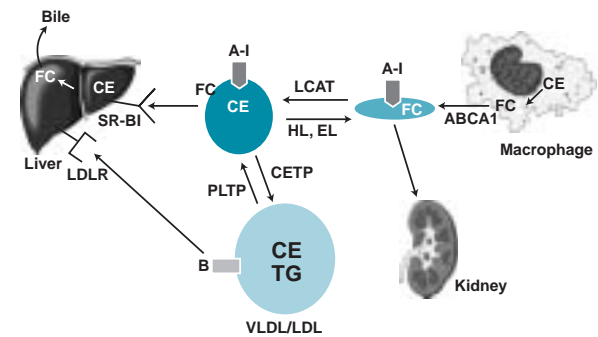
Some causes of low HDL-C are genetic, although only a few of the genes responsible for inherited low HDL syndromes have been identified. Rare mutations in apoA-I itself can cause low HDL-C. The first of these to be described was apoA-I<sub>Milano</sub> which, despite low levels of HDL-C, is not associated with increased premature CHD. Deficiency of LCAT (lecithin:cholesterol acyltransferase) causes very low HDL-C levels (<15 mg/dL), corneal opacities, and chronic renal failure, but interestingly, not an increased risk of atherosclerosis.<sup>12</sup> Tangier disease is a rare genetic disease characterized by extremely low HDL-C (<5 mg/dL) and cholesterol accumulation in the reticuloendothelial system resulting in hepatosplenomegaly, intestinal mucosal abnormalities, and enlarged orange tonsils.<sup>13</sup> Tangier disease is caused by mutations in ABCA1 (ATP-binding cassette protein 1), resulting in impaired removal of excess cholesterol from cells and rapid catabolism of poorly-lipidated apoA-I. Heterozygotes for ABCA1 mutations have low levels of HDL-C (15-35 mg/dL) and this may be a relatively common cause of low HDL.<sup>6</sup> Patients with ABCA1 mutations appear to have an increased risk of premature atherosclerosis.<sup>6</sup> The most common inherited form of low HDL is termed primary or familial hypoalphalipoproteinemia,<sup>2</sup> defined as an HDL-C level below the 10th percentile without a secondary cause of low HDL-C, in association with a family history of low HDL-C. The genetic etiology of this syndrome is currently unknown, although the metabolic etiology appears to be accelerated catabolism of HDL and its apolipoproteins.<sup>14</sup> The relationship of this syndrome with premature atherosclerosis may depend on the specific nature of the gene defect(s).<sup>3</sup>

### Evidence for benefit of raising HDL-C levels in humans

Smoking cessation, regular aerobic exercise, weight control, and control of diabetes all result in increased HDL-C levels and are associated with reduced cardiovascular risk, although the specific contribution of the increased HDL-C to reduced risk is unknown. Clinical trials of the effect of drug therapy targeted toward low HDL-C on clinical cardiovascular events are very limited, reflecting in part the paucity of interventions that substantially raise HDL-C levels. Statins, though

**Figure 2: HDL metabolism and reverse cholesterol transport.**

Macrophages efflux excess free cholesterol (FC) to acceptors in the extracellular environment. Lipid-poor apolipoprotein A-I (A-I) acquires free cholesterol through a transport process facilitated by the cellular protein ATP-binding cassette protein A1 (ABCA1). Unesterified cholesterol in HDL is converted to cholesteryl ester (CE) within the HDL particle by the enzyme lecithin:cholesterol acyltransferase (LCAT). HDL cholesterol can be taken up selectively by the liver through the action of the SR-B1. The liver secretes free cholesterol (FC) directly into the bile or converts it to bile acids that are then secreted into the bile. Ultimately, biliary sterols are excreted in the feces. HDL cholesteryl ester can also be selectively transferred to apo B-containing lipoproteins in exchange for triglyceride through the action of cholesteryl ester transfer protein (CETP). Hepatic lipase (HL) and endothelial lipase (EL) hydrolyze HDL lipids, generating smaller HDL particles and promoting their catabolism.



VLDL/LDL = very low and low-density lipoproteins  
 B = apolipoprotein B; LDLR= low-density lipoprotein receptors  
 PLTP = phospholipid transfer protein; TG = triglycerides

not generally considered HDL-raising agents, raise HDL-C by about 5%-10% and significantly reduce risk in patients with low HDL-C and average or elevated LDL-C levels.<sup>15</sup> The AFCAPS/TextCAPS trial was a trial in healthy subjects with a mean LDL-C level of 150 mg/dL who were selected for relatively low HDL-C levels.<sup>15</sup> Treatment with lovastatin significantly reduced major coronary events by 36% and the relative risk reduction was greatest in the group with the lowest tertile of baseline HDL-C levels. In the Heart Protection Study, high-risk patients were randomized to simvastatin 40 mg vs placebo regardless of baseline cholesterol levels.<sup>16</sup> Simvastatin treatment was associated with a significant reduction in major coronary events, including those subjects with low HDL-C levels at baseline. Thus, statin therapy in patients with low HDL-C is an effective method of reducing cardiovascular risk.

Fibric acid derivatives, or fibrates, are agonists of PPAR $\alpha$  (peroxisome proliferator-activated receptors), a nuclear hormone receptor involved in energy and lipid metabolism. This class includes gemfibrozil, fenofibrate, and bezafibrate. Fibrates lower triglyceride levels effectively and generally raise HDL-C levels modestly (5%-15%). Fibrates are more effective in raising HDL-C when triglycerides are elevated. The Helsinki Heart Study in healthy men with elevated non-HDL cholesterol > 200 mg/dL demonstrated a significant 34% reduction in combined fatal and nonfatal myocardial infarction (MI) associated with gemfibrozil therapy, and at least part of the benefit was attributed to the modest increase in HDL cholesterol.<sup>17</sup> The Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) tested the benefit of gemfibrozil therapy targeted specifically to patients with low

**Table 1: Low HDL-C is a criterion for the diagnosis of the metabolic syndrome.<sup>41</sup>**

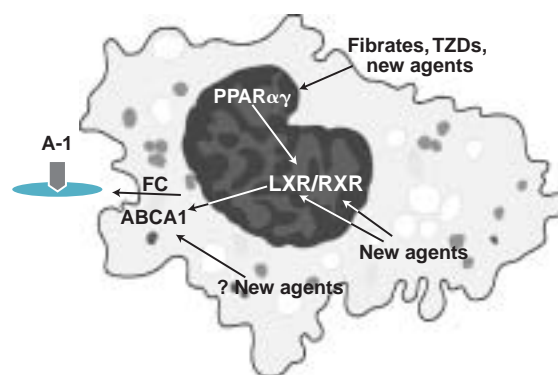
Risk factor	Defining level
• Abdominal obesity (Waist circumference)	
Men	> 102 cm (> 40 inches)
Women	> 88 cm (> 35 inches)
• Triglycerides	≥ 150 mg/dL
• HDL-C	
Men	< 40 mg/dL
Women	< 50 mg/dL
• Blood pressure	≥ 130/≥ 85 mm Hg
• Fasting glucose	≥ 110 mg/dL

HDL and low LDL cholesterol levels.<sup>18</sup> Men with CHD (n = 2531), low HDL-C (mean 32 mg/dL), low LDL cholesterol (mean 112 mg/dL), and triglycerides < 300 mg/dL were randomized to treatment with gemfibrozil (1200 mg daily) or placebo and followed for an average of 5.1 years. Gemfibrozil therapy was associated with a significant 22% reduction in the primary endpoint (nonfatal MI and coronary death) compared to placebo. Compared with placebo, gemfibrozil resulted in a 6% increase in HDL-C, a 31% decrease in triglycerides, and no change in LDL-C levels. An analysis suggested that the benefit might have been associated more with the modest increase in HDL-C than with the reduction in triglycerides. In contrast, the Bezafibrate Infarction Prevention (BIP) trial tested the effect of another fibrate, bezafibrate, in 3090 patients with CHD, low HDL cholesterol, and moderately elevated LDL cholesterol (mean 150 mg/dL) and found no significant reduction in major coronary events in the bezafibrate group compared with placebo.<sup>19</sup> However, a subgroup analysis indicated that those individuals with elevated triglyceride levels at baseline did have a significant benefit from bezafibrate therapy. VA-HIT and BIP differed in a number of important ways, including the fibrate used and the baseline LDL-C levels. In any case, the results of VA-HIT suggest that gemfibrozil therapy in CHD patients with low LDL-C and low HDL-C reduces cardiovascular events.

Nicotinic acid, or niacin, is the most effective method of raising HDL-C and can result in up to a 30% increase in HDL-C. In a direct comparison to gemfibrozil, an extended-release form of niacin at a dose of 2 gm daily had a significantly greater effect on HDL-C (+26%) compared with gemfibrozil 1200 mg daily (+13%).<sup>20</sup> However, there have been few clinical outcome studies with niacin. The Coronary Drug Project demonstrated a nonsignificant reduction in nonfatal MI with immediate release niacin after 6 years of treatment and a significant reduction in total mortality after 15 years of follow-up.<sup>21</sup> Immediate-release niacin often causes flushing that has limited its use; an extended-release form of niacin is better tolerated,<sup>22</sup> but no outcome data are yet available.

Many patients treated with a statin for LDL-C reduction achieve the LDL-C goal, but continue to have low HDL-C levels. Epidemiologic data suggest that a low HDL-C is a risk factor even in the setting of an LDL-C < 100 mg/dL. The addition of niacin<sup>23,24</sup> or a fibrate<sup>25</sup> to a statin can effectively raise HDL-C levels in this setting. However, there are no published outcome trials testing the benefit of combining a fibrate or

**Figure 3: Molecular regulation of cholesterol efflux in the macrophage and its pharmacologic manipulation.**



TZDs = thiazolidinediones; ABCA1 = ATP-binding cassette protein 1; LXR/RXR = liver x receptor/rexinoid receptor; PPAR $\alpha\gamma$  = peroxisome proliferator-activated receptors, alpha and gamma; FC = free cholesterol; A-I = apolipoprotein A-I

niacin with a statin compared with a statin alone; this is clearly a major unmet need with regard to future lipid modification trials.

### New approaches to therapeutic targeting of HDL metabolism

New and more effective approaches to raising HDL-C and increasing reverse cholesterol transport are needed. New approaches to HDL can be separated into at least 3 categories:

- increasing apoA-I production;
- promoting cellular cholesterol efflux and reverse cholesterol transport;
- delaying the turnover of HDL cholesterol and/or apoA-I.

As noted above, there is a wealth of animal data suggesting that increasing apoA-I production reduces progression and even induces regression of atherosclerosis. Therefore, a small molecule that increases apoA-I production, perhaps through increasing gene transcription in the liver and/or the intestine, would be highly desirable. However, despite decades of intense effort, no such small molecules have yet advanced to the point of large clinical trials. Therefore, other approaches to increasing apoA-I, such as administration of the intact protein or peptides, are being actively investigated.

A second strategy involves the promotion of cellular cholesterol efflux and reverse cholesterol transport. HDL and apoA-I are thought to protect against atherosclerosis, in part, by promoting efflux of excess cholesterol from macrophages in the arterial wall and returning that cholesterol to the liver for excretion into the bile, a process known as “reverse cholesterol transport” (Figure 2).<sup>5</sup> Pharmacologic upregulation of ABCA1 could promote cellular cholesterol efflux and reduce atherosclerosis. There has been tremendous interest in understanding the transcriptional regulation of ABCA1 that appears to be primarily through the nuclear heterodimer LXR/RXR (Figure 3). Synthetic ligands for either LXR or RXR are being explored as therapeutic approaches. Furthermore, PPAR $\alpha$  agonists (fibrates) and PPAR $\gamma$  agonists (thiazolidinediones) have been shown to upregulate LXR, ABCA1, and cholesterol efflux;<sup>26</sup> therefore, this may be another strategy to promote

cholesterol efflux and reverse cholesterol transport *in vivo*. In theory, upregulation of LCAT (lecithin: cholesterol acyltransferase) or SR-BI (scavenger receptor class B type I, Figure 2) could also be strategies for promoting reverse cholesterol transport, but these approaches have not been proven.

Finally, plasma HDL-C and apoA-I levels could be increased by interventions that slow their catabolism. One major therapeutic target is cholesteryl ester transfer protein (CETP) that transfers cholesteryl esters from HDL to apoB-containing lipoproteins in exchange for triglycerides (Figure 2).<sup>27</sup> Genetic homozygous CETP deficiency, found primarily in Japan, is associated with markedly increased HDL-C levels.<sup>28</sup> The relationship between CETP deficiency and atherosclerosis is still in question. One report suggested that homozygous CETP deficiency was protective against coronary heart disease,<sup>29</sup> but another suggested it may be associated with increased atherosclerotic disease.<sup>30</sup> Studies of CETP inhibition in rabbits (with high levels of CETP) have demonstrated significant reductions in atherosclerosis, both using a small molecule inhibitor<sup>31</sup> as well as an anti-CETP immunization strategy.<sup>32</sup> A CETP inhibitor has been shown to raise levels of HDL-C in humans.<sup>33</sup> There remains substantial uncertainty about whether CETP inhibition will reduce atherosclerosis in humans, and this question will only be definitely answered through appropriate clinical trials.

ApoA-I is catabolized in part by the kidney (Figure 2). It is believed that lipid-poor apoA-I is more likely to be filtered and degraded by the kidney. Therefore, factors that generate increased amounts of lipid-poor apoA-I are likely to promote apoA-I catabolism and could be targets for inhibition.

Remodeling of HDL is a critical process that regulates HDL size/density heterogeneity.<sup>34</sup> Hepatic lipase (HL) is one factor that plays a role in the conversion of the larger HDL<sub>2</sub> particles to the smaller HDL<sub>3</sub> particles through hydrolysis of HDL triglycerides and possibly phospholipids.<sup>35</sup> Endothelial lipase (EL) is a member of the same triglyceride lipase gene family as LPL (lipoprotein lipase) and HL. It was cloned independently by two different groups.<sup>36,37</sup> EL has triglyceride lipase activity,<sup>38</sup> but relative to LPL and HL, it has substantially greater phospholipase activity, putting it at the other end of the lipolytic spectrum from LPL.<sup>39</sup> EL is highly effective at hydrolyzing HDL lipids *ex vivo*.<sup>38</sup> Plasma concentrations of HDL-C and apoA-I were markedly reduced by overexpression of EL in mice.<sup>36</sup> Antibody inhibition of EL in mice significantly increased plasma levels of HDL-C and apoA-I.<sup>40</sup> Therefore, EL may be a target for inhibition as a novel therapeutic approach to raising HDL-C and apoA-I levels.

### Summary and recommendations

The National Cholesterol Education Program (NCEP) guidelines recommend that all adults over age 20 be screened with a total fasting lipid profile, including HDL-C (ATPIII).<sup>41</sup> There have been no formal guidelines

**Table 2: Interventions in patients with low HDL-C levels**

#### Therapeutic lifestyle changes

- Smoking cessation
- Aerobic exercise
- Replace saturated fat with monounsaturated fat in diet
- Reduction in simple carbohydrate intake
- Weight loss

#### Pharmacologic therapy

- Consider a thiazolidinedione (if type II diabetic)
- Consider a statin (if LDL-C not at goal)
- Consider a fibrate (if triglycerides elevated)
- Consider niacin (if low HDL-C is primary abnormality)
- Consider combination therapy (if high risk)

developed specifically for the classification and management of patients with low levels of HDL cholesterol. However, several recommendations can be reasonably made and are summarized in Table 2. The approach to the patient with a low HDL-C level should focus initially on lifestyle and nonpharmacologic issues. Patients who smoke should be encouraged to stop, those who are sedentary to develop a regular aerobic exercise program, and those who are overweight to lose weight. All of these interventions can be expected to have modest effects in raising HDL-C and are additive in their effects. Dietary recommendations need to be individually tailored, but in general, patients should be advised to limit total fat intake to 30% of total calories, to replace saturated fat with monounsaturates rather than polyunsaturates, and to limit intake of simple carbohydrates. Alcohol use is clearly associated with increased HDL-C levels in a dose-dependent fashion, but is not recommended as a therapeutic strategy for raising HDL-C levels. Hormone replacement therapy (HRT) can raise HDL-C levels, but HRT is not currently recommended for reduction of cardiovascular risk. Diabetes mellitus should be optimally controlled. Thiazolidinediones have been shown to increase HDL-C levels in diabetics. For patients with substantially elevated triglyceride levels (> 400 mg/dL), both lifestyle and, if indicated, pharmacologic interventions such as fibrates, niacin, or fish oils should be considered to reduce the triglycerides, which usually increase HDL-C levels.

Patients with low HDL-C and elevated or borderline LDL-C levels should be treated to reduce the LDL-C, and in most cases, a statin is the appropriate choice. For patients with low HDL-C and substantially elevated triglycerides (ie, > 400-600 mg/dL), initial treatment with a fibrate should be considered. If the HDL-C is low, the LDL-C is already well-controlled (ie < 130 mg/dL), and the triglycerides are < 400 mg/dL, a more difficult issue is whether pharmacologic intervention should be targeted specifically toward the HDL-C level. In persons with established CHD or who have a CHD risk equivalent, this may be a reasonable approach, especially in light of the results of the VA-HIT study. In healthy persons, there

are no published clinical trials demonstrating benefits of treatment targeted specifically toward a low HDL-C. Every effort should be made to optimize lifestyle intervention in such patients. However, in high-risk individuals, including those with diabetes or metabolic syndrome and those with strong family histories of premature CHD, drug therapy targeted toward low HDL-C could be reasonably considered. Fibrates have more overall outcome data, whereas niacin is more effective in raising HDL-C levels; neither has been used in clinical outcome trials in a primary prevention population with isolated low HDL-C.

Another common scenario is the patient with CHD, diabetes mellitus, or with other high cardiovascular risk who has been treated with a statin and has reached LDL-C goal, but still has a low HDL-C level. Both fibrates and niacin have been tested in combination with statins and they are generally safe and effective in raising HDL-C. (Note: The potential for myopathy when using the combination of a statin and a fibrate must be carefully considered. However, when patients are appropriately selected and educated, this risk is rare). No outcome trials comparing either of these combinations to statin therapy alone have been reported; nevertheless, in patients with CHD or high cardiovascular risk who are on statin therapy with a well-controlled LDL-C, but a low HDL-C, the addition of niacin or a fibrate should be considered.

Much has been learned about HDL metabolism and reverse cholesterol transport. However, more translational research in humans should be conducted in the area of HDL metabolism, reverse cholesterol transport, and their relationship to atherosclerosis. New therapeutic approaches to raising HDL-C levels and promoting reverse cholesterol transport, such as CETP inhibitors, dual PPAR $\alpha$  agonists, and intravenous infusion of phospholipid vesicles, are currently in clinical development. The next decade will witness clinical trials evaluating a variety of new therapies targeted toward HDL metabolism and reverse cholesterol transport in the hope of improved prevention or regression of atherosclerotic cardiovascular disease.

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