High-Density Lipoprotein and Coronary Heart Disease

Current and Future Therapies

Pradeep Natarajan, MD,* Kausik K. Ray, MD,‡ Christopher P. Cannon, MD*†
Boston, Massachusetts; and Cambridge, England

Coronary heart disease remains a major cause of worldwide morbidity and mortality despite therapeutic advances that control many risk factors such as low-density lipoprotein cholesterol to levels lower than previously possible. Population studies have consistently demonstrated an inverse association between high-density lipoprotein cholesterol (HDL-C) levels with the risk of coronary heart disease. As a result, HDL-C is gaining increasing interest as a therapeutic target. In this review, we explore the protective mechanisms of HDL and how current and future therapies harness these beneficial properties. We offer a biological framework to understand treatment strategies as well as their resultant successes and failures to guide management and future directions. At present, raising HDL-C level holds great promise, on the basis of epidemiology and initial trials, but we await the outcomes of the many large clinical outcomes trials currently under way to define the clinical role of older and novel therapies to raise HDL-C level. (J Am Coll Cardiol 2010;55:1283–99) © 2010 by the American College of Cardiology Foundation

Currently, our therapy for lipid modification for atherosclerosis treatment and prevention focuses on lowering low-density lipoprotein cholesterol (LDL-C). Lipid-lowering treatment directed at LDL-C with standard doses of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (“statins”) has resulted in a relative risk reduction of one-third in major vascular events as compared with placebo (1). In patients at very high risk for vascular events, intensive lipid-lowering has been shown to be beneficial compared with standard therapy (2–4). However, despite such notable progress, cardiovascular disease continues to be the leading cause of death and disease worldwide. As a result, novel strategies to address this residual risk have been sought.

The Framingham Heart Study in the 1980s demonstrated that the risk of coronary heart disease (CHD) was significantly lower among persons with higher levels of high-density lipoprotein cholesterol (HDL-C) (normal range 40 to 60 mg/dl) (5). A number of studies have supported this inverse correlation between HDL-C and CHD (5–9); hence, HDL-C has quickly evolved as one of the “traditional” risk factors used by clinicians to predict risk of incident CHD (4). An estimated 1 mg/dl higher HDL-C is associated with a 2% lower risk of CHD for men and a 3% lower risk for women (10). Current guidelines recommend lowering non–HDL-C as a secondary target after LDL-C lowering in recognition of the atherogenicity of lipoproteins associated with hypertriglyceridemia (4). Traditional lipid-lowering therapy appears to lower LDL-C and non–HDL-C similarly, and these parameters are often not distinguished in trials. Even after LDL-C is aggressively controlled to very low levels with statin therapy, low HDL-C still remains a significant cardiovascular risk factor (11,12). As a result, there has been increasing interest in HDL-C as a therapeutic target (13).

Prevalence

The prevalence of low levels of HDL-C (e.g., <40 mg/dl) varies geographically (14) and is particularly high in Latin American countries, where the prevalence is as high as 46% in men (15). Over a 7-year period, this prevalence has continued to rise in Mexico by 2% to 3% (16). Approximately 25% of men in the United Kingdom have low levels of HDL-C (17). A more recent Pan–European survey suggests that the prevalence throughout Europe is similar to that in the U.S., with low HDL-C levels in nearly one-half of the Dutch (18). Although a significant number in China have low HDL-C levels, the prevalence is much lower than in North America, with ≈7% of men and <2% of women having low levels (19). In the international study evaluating...
risk factors for acute myocardial infarction known as the INTERHEART study, it was recently shown that there is specifically a higher prevalence of low HDL-C levels in South Asians compared with other Asians (20).

**Biological Role of High-Density Lipoprotein (HDL)**

The equilibrium between atherogenic lipoproteins, such as low-density lipoprotein (LDL), and antiatherogenic HDL can affect endothelial dysfunction and inflammation (21). In the face of elevated LDL-C levels, HDL-C appears to progressively protect against atherosclerosis (21).

Circulating HDL particles are greatly heterogeneous with a very complex metabolic profile (Table 1). The various HDL subclasses vary in quantitative and qualitative content of lipids, apolipoproteins, enzymes, and lipid transfer proteins, resulting in differences in shape, density, size, charge, and antigenicity. Discoid HDL particles are small, lipid-poor particles made of apolipoprotein in a monolayer of phospholipids and free cholesterol (21–23). Spherical HDL particles are larger, are made from discoid HDL, and contain a hydrophobic core of cholesterol esters (21–23).

Reverse cholesterol transport, the process of transporting excess cholesterol from the arterial wall’s foam macrophages to the liver, bile, and feces is one of HDL’s antiatherogenic properties (24,25) (Fig. 1). Lipid-free HDL, or apolipoprotein A-I, mediates this through the adenosine triphosphate (ATP)-cassette binding transporter (ABC) A1. Then esterification of HDL-C by lecithin-cholesterol acyltransferase (LCAT) generates more mature HDL particles, including small, dense spherical HDL3 and large, less dense spherical HDL2 (22,24). These mature HDL particles may induce further cholesterol efflux through ABCG1 and ABCG4 (21,24,26). HDL-C measures the cholesterol content of nascent HDL, HDL2, and HDL3 particles and is, therefore, a crude marker of reverse cholesterol transport. The smaller HDL3 particles more efficiently promote cholesterol efflux through the ABCA1 pathway than do their larger counterparts, but they are equally as effective through the ABCG1 pathway (27–29).

After cholesterol efflux from the plaque, reverse cholesterol transport is completed by transport back to the liver. Through the scavenger receptor B1, hepatocytes and steroid-producing cells can uptake these mature HDL particles (25,30). Furthermore, cholesterol esters from these particles may be transferred to apolipoprotein B-containing particles, such as LDL or very low-density lipoprotein (VLDL), through the cholesterol ester transfer protein (CETP) (22,24,25). Hepatic LDL receptors can then scavenge these apolipoprotein B-containing particles enriched with cholesterol esters, further contributing to reverse cholesterol transport (25). The subsequent HDL particle enriched with triglycerides may regenerate small HDL particles through hydrolysis from hepatic lipase (21,24,25).

In addition to HDL protecting against atherosclerosis through reverse cholesterol transport, HDL’s antioxidative activity further protects against atherosclerosis (21,31) (Table 2). Apolipoprotein A-I is a major factor in this process (31). In addition to HDL-C esterification, LCAT can also hydrolyze oxidized phospholipids of LDL (22,31,32).

For monocytes to gain entry into the subendothelial space to promote atherosclerosis, their circulation must be arrested, which is accomplished by binding to adhesion molecules in the blood vessel wall (33,34). Expression of these adhesion molecules depends on inflammatory cytokines and vascular injury, and is up-regulated in atherosclerosis (35–38). Animal models have demonstrated that HDL inhibits the expression of adhesion molecules (39,40). HDL can also directly inhibit the migration of these monocytes into the subendothelial space (41). In the endothelium, nitric oxide protects against inflammation and activation (42). HDL promotes vasoprotection by enhancing nitric oxide synthase and thereby increasing the production of nitric oxide (42,43). In addition to protection against platelet activation through endothelial protection, HDL inhibits the coagulation cascade through serine protease protein C, which inactivates factors Va and VIIa (42,44–46).

**“Dysfunctional” HDL**

Structural and functional changes accompany HDL in the setting of acute or chronic inflammation. Leukocyte myeloperoxidase may alter the function of normally atheroprotective molecules into so-called “dysfunctional” HDL with proinflammatory properties (47). During inflammation, HDL-C levels can be reduced because of increased HDL catabolism, decreased apolipoprotein A-I synthesis, and displacement of apolipoprotein A-I from HDL with serum amyloid A, an acute-phase protein (48,49). Additionally, platelet-activating acetylhydrolase and LCAT can become dysfunctional or diminished during inflammation, and among persons with low HDL-C levels such as those with

### Table 1 Physical Properties of HDL Particles

<table>
<thead>
<tr>
<th>Particle</th>
<th>Diameter, nm</th>
<th>Density, g/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discoid HDL</td>
<td>&lt;8</td>
<td>—</td>
</tr>
<tr>
<td>Spherical HDL3</td>
<td>8–9</td>
<td>1.125–1.121</td>
</tr>
<tr>
<td>Spherical HDL2</td>
<td>9–10</td>
<td>1.063–1.125</td>
</tr>
</tbody>
</table>

Discoid high-density lipoprotein (HDL) is quickly degraded when extracted from plasma. As a result, when human HDL is processed through density gradient ultracentrifugation, the predominant subfractions include HDL2 and HDL3. HDL3 is smaller and denser, and is relatively protein rich and lipid poor (21–23).
type 2 diabetes mellitus and CHD (31,41,50–52). Furthermore, in the metabolic syndrome, hypertriglyceridemic states and the acute-phase response, largely through CETP, enrich the triglyceride content of HDL-C (48,53). In turn, triglyceride-rich HDL-C particles result in a lowering of circulating HDL-C levels through their inherent instability and subsequent degradation as well as through hydrolysis from hepatic lipase (53). Furthermore, triglyceride-rich HDL-C cannot be taken by hepatocytes through scavenger receptor B1 as readily, resulting in reduced efficacy of reverse cholesterol transport (53,54). Therefore, a combination of metabolic abnormalities and inflammatory milieu may result in “dysfunctional” HDL (31,55).

Nonpharmacological Interventions

Observational and interventional studies have assessed the relationship between lifestyle factors and circulating HDL-C levels. Aerobic exercise. In young adult women, moderate activity was shown to significantly increase HDL-C over the course of 6 months (56). In a population of men and women ranging from 50 to 65 years of age, however, an increased frequency of exercise resulted in the highest HDL-C levels
The Framingham study group showed that cigarette smoking accounted for a drop in HDL-C by 4 mg/dl in men and 6 mg/dl in women (80). A meta-analysis demonstrated that smokers generally have a 9% lower HDL-C level and a 6% lower apolipoprotein A-I level compared with matched nonsmokers (81). This inverse association of cigarette smoking and HDL-C levels is dose dependent (81–84). Increased CETP activity and the resultant transfer of cholesterol esters from HDL to apolipoprotein B-containing particles mediate tobacco smoking’s atherogenic lipoprotein changes (85,86). Furthermore, in a meta-analysis of 27 studies, it was observed that when participants quit smoking tobacco, their HDL-C levels rose by 4 mg/dl without a significant effect on total cholesterol, LDL-C, or triglyceride levels (87). Additionally, smoking cessation results in an increase in apolipoprotein A-I (88). These favorable effects on the lipid profile can be seen as early as 30 days after quitting smoking (89).

**Alcohol.** While heavy alcohol intake is associated with increased all-cause mortality and cardiovascular-related mortality (90–94), moderate alcohol intake appears to have a protective effect on CHD (95–99). Part of this protection may be mediated by an associated increase in HDL-C (100–103). An increase in both the HDL2 and HDL3 subfractions, but with relatively larger increase in HDL2, is observed with moderate alcohol consumption (103,104). A systematic review showed that all forms of alcohol (e.g., beer, wine, and spirits) had a favorable cardioprotective effect (105). However, data suggest that wine consumption provides more cardioprotection (106). Some of this additive benefit may be from “flavonoids” such as resveratrol that act as lipoprotein antioxidants (107). The recommendation of moderate alcohol consumption for cardiovascular protection is limited by the potential for abuse, dependence, and caloric intake.

**Pharmacological Interventions**

Various randomized controlled trials have evaluated the efficacy and safety of pharmacologically modifying HDL (Table 3).

**Statins.** The reduction of LDL-C with statins has a positive effect on the occurrence of cardiovascular events (108–112). A decrease in LDL-C levels from statin therapy is associated with a decrease in the progression of atherosclerosis (113–115). Increases in HDL-C between 5% and 15% have been reported with statin-mediated therapy, with an average increase of ~9% (108,110,111,116). However, the data regarding the clinical significance of this are unclear. The statin-induced HDL-C effects are relatively small compared with the LDL-C effects, so the effects of statins on HDL-C are likely to be small. Nevertheless, a recent meta-analysis of statin therapy demonstrated that, in patients with CHD in whom LDL-C levels are aggressively reduced to <87.5 mg/dl, an increase in HDL-C by 7.5% is independently associated with a regression in coronary atherosclerosis (116). Statins also promote the formation of a more favorable HDL subfraction profile by creating more cholesterol–rich HDL particles, perhaps through the reduc-
tion of cholesterol transfer from HDL (117–120). That may occur through the reduction in available apolipoprotein B-containing atherogenic particles to accept cholesterol esters and down-regulation of CETP expression (121,122).

**Niacin.** Currently, niacin (vitamin B3) is the most effective available pharmacologic means to raise HDL-C levels. Interest in niacin developed 50 years ago when it was noted to decrease total cholesterol, lower LDL-C, and raise HDL-C (123,124). Niacin increases HDL-C levels by 15% to 35% with a nonlinear dose-dependent response (125–129). Therefore, the majority of the beneficial effects of niacin occurs at doses of 1 to 1.5 g per day (126,129).

Niacin accomplishes this effect on HDL through multiple mechanisms. It selectively inhibits hepatic clearance of HDL’s apolipoprotein A-I and not the cholesterol esters (130,131). As a result, the cholesterol-deficient apolipoprotein A-I–containing HDL particles are recycled into the circulation and freed for further reverse cholesterol transport (130,132). Furthermore, niacin directly inhibits the transfer of cholesterol esters through CETP from HDL to apolipoprotein B-containing particles by directly inhibiting CETP activity as well as by reducing the hepatic synthesis of CETP (133). Niacin also targets this pathway by reducing the lipolysis in adipose tissue. That reduces the release of free fatty acids into plasma, with a consequent decrease in free fatty acid uptake by the liver that leads to a secondary decrease in hepatic triglyceride synthesis. The resulting decrease in concentration of plasma VLDL results in a reduction in the transfer of cholesteryl esters from HDL to VLDL, and hence an increase in concentration of HDL-C (134). At a more local level, through the cyclic adenosine monophosphate/protein kinase A secondary messengers, niacin promotes the formation of HDL particles with targets for reverse cholesterol transport (135). Moreover, niacin tends to promote the formation of HDL2 through its inhibition of hepatic lipase (136).

The CDP (Coronary Drug Project) evaluated the effect of niacin on 8,341 men with a history of myocardial infarction during 1966 to 1975 (137). Over a 5-year follow-up period, the incidence of nonfatal reinfarction was reduced by 27%. Even more compelling is that 15 years later, niacin contributed to a significant decrease in all-cause mortality by 9% (138).

Additional clinical studies of niacin have typically been in the setting of combination therapy. When combined with colestipol, a bile-acid sequestrant, in the FATS (Familial

### Table 3 Pharmacotherapy and Effects on HDL-C

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Mechanism</th>
<th>Phase II/III Trials</th>
<th>HDL-C Increase</th>
<th>Ongoing Large Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td>Reduced cholesterol transfer from HDL through decreased ApoB-containing particles and reduced CETP expression (117–122)</td>
<td>CDP (137), FATS (139), CLAS (141), Stockholm Ischaemic Heart Disease Secondary Prevention Study (143), ARBITER 2 (154), ARBITER 6-HALTS (155)</td>
<td>15%–35%</td>
<td>AIM-HIGH (156); HPS2-THRIVE (157)</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td>Inhibition of hepatic clearance of ApoA-I, CETP inhibition, reduced CETP synthesis, reduced adipose tissue lipolysis, ABC2A1 transcription promotion, hepatic lipase inhibition (130–136)</td>
<td>PROACTIVE (193), CHICAGO (194), PERISCOPE (195), RECORD (197)</td>
<td>5%–10%</td>
<td>—</td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td>PPARα agonism resulting in ABC2A1 up-regulation and synthesis, and ApoA-I transcription (122.126–167)</td>
<td>Helsinki Heart Study (168), VA-HIT (169), BIP (171), FIELD (173)</td>
<td>10%–15%</td>
<td>ACCORD (188)</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td>PPARγ agonism resulting in cellular differentiation in vascular tissue and adipocytes (190)</td>
<td>ILLUMINATE (228), ILLUSTRATE (232), RADIANCE1 (234), RADIANCE2 (235)</td>
<td>40%–130%</td>
<td>dal-OUTCOMES (241), dal-VESSEL (242), dal-PLAQUE (243), DEFINE (246)</td>
</tr>
<tr>
<td><strong>Glitazars</strong></td>
<td>PPARα and PPARγ agonism (199–201)</td>
<td>Kendall et al. (205)</td>
<td>15%–30%</td>
<td>Aleglitazar (211)</td>
</tr>
<tr>
<td><strong>CETP inhibitors</strong></td>
<td>CETP inhibition (122.212–219)</td>
<td>dal-OUTCOMES (241), dal-VESSEL (242), dal-PLAQUE (243), DEFINE (246)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACAT inhibitors</strong></td>
<td>ACAT-1 and ACAT-2 inhibition reducing intracellular cholesterol esterification (247,248)</td>
<td>ACTIVATE (253), CAPTIVATE (254)</td>
<td>0%–5%</td>
<td>—</td>
</tr>
<tr>
<td><strong>Recombinant HDL infusion</strong></td>
<td>Reverse cholesterol transport (259), increased nitric oxide bioavailability (257,258)</td>
<td>ERASE (260)</td>
<td>†</td>
<td>—</td>
</tr>
<tr>
<td><strong>ApoA-I Milano infusion</strong></td>
<td>Antioxidation from free cysteine residues (264–266)</td>
<td>Nissen et al. (270)</td>
<td>†</td>
<td>—</td>
</tr>
<tr>
<td><strong>ApoA-I mimetics</strong></td>
<td>Saponification by amphiphatic alpha-helices (273,274), ABCA1-dependent reverse cholesterol transport (273), antioxidation (281)</td>
<td>—</td>
<td>‡</td>
<td>—</td>
</tr>
<tr>
<td><strong>ApoA-I up-regulators</strong></td>
<td>Promotion of ApoA-I transcription (287)</td>
<td>—</td>
<td>‡</td>
<td>—</td>
</tr>
</tbody>
</table>

*There are several phase III trials with statins targeted specifically to low-density lipoprotein cholesterol (LDL-C) lowering, which is outside the scope of this review. †High-density lipoprotein cholesterol (HDL-C) levels after infusions were not routinely measured in the ERASE study or in apolipoprotein (Apo) A-I trials (258,268). ‡Only phase I safety data in humans are currently available for the Apo A-I mimetic, 4F, and the Apo A-I up-regulator, RVX-208 (281,288,289)."
Atherosclerosis Treatment Study), HDL-C increased by 43%, with angiographic atherosclerotic regression in 39% and a 73% reduction in CHD rates over a 2.5-year follow-up period (139). After 10 years of niacin combined with both colestepl and lovastatin, there was an 18.5% absolute risk reduction in all-cause mortality (140). The CLAS (Cholesterol-Lowering Atherosclerosis Study) also evaluated the effect of combining colestepl with niacin in 162 men who had prior coronary artery bypass graft surgery, and demonstrated an HDL-C increase by 37%, with angiographic regression of atherosclerosis of 16% at 2 years and 18% at 4 years (141,142).

Combining niacin with a fibrate has also been shown to be effective. In the Stockholm Ischaemic Heart Disease Secondary Prevention Study, 554 post-myocardial infarction patients were randomly assigned to placebo or to a combination of niacin and clofibrate, and those in the active treatment arm experienced a 26% reduction in all-cause mortality and a 36% reduction in CHD mortality (143). However, this beneficial effect was more correlated with the extent of reduction in serum triglyceride levels. When examined among patients with CHD and low HDL-C levels, triple therapy with clofibrate and nicotinic acid, a bile-acid sequestrant, gemfibrozil, and niacin resulted in a 36% increase in HDL-C and a 13.7% reduction in CHD events (144).

A common limiting side effect of niacin is facial pruritis and flushing caused by prostaglandin-mediated vasodilation through the G-coupled protein receptor, GPR109A (132,145). This pathway additionally, at least partially, mediates the niacin-mediated antilipolytic effects in murine models (145). Interestingly, flushing may be a marker of an increased lipid response to niacin (146). Paradoxically, the presence of flushing as a surrogate for niacin’s efficacy may promote adherence through appropriate patient education. Meanwhile, these flushing symptoms can be ameliorated with the once-daily extended-release formulation, which is equally as efficacious as the immediate-release formulation (147). This flushing can also be addressed by taking aspirin 30 minutes before dosing and by avoiding spicy foods. Niacin in its immediate-release or extended-release form is safe and tolerable for diabetic patients as well (148). However, higher doses of niacin resulted in a slight worsening of glycemic control (p = 0.048) in the ADVENT (Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial) of type 2 diabetic patients randomly assigned to niacin or placebo (148). When niacin is given at doses <2.5 g, it is associated with a 4% to 5% increase in fingerstick glucose levels and may or may not have effects on hemoglobin A1c, and these effects on hemoglobin A1c may be transient only during up titration of doses (149). Guidelines from the National Cholesterol Education Program, American Heart Association, American Diabetes Association, and National Lipid Association all consider niacin at doses <2 g daily safe for diabetic patients to manage dyslipidemia, and the cardiovascular benefits may outweigh the risks (14,150–152). Additionally, the National Lipid Association further asserts that patients with impaired glucose tolerance without overt diabetes mellitus (e.g., fasting glucose 110 to 125) can safely take niacin with careful monitoring of glycemic control, similar to that for diabetic patients when niacin therapy is initiated (152).

Both formulations have been evaluated in combination with statins. In the HATS (HDL-Atherosclerosis Treatment Study), patients with CHD, HDL-C <35 mg/dl, and LDL-C <145 mg/dl treated with both simvastatin and extended-release niacin had an increase in HDL-C levels by 26%, slight regression in proximal coronary artery stenosis by angiography, and a 90% reduction in CHD events versus dual placebo, although this represented 9 versus 1 events (153). In the ARBITER 2 (Arterial Biology for the Investigation of Treatment Effects of Reducing Cholesterol 2) trial, extended-release niacin was given to patients with CHD, HDL-C <45 mg/dl, and LDL-C <120 mg/dl who were already receiving statin therapy (154). This treatment resulted in a 21% increase in HDL-C and a trend toward a decrease in the progression of carotid intima media thickness as assessed by ultrasonography over a 1-year follow-up period (154). The follow-up study, ARBITER 6 (HDL and LDL Treatment Strategies in Atherosclerosis), was designed to compare the effects of HDL-C-lowering therapy with extended-release niacin versus additional LDL-C-lowering therapy with ezetimibe on atherosclerosis progression in patients already receiving statin therapy (155). This trial was stopped early in 2009 with just 208 evaluable patients when it was seen that patients receiving niacin had a significant reduction in carotid-intima media thickness at both 8 months and 14 months (155).

Currently, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) study has enrolled 3,300 patients with CHD and evidence of the metabolic syndrome with HDL-C <40 mg/dl and triglycerides >150 mg/dl not already given statin therapy (156). In this U.S.-Canadian, multicenter, randomized, double-blind, parallel-group, controlled clinical trial, patients have been randomly allocated to therapy with simvastatin alone or simvastatin and extended-release niacin and are being evaluated over a 5-year period to better define the additive effect of HDL-raising therapies. Another trial, the HPS2-THRIVE (Heart Protection Study 2 Treatment on HDL to Reduce the Incidence of Vascular Events) is recruiting 25,000 patients with a history of CHD, stroke, or peripheral arterial disease and randomizing them to placebo or a new tablet containing extended-release niacin plus a specific blocker of prostaglandin D2, called laropiprant, to prevent the flushing associated with niacin (157).

Fibrates. Fibrates are peroxisome proliferator-activated receptor (PPAR)-α agonists that lower LDL-C by 10% to 20%, lower triglycerides by 25% to 45%, and increase HDL-C modestly by 10% to 15% (158–161). Through the activation of PPARα, ABCA1 is up-regulated as well as hepatic HDL synthesis (162,163). The HDL production is
largely mediated through PPARα’s stimulation of the apo-
lipoprotein A-I gene’s promoter (164–166). PPARα ago-
nism may also decrease CETP gene expression, resulting in
lower levels of plasma CETP (122). Additionally, by reduc-
ing triglyceride-rich lipoproteins available to accept choles-
terol esters, HDL-C levels are boosted (122,167).

In the Helsinki Heart study, 4,081 healthy men without
CHD with non–HDL-C >200 mg/dl were randomly
assigned to gemfibrozil versus placebo (168). LDL-C de-
creased by 11%, triglycerides decreased by 35%, and
HDL-C increased by 11%. Although the more pronounced
effect was on triglycerides, the 34% reduction in CHD
events was significantly associated with both LDL-C low-
ering and HDL-C elevation. The VA-HIT (Veterans
Affairs High-Density Lipoprotein Cholesterol Interven-
tion Trial) evaluated patients with CHD, LDL-C <140 mg/dl,
triglycerides <300 mg/dl, and HDL-C <40 mg/dl on
gemfibrozil (160). LDL-C levels did not differ significantly
between the study groups over the 5-year study period, so
the 22% reduction in CHD events was attributed to the 6% in-
crease in HDL-C in a subsequent multivariable analysis
(160,169). It was the first trial that demonstrated a relation-
ship between HDL-C increase and CHD event reduction
in patients with moderate LDL-C levels. Another analysis
of the VA-HIT study demonstrated that gemfibrozil ther-
apy for patients with CHD and low HDL-C was cost
effective in terms of the cost of quality-adjusted life-years
saved (170).

The effects of the fibrates on coronary events have been
variable. Although bezafibrate therapy in patients with
CHD and low HDL-C levels increases HDL-C by 18%,
there was only a trend toward the reduction of CHD events
in the BIP (Bezafibrate Infarction Protection) study (171).
A 16-year follow-up of this trial demonstrated that subjects
with the highest HDL-C response to therapy had a signifi-
cant reduction in the risk of death (172). In the FIELD
(Fenofibrate Intervention and Event Lowering in Diabetes)
study, the authors studied the effect of fenofibrate therapy
on 9,795 randomized patients with type 2 diabetes mellitus
not receiving statin therapy and with a total cholesterol level
of <251 mg/dl (173). However, fenofibrate did not signifi-
cantly alter HDL-C levels but it did lower LDL-C and
triglyceride levels. There was no significant effect on total
coronary events, but a significant 24% reduction in nonfatal
myocardial infarction was observed. Overall, the FIELD
trial failed to demonstrate a significant benefit of an agent
that predominantly reduces triglycerides in a high-risk
population. That may have resulted from a greater use of
open-label statin therapy for subjects allocated to placebo.
Studies of clofibrate have been plagued with concerns
regarding potential safety (174–176).

The fibrates are primarily excreted renally, and there are
retrospective observational data suggesting that they may
result in reversible worsening renal function in patients with
baseline renal impairment (177,178). In severe renal impair-
ment, the drug’s half-life is prolonged and is not dialyzable,
and there is concern regarding permanent renal dysfunction
in kidney transplant patients (177,179). Although the
mechanism of inducing renal dysfunction is unclear, inter-
esting data propose that fibrates result in increased creat-
ine levels from increased creatinine production without an
actual change in creatinine clearance (180). Renal function
in patients with severe nondialysis–dependent renal disease
should be monitored during the initiation of fibrate therapy
for dyslipidemia, but fibrates are not contraindicated in
patients with baseline renal impairment.

Given the benefits of statin therapy for diabetic patients,
there is little evidence to recommend fibrates as an alternative
first-line treatment to statins for the management of dysli-
pidemia among diabetic patients (181,182). The combination
of statins and fibrates bears the risk of myotoxicity with an
incidence of 0.12%, but there are some data suggesting the
benefits of combined statin and fibrate therapy, particularly
for diabetic patients (14,183–185). All fibrates have been associ-
ated with reports of creatinine kinase elevations and myopathy
when given with statins, but that appears to occur more
frequently with gemfibrozil than with fenofibrate (186). Gem-
fibrozil, more than fenofibrate, inhibits hepatic glucoroni-
adation of various statins, thereby preventing statin clearance
and increasing serum levels of statins in their active form (187).
The ACCORD (Action to Control Cardiovascular Risk in
Diabetes) study is a large-scale trial that is currently prospec-
tively evaluating the safety and efficacy of the combination of
simvastatin and fenofibrate in managing dyslipidemia in type 2
diabetes (188).

Thiazolidinediones. The insulin-sensitizing thiazolidinediones,
which include pioglitazone and rosiglitazone, were approved
in the U.S. in the late 1990s for the treatment of type 2
diabetes mellitus. Troglitazone was also a member of this
class but was withdrawn because of idiosyncratic liver injury
(189). These agents are agonists of peroxisome proliferator-
activated receptor (PPAR)-γ, a nuclear receptor involved in
cellular differentiation, largely in vascular tissue and adipocytes
(190). Insulin resistance contributes to the metabolic
syndrome, which includes hyperglycemia, elevation in tri-
glycerides, and reductions in HDL-C levels. As a result,
insulin-sensitizers such as thiazolidinediones were proposed
to not only correct dysglycemia but also to potentially
correct lipid abnormalities (189).

A meta-analysis of 23 randomized trials demonstrated
that pioglitazone increased HDL-C levels by 4.6 mg/dl and
that rosiglitazone increased HDL-C levels by 2.7 mg/dl
(191). However, unlike pioglitazone, rosiglitazone increased
LDL-C and total cholesterol and did not decrease triglyc-
erides (191). Even in patients without overt diabetes mel-
litus but with evidence of insulin resistance, pioglitazone
increases HDL-C levels (192). The PROACTIVE (Pro-
spective Pioglitazone Clinical Trial in Macrovascular
Events) assessed the benefit of pioglitazone in a higher risk
population, type 2 diabetes with a hemoglobin A1c level
>6.5%, and stable macrovascular disease (193). Piogli-
tazone increased HDL-C by 8.9% and decreased triglycerides
by 9.6% without a significant reduction in the primary end point but with a 16% reduction in the combined secondary end point of mortality and nonfatal myocardial infarction and stroke (193). Given the modest 0.6% decrease in hemoglobin A1c, many have speculated that part of the clinical benefits of these agents could be related to the HDL-C–raising benefits of these agents.

Ragaglitazar increased HDL-C by 31%, decreased triglycerides by 62%, and decreased hemoglobin A1c by 1.3%, but the adverse events of edema, anemia, and leukopenia have drawn concern (202,203). Muraglitazar increases HDL-C by as much as 16% in type 2 diabetic patients, but, as with ragaglitazar and the thiazolidinediones, weight gain and edema were more common with muraglitazar therapy (204,205). An analysis of muraglitazar’s phase 2 and 3 data revealed an increase in risk of death, cardiovascular events, and congestive heart failure associated with muraglitazar (206). Tesaglitazar, a third agent in this drug class, can increase HDL-C by 13% (207–209). Recently, a phase 2 trial of aleglitazar was shown to increase HDL-C by 20% and also decrease hemoglobin A1c in a dose-dependent manner, with an increase in edema but not congestive heart failure or myocardial infarction (210). As a result, a phase 3 study of aleglitazar in type 2 diabetic patients with a recent acute coronary syndrome has been announced (211).

CETP inhibitors. Humans with CETP deficiency due to molecular defects in the CETP gene have markedly elevated plasma levels of HDL-C and apolipoprotein A-1 (212,213). Studies regarding the association of lower CETP levels and atherothrombosis are mixed, but patients with CETP deficiency and higher HDL-C levels tend to have lower rates of atherothrombotic disease (214–217). There was initial concern that the larger, cholesterol-rich HDL particles formed through CETP inhibition would not as efficiently allow for reverse cholesterol transport (218). In response, a study showed that these larger particles promote cholesterol efflux through the ABCG transporter (219). Such observations led to the concept that pharmacological CETP inhibition might favorably increase HDL-C levels (122).

Animal models of CETP inhibitors using a variety of different pharmacological strategies have resulted in an increase in HDL-C and an attenuation of atherothrombosis (220–226). Early small studies of torcetrapib, a direct CETP inhibitor, in healthy subjects and patients with HDL-C <40 mg/dl demonstrated significant increases in HDL-C levels of 50% to 60% (218,227). Torcetrapib was evaluated on a much larger scale through the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) trial (228). In that trial, 15,067 patients with a history of cardiovascular disease or type 2 diabetes mellitus receiving atorvastatin were randomly assigned to torcetrapib or placebo. Patients receiving torcetrapib experienced a 72.1% increase in HDL-C, a 24.9% decrease in LDL-C, and a 9% decrease in triglycerides over 1 year. However, the ILLUMINATE trial was prematurely terminated because of an increase in cardiovascular events (hazard ratio: 1.25; 95% confidence interval: 1.09 to 1.44) and all-cause mortality (hazard ratio: 1.58; 95% confidence interval: 1.14 to 2.19). Off-target toxic effects including hyperaldosteronism as reflected by the observed hypokalemia, hypernatremia, and increase in systolic blood pressure by a median of 5.4 mm Hg specific to the molecule itself may have been the culprits (228,229). Additionally, there is speculation that the HDL particles formed by torcetrapib may not participate in reverse cholesterol transport and other cardioprotective qualities, but recent data suggest that these particles do participate in reverse cholesterol transport (229–231).

The ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) study concurrently did not show an effect of torcetrapib on coronary atherothrombosis (232). A post-hoc analysis suggested that patients who experienced the highest level of HDL-C increase did have some regression of coronary atherothrombosis (233). Patients with familial hypercholesterolemia treated with torcetrapib in the RADIANCE1 (Rating Atherosclerotic Disease Change by Imaging With a
New CETP Inhibitor 1) study did not demonstrate a change in carotid intima media thickness despite a 55.5% increase in HDL-C (234). There was also progression of disease in the common carotid segment, raising the concern of a directly toxic effect of torcetrapib on the endothelium (229,234). In the RADIANCE2 trial, patients with mixed dyslipidemia also had a similar increase in HDL-C, without an effect on carotid intima media thickness (235). Similar to in the ILLUMINATE trial, torcetrapib was associated with an effect on carotid intima media thickness (235). In the RADIANCE2 trial, patients with mixed dyslipidemia on pravastatin therapy showed an associated 28% increase in HDL-C with dalcetrapib (238). Neither study had an increase in blood pressure or cardiovascular adverse events, as seen in the torcetrapib trials (237–239). In vitro, dalcetrapib does not activate the renin-angiotensin-aldosterone pathway (240). Currently, the phase 3 dal-OUTCOMES trial is recruiting ~15,600 patients with recent acute coronary syndromes to further study dalcetrapib’s effect on cardiovascular morbidity and mortality as well as its safety profile (241). Also, the phase 2b dal-VESSEL study will further evaluate dalcetrapib’s favorable effect on endothelial function in hypercholesterolemic patients with a low baseline HDL-C level (242). And the phase 2b dal-PLAQUE study plans to characterize its effects on atherosclerotic plaque with magnetic resonance imaging and positron emission tomography/computed tomography (243).

Anacetrapib (also known as MK-0859) is a novel, potent CETP inhibitor also being studied. A phase 1 trial involving healthy subjects documented an increase in HDL-C up to 129% without an effect on blood pressure (244). Recently, a phase 2 trial showed that 589 patients with dyslipidemia receiving atorvastatin randomly assigned to anacetrapib had a >130% increase in their HDL-C levels and a decrease of >40% in their LDL-C levels without an effect on blood pressure (245). The DEFINE (Efficacy and Tolerability of CETP Inhibition With Anacetrapib) trial has recruited 1,623 patients with CHD already receiving statin therapy for an anacetrapib phase 3 safety trial, and a larger outcomes study is planned (246).

**ACAT inhibitors.** A target for treating atherosclerosis has been the inhibition of acyl-coenzyme A cholesterol acyltransferase (ACAT), which esterifies cholesterol in a range of tissues (247,248). Theoretically, ACAT, specifically ACAT-1, inhibition would slow the progression of foam macrophage cells in theory (249). Subsequently, free cholesterol would be available for reverse cholesterol transport (250). ACAT-2, the other identified ACAT isoform, is present in the liver and intestine, so inhibition of this enzyme would reduce LDL formation (251).

Avasimibe, a nonselective ACAT inhibitor, was assessed in 639 randomized patients with CHD in the phase 2 A-PLUS (Avasimibe and Progression of Lesions on Ultra-Sound) study (252). Unfortunately, avasimibe did not alter HDL-C levels, and it did not have an impact on coronary atherosclerosis as assessed by intravascular ultrasonography (252). Pactimibe, another nonselective ACAT inhibitor, was evaluated by intravascular ultrasonography in the ACTIVATE (ACAT Intravascular Atherosclerosis Treatment Evaluation) trial of 408 patients with CHD (253). Pactimibe resulted in a 5.4% (p = 0.04) increase in HDL-C, but although there was no difference compared with placebo with respect to atherosclerosis progression, secondary variables suggested that pactimibe limited atherosclerosis regression compared with placebo (253). Furthermore, the more recent CAPTIVATE (Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects) evaluated the effects of pactimibe on carotid atherosclerosis using ultrasonography of carotid intima media thickness in 892 patients with familial atherosclerosis (254). There was no change in HDL-C levels, and although there was no change in maximum carotid intima media thickness, but there was an increase in mean carotid intima media thickness by 2.9% (p = 0.05) after 1 year, and, notably, there was a significant absolute risk increase of 2.1% of cardiovascular death, myocardial infarction, and stroke with pactimibe (254). Potential explanations for this proatherogenic effect of ACAT inhibition is that the accumulation of free cholesterol in macrophages results in ABCA1 degradation, limiting reverse cholesterol transport, and such free cholesterol abundance causes cellular death, stimulating and intensifying the development of atherosclerosis (255,256).

**Reconstituted HDL infusion.** Short-term infusions of reconstituted HDL have been a target of reverse cholesterol transport therapy. The HDL infusions also increase nitric oxide bioavailability for endothelial protection (257,258). In a small study of healthy subjects, these intravenous infusions promoted reverse cholesterol transport (259).

On the basis of these data, the ERASE (Effect of rHDL on Atherosclerosis–Safety and Efficacy) study randomly assigned 183 patients within 2 weeks of an acute coronary syndrome to 4 weekly infusions of CSL-111, reconstituted HDL made of purified human apolipoprotein A-I and soybean phosphatidylcholine (260). There was a nonsignificant trend toward an improvement in coronary atheroma volume when measured by intravascular ultrasonography, but the study was prematurely terminated because of a high incidence of liver function test abnormalities (260). Nonetheless, there is some evidence that reconstituted HDL infusion promotes a favorable change in the quality of coronary atheroma (260,261). In type 2 diabetic patients, recent data suggest that reconstituted HDL infusion not only suppresses the expression of inflammatory markers and enhances reverse cholesterol efflux, but also augments glycemic control by increasing plasma insulin and activating...
Apolipoprotein A-I Milano infusion. In 1980, a group in Milano described 40 persons in a small village in northern Italy called Limone sul Garda who, despite very low HDL-C levels (10 to 30 mg/dl), had a reduced atherosclerotic disease burden and longer lives (264–266). This was attributed to an arginine to cysteine mutation at position 173 of apolipoprotein A-I, termed apolipoprotein A-I Milano, allowing for disulfide bond dimer formation (264–266). Not all of the cysteine residues dimerize, and the free thiol groups have antioxidant properties (267). Recombinant apolipoprotein A-I Milano infusions in animals demonstrated evidence of atherosclerosis regression, which can occur in as little as 48 h (268,269).

This therapy was piloted in humans when ETC-216, recombinant apolipoprotein A-I Milano complexed with phospholipid, was randomly infused in 57 patients within 2 weeks of an acute coronary syndrome over 5 weekly treatments (270). There was significant reduction in intravascular ultrasound–measured coronary atheroma burden with ETC-216, with 1 patient reported to have a significant rise in transaminases (270). In a trial of 47 patients after an acute coronary syndrome, recombinant apolipoprotein A-I Milano infusion was associated with reverse coronary remodeling whereby atheroma burden was reduced but luminal size was unchanged (271).

Apolipoprotein A-I mimetics. Apolipoprotein A-I is a protein with 243 amino acids and consists of a tandem assortment of amphipathic helices (272). Reverse cholesterol transport by the ABCA1 pathway is mediated by the detergent-like properties of these amphipathic helical segments (273,274).

The development of smaller peptides that retain such activity began with the development of peptide mimetic 18A, consisting of 18 amino acids, which does not share sequence homology of apolipoprotein A-I but can form a similar amphipathic helix (275). Multiple modifications have been studied, but the most studied is 4F, which is a dimerized version of 18A with 2 phenylalanine substitutions (273,275–278).

An orally active 4F peptide made with D-amino acids, D-4F, given to mice decreases atherosclerotic lesions and promotes reverse cholesterol transport (279,280). Phase I data suggest that D-4F may be safe for humans with CHD, and although it does not alter lipoprotein levels, it may improve the HDL anti-inflammatory index, but further clinical studies are needed to elucidate this significance (281).

Given concerns regarding possible cytotoxicity through ABCA1-independent lipid efflux, additional peptide mimetics have been engineered (282). Twenty-two amino acid peptides based on domains of apolipoprotein A-I that have a higher affinity for ABCA1 have been shown to promote cholesterol efflux without cytotoxic effects (282–284). Furthermore, such domains are conserved across other apolipoproteins, and similarly designed peptides from apolipoprotein E promote ABCA1-mediated reverse cholesterol transport (285). Recently, 5A, an asymmetric bihelical peptide based on 2F, with 1 of the domains containing more alanine residues and thereby reducing its helical content, has been constructed to more closely reflect the combination of low- and high-affinity helices on apolipoprotein A-I (286). The 5A peptide had increased ABCA1-dependent cholesterol efflux and decreased hemolysis compared with its parent compound (286).

The strategy of using peptide mimetics to treat atherosclerotic disease is in its infancy but carries the potential to treat disease through specific, endogenous pathways.

Apolipoprotein A-I up-regulators. Recently, a novel particle called RVX-208 that increases the transcription of apolipoprotein A-I to promote reverse cholesterol transport has been announced (287). This transport was facilitated through the ABCA1, ABCG1, and SR-B1 pathways through apolipoprotein A-I up-regulation (288). Phase I data from 24 healthy subjects have shown a dose-dependent increase in apolipoprotein A-I, and thereby HDL functionality (288,289). Further data and investigation are needed to fully examine the ability of small molecules up-regulating apolipoprotein A-I to impact the burden of atherosclerosis.

Conclusions

There is overwhelming evidence that high levels of HDL-C in nature are associated with a lower risk of CHD. Unlike LDL-C, the mechanisms controlling HDL-C are more complex. Lifestyle interventions are safe but only modestly increase HDL-C. The best treatments available currently are the niacin derivatives, although the newer CETP inhibitors, apolipoprotein mimetics, and apolipoprotein up-regulators hold much promise. The next 5 years should provide information on whether the flux or cycling of HDL is more important than HDL-C levels and also whether we should target raising specific HDL subclasses rather than HDL-C itself.

Acknowledgment

The authors would like to thank Philip Barter, MD, PhD, for his thoughtful and helpful review of this manuscript.

Reprint requests and correspondence: Dr. Christopher P. Cannon, Brigham and Women’s Hospital, Cardiovascular Division, TIMI Study, 350 Longwood Avenue, First Floor Office, Boston, Massachusetts 02115. E-mail: cpcannon@partners.org.

REFERENCES


70. Nash DT, Nash SD. Grapeseed oil, a natural agent which raises dietary insulin and glycemic index and glycemic load are associated with high-density-lipoprotein cholesterol at baseline but not with increased risk of diabetes in the Whitehall II study. Am J Clin Nutr 2007;86:988–94.
89. Moffatt RJ. Effects of weight reduction on plasma lipids and lipoproteins of cigarette smokers from randomly selected families: enhancement of hyperlipidemia and depression of high-density lipoprotein. Atherosclerosis 1980;62:IV70–6.


Natarajan et al. 1295

HDL Therapies

JACC Vol. 55, No. 13, 2010
March 30, 2010:1283-99


Auwerx J. PPARs, the ultimate thrifty gene. Diabetologia 1999;42: 1033–49.


Whitlock ME, Swenson TL, Ramakrishnan R, et al. Monoclonal antibody inhibition of cholesteryl ester transfer protein activity in the


229. Tall AR, Yvan-Charvet L, Wang N. The failure of torcetrapib: was it the molecule or the mechanism? Arterioscler Thromb Vasc Biol 2007;27:257–60.


Key Words: high-density lipoprotein • coronary artery disease • prognosis • prevention.