HDL Cholesterol and Protective Factors in Atherosclerosis

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Abstract—A low level of high-density lipoprotein cholesterol (HDL-C) is an important risk factor for cardiovascular disease. Epidemiological and clinical studies provide evidence that HDL-C levels are linked to rates of coronary events. The cardioprotective effects of HDL-C have been attributed to its role in reverse cholesterol transport, its effects on endothelial cells, and its antioxidant activity. Although some clinical trials suggest a benefit of raising HDL-C to reduce risk, further studies are needed, and HDL-C is still not considered a primary target of therapy in the National Cholesterol Education Program guidelines. However, HDL-C should be considered as part of the patient’s overall profile of established risk factors in determining treatment strategies. (Circulation. 2004;109[suppl III]:III-8–III-14.)

Key Words: atherosclerosis ■ cardiovascular diseases ■ cholesterol ■ high-density lipoprotein (HDL) ■ lipoproteins ■ risk factors

The association between low levels of high-density lipoprotein cholesterol (HDL-C) and an increased risk for cardiovascular disease has been well established through epidemiological and clinical studies. This relationship is supported by the potential antiatherogenic properties of HDL, including its mediation of reverse cholesterol transport, in which cholesterol from peripheral tissues is returned to the liver for excretion in the bile. This review considers the potential mechanisms by which HDL-C may exert its anti-atherogenic effects, discusses disorders of HDL and how to interpret them in the clinical setting, and presents current and potential treatment strategies for patients with low HDL-C.

Structure and Metabolism of HDL and Relation to Potential Mechanisms of Benefit

Overview of HDL Structure and Heterogeneity

HDL is a class of heterogeneous lipoproteins containing approximately equal amounts of lipid and protein. HDL particles are characterized by high density (>1.063 g/mL) and small size (Stoke’s diameter = 5 to 17 nm). 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. Most of apolipoprotein A-I (apo A-I), the predominant HDL protein, migrates in agarose gels with α-electrophoretic mobility and is designated α-LpA-I. This fraction accounts for almost all of the cholesterol quantified in the clinical laboratory as HDL-C. α-HDL can be further fractionated by density into HDL₂ and HDL₃, by size, or by apolipoprotein composition. Approximately 5% to 15% of apo A-I in human plasma is associated with particles with pre-β-electrophoretic mobility. These can be further differentiated into pre-β₁-LpA-I, pre-β₂-LpA-I, and pre-β₃-LpA-I particles. These lipid-poor particles are increased in extravascular compartments where reverse cholesterol transport takes place. The origin of HDL particles with pre-β -electrophoretic mobility is not entirely clear. Several mechanisms have been proposed, including direct secretion into plasma from hepatocytes or enterocytes; release during the interconversion of various HDL subpopulations by phospholipid transfer protein (PLTP), cholesteryl ester transfer protein (CETP), or hepatic lipase (HL); or direct interaction of free apolipoproteins with cell membrane.

HDL and Reverse Cholesterol Transport

Mechanisms. Reverse cholesterol transport describes the transfer of cholesterol from nonhepatic cells to the liver. Lipid-free apo A-I or lipid-poor pre-β-HDL particles produced in the intestine or liver or shed during lipolysis of triglyceride-rich lipoproteins (TGRL) initiate efflux of phospholipids and cholesterol from cell membranes in a process facilitated by PLTP. Cholesterol in these nascent discoidal HDL particles is then esterified by lecithin-cholesterol acyltransferase (LCAT). Cholesteryl esters readily move to the core of HDL particles, producing a steady gradient of free cholesterol and enabling HDL to accept cholesterol from various donors. The reciprocal exchange of cholesteryl ester for triglycerides mediated by CETP moves the bulk of the cholesteryl esters to lipoprotein remnant particles, which are subsequently cleared by the liver. At the same time, HDL becomes enriched with triglycerides, which are substrates for HL. The concerted action of CETP-mediated cholesteryl ester transfer and HL-mediated hydrolysis of triglycerides and phospholipids helps to form the smaller HDL particles that are the preferred binding partners for scavenger receptor type B1 (SR-B1), the major HDL receptor on hepatocytes. The

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III-8
binding of HDL with SR-B1 mediates the selective uptake of cholesteryl esters that have not undergone CETP-mediated transfer to apo B–containing particles (intermediate-density lipoprotein and low-density lipoprotein [LDL]). Lipid-free apolipoproteins or lipid-poor pre-β-HDL are formed in reactions catalyzed by PLTP, CETP, and HL. Thus, as shown in the Figure, reverse cholesterol transport can be envisioned as a cycle in which acceptors of cellular cholesterol (ie, apo A-I, pre-β-HDL) are perpetually regenerated to undertake their function of inducing cholesterol efflux.

Experiments with transgenic animals suggest that disruption of one or more steps in reverse cholesterol transport results in accelerated atherosclerosis, whereas overexpression of pivotal proteins in reverse cholesterol transport, such as apo A-I, PLTP, LCAT, and SR-B1, exerts atheroprotective effects.4 The important lesson from these experimental approaches is that disruption of reverse cholesterol transport and resulting atherosclerosis may occur in the presence of either decreased or increased HDL-C levels, depending on which step of reverse cholesterol transport is dysfunctional. For instance, decreased HDL levels associated with increased accumulation of cholesterol in peripheral tissues and/or atherosclerosis were observed in humans and animals with apo A-I or adenosine triphosphate–binding cassette transporter A1 (ABCA1) deficiency, in which the initial steps of reverse cholesterol transport are impaire. By contrast, animals with dysfunctional SR-B1 presented with enhanced arteriosclerosis combined with increased HDL concentrations.4

Cholesterol Efflux and ABCA1. As a result of efflux of cholesterol and phospholipid from cells induced by apo A-I, apo A-II, apo A-IV, and apo E, HDL-like lipoproteins with pre-β-mobility are produced. Apolipoprotein-mediated cholesterol efflux involves specific interactions with plasma membrane proteins, with subsequent generation of intracellular signals and translocation of cholesterol from endoplasmic reticulum, the trans-Golgi network, or endosomes to the plasma membrane. Several lines of evidence suggest that apo A-I–binding protein may be directly linked to ABCA1, defects of which have been identified in patients with familial analphalipoproteinemia (Tangier disease, familial HDL deficiency).5–7 Membrane topological models of ABCA1 predict the presence of 2 exocytotic domains that could act as apo A-I docking sites.8 Furthermore, the number of apo A-I membrane binding sites correlates closely with ABCA1 expression levels.9,10 However, other mechanisms underlying ABCA1-mediated cholesterol efflux have also been proposed. As a member of a large family of membrane transporters, ABCA1 may move cellular lipids across the bilayer in a process requiring hydrolysis of adenosine triphosphate (ATP). As ABCA1 does not seem to bind cholesterol, it is more likely that ABCA1 induces translocation of phospholipids and thereby facilitates the lipidation of apo A-I and the generation of effective cholesterol acceptors such as pre-β-HDL.11 The identity of the preferred phospholipid substrate for ABCA1 remains a matter of debate, but phosphatidylserine (PS) and phosphatidylcholine (PC) are major candidates. Phosphatidylserine could influence the arrangement of lipids in a way that favors apo A-I binding.12 On the other hand, PC-enriched domains have been identified that serve as a primary source of phospholipids and cholesterol for ABCA1–mediated efflux.13

Although abundant evidence suggests that ABCA1 acts as a phospholipid translocase, no rigorous proof has been presented as yet. Immunocytochemical studies suggest that ABCA1 shuttles between the plasma membrane and late endosomes.14 Furthermore, ABCA1 appears to interact with several important components of vesicular traffic machinery such as cdc42, a small G protein, and the beta-subunit of coat protein I (COPI-I) coatamer complex essential for the formation of transport vesicles.15,16 It seems, therefore, that ABCA1 may regulate cholesterol and/or phospholipid sorting in the endosomal compartment. The regulation of endosomal ves-
cle formation by ABCA1 may also be important to exocytosis of apo E, which is able to initiate cholesterol efflux locally and thereby to promote reverse cholesterol transport.17

**ABCA1, HDL-C, and Atherosclerosis.** The most prominent abnormality observed in an ABCA1−/− mouse model was the lack of HDL-C and apo A-I, accompanied by accumulation of lipid-laden macrophages in the lungs.18 In ABCA1-deficient hypercholesterolemic animals (ABCA1−/−/apo E−/− or ABCA1−/−/LDL-receptor−/− double knockout mice), the accumulation of foam cells in peripheral tissue was especially pronounced.19 However, no accelerated development of atherosclerotic lesions could be observed in ABCA1 knockout mice. It is possible that the reduced cholesterol efflux resulting from ABCA1 deficiency could be balanced by decreased cholesterol influx caused by a less atherogenic profile (lower total and LDL-cholesterol [LDL-C], lower triglycerides), because ABCA1-deficient mice also seem to have decreased cholesterol synthesis.19 Experiments with ABCA1 transgenic animals produced equally contradictory results. Transgenic mice strongly expressing ABCA1 showed an antiatherogenic lipid profile with elevated levels of HDL-C and apo A-I, and significantly less aortic atherosclerosis.20,21 However, selective overexpression of ABCA1 in macrophages had minimal effect on plasma HDL-C.22 The major cholesterol contribution to HDL generation presumably comes from ABCA1-deficient leukocytes (monocytes/macrophages) into the arterial wall of LDL-receptor-deficient mice.23

**HDL and Endothelial Function**

Endothelial dysfunction characterized by decreased bioavailability of nitric oxide (NO), a potent vasodilator, and increased affinity of the endothelial surface for leukocytes is often encountered in the early stages of atherosclerosis. In advanced plaques, denudation of the endothelium as a consequence of increased apoptotic cell death can be observed. Several in vivo studies provide evidence for the beneficial effects of HDL on endothelial function. Compared with normcholesterolemic patients, those with hypercholesterolemia appear to have reduced NO-dependent vasodilation, and restoration of endothelial function has been observed after infusion of cholesterol-free reconstituted HDL in hypercholesterolemic subjects.24 Elevation of plasma HDL concentrations reduced interleukin (IL)-1–induced expression of leukocyte adhesion molecules such as E-selectin.25 The expression of vascular cell adhesion molecule (VCAM)-1, which binds leukocytes in early athemora, and the formation of neointima were also inhibited by reconstituted HDL in a mouse model of carotid artery injury.26

HDL functions as an autonomous protective factor for the endothelium. HDL-induced activation of endothelial nitric oxide synthase (eNOS), NO release, and vasorelaxatory effects were documented in 2 recent studies.27,28 Other studies confirmed that HDL attenuates expression of VCAM-1, intracellular adhesion molecule (ICAM)-1, and E-selectin, as well as cytokines such as IL-8 that promote leukocyte extravasation.29,30 Endothelial apoptosis was prevented in the presence of HDL, and this effect was associated with inhibition of typical apoptosis pathways such as the activation of caspases.30,31 In addition, HDL activates protein kinase Akt, a ubiquitous mediator of antiapoptotic signaling.30

The observation that only binding of native HDL is associated with generation of NO, whereas binding of apo A-I is without any effect, suggests that some distinct biological activity stimulating NO production is present in HDL particles. Several groups of investigators demonstrated that HDL serves as a carrier of bioactive lysosphingolipids such as sphingosine-1-phosphate (S-1-P), sphingosylphosphorylcholine (SPC), and lysosulfatide (LSF).30–32 The intracellular signaling events initiated by lysosphingolipids and HDL show striking similarities. Furthermore, these substances fully mimic HDL in their ability to induce vasorelaxation and inhibit apoptosis. Because of their lipophilicity, lysosphingolipids were thought to act primarily in a paracrine fashion. However, defining HDL as a carrier for lysosphingolipids suggests that whole endothelium may constitute an important physiological target for these substances.

**HDL and Antioxidative Mechanisms**

A growing body of evidence suggests that HDL exerts part of its antiatherogenic effect by counteracting LDL oxidation. Some hints pointing to the antioxidant effects of HDL come from epidemiological studies. For example, although smokers in the Prospective Cardiovascular Münster (PROCAM) study experienced more major coronary events than did nonsmokers, increasing HDL levels were associated with greater reduction in the number of events in the smoker versus the nonsmoker populations.33 HDL inhibits the oxidation of LDL by transition metal ions, but also prevents 12-lipoxygenase–mediated formation of lipid hydroperoxides.34 Inhibition of LDL oxidation by HDL is usually attributed to the high content of antioxidants in this lipoprotein; to antioxidative properties of apo A-I; and to the presence of several enzymes, such as paraoxonase (PON), platelet activating factor acetylhydrolase (PAF-AH), and glutathione peroxidase (GPX), which prevent LDL oxidation or degrade its bioactive products. Apo A-I was shown to reduce peroxides of both phospholipids and cholesteryl esters and to remove hydroperoxyicosatetraenoic acid (HPETE) and hydroperoxycadecadienic acid (HPODE), which are products of 12-lipoxygenase, from native LDL.35,36 Both HPETE and HPODE are examples of so-called “seeding molecules,” compounds necessary for induction of the nonenzymatic oxidation of lipoprotein phospholipids.37 Oxidized phospholipids found in LDL, including 1-palmitoyl-2(5-oxovaleroyl)-sn-glycero-3-phosphorylcholine (POVPC) and 1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphorylcholine (PGPC), have been shown to stimulate production of cytokines (monocyte chemotactic protein-1, IL-8, macrophage colony-stimulating factor) and to induce adhesion of monocytes to the endothelial surface. Paraoxonase catalyzes the breakdown of oxidized phospholipids in LDL. Studies have found that transgenic animals
deficient in this enzyme are significantly more susceptible to the development of diet-induced atherosclerosis.\(^{38,39}\) On the other hand, expression of PON transgene in mice produces HDL resistant to oxidation.\(^{40}\) Degradation of oxidized phospholipids has also been attributed to PAF-AH. Overexpression of human apo A-I in apo E knockout mice increases PAF-AH activity and simultaneously reduces oxidative stress in plasma, decreases ICAM and VCAM expression, and decreases monocyte recruitment into the arterial wall.\(^{41}\)

**HDL-C as a Risk Factor and a Therapeutic Target**

**Epidemiological Evidence**

In general, large prospective epidemiological studies such as the Framingham Heart Study in the United States and the PROCAM study in Europe have found that low HDL-C is independently associated with increased risk for coronary artery disease (CAD).\(^{1,42}\) However, exceptions to this association suggest that the atherogenicity of HDL-C may be influenced by unmeasured variables, including genetic and acquired factors, or that the concentration of HDL subclasses and the kinetics of HDL metabolism, not the absolute quantity of HDL, may contribute to the antiatherogenic effect.\(^{3,43}\)

Studies in different patient populations have shown that the higher risk for coronary heart disease (CHD) at lower HDL levels is multifactorial in causation.\(^{42}\) Other lipid abnormalities that tend to accompany low HDL include elevated triglyceride levels, especially in the presence of a high ratio of LDL-C to HDL-C;\(^{44,45}\) increased concentrations of remnant lipoproteins;\(^{46}\) and small, dense LDL particles.\(^{37}\) In many persons, these characteristics occur as part of the metabolic syndrome, a constellation of risk factors that also includes abdominal obesity, insulin resistance, elevated fasting glucose, hypertension, and prothrombotic/proinflammatory states.\(^{42,45}\) Low HDL-C is also caused by cigarette smoking, very high carbohydrate intake, and the use of certain drugs (eg, progesterational agents, anabolic steroids).\(^{42}\)

**Clinical Guidelines**

In the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines, LDL-C is the primary target of CHD risk-reduction therapy.\(^{42}\) Low HDL-C (\(\leq 40\) mg/dL) is one of 5 major CHD risk factors, and HDL level is also a component of the Framingham scoring system, the method used to estimate 10-year CHD risk and determine the intensity of lipid-lowering therapy. The guidelines do not regard low HDL-C as a therapeutic target, stating that there is insufficient clinical trial evidence to support a numeric goal and also a lack of available drugs that can robustly modify HDL levels. To raise HDL-C, the guidelines recommend increased physical activity, particularly in patients with the metabolic syndrome.\(^{42}\)

For patients with low HDL-C levels accompanied by high triglycerides (200 to 499 mg/dL; \(\geq 150\) mg/dL, in the metabolic syndrome), non–HDL-C (ie, LDL-C plus very-low-density lipoprotein cholesterol) is a secondary target of therapy after the LDL-C goal has been achieved. Drug therapy to raise HDL-C may be considered in patients without triglyceride elevations (“isolated” low HDL-C), a strategy reserved primarily for high-risk individuals.\(^{42}\) However, an increasing number of experts believe that low HDL-C may warrant treatment in a wider range of patients, even when LDL-C or non–HDL-C levels have not yet been reduced to target levels.

**Clinical Trial Evidence**

In an analysis of 4 American studies (2 observational studies and the control groups of 2 clinical trials), CHD risk was found to decrease by 2% to 3% with each increment of 1 mg/dL in HDL-C levels.\(^{48}\) However, clinical trials do not yet provide strong and consistent evidence concerning the benefit of raising HDL levels.

Fibric acid derivatives are widely used to treat low HDL-C levels. In the Helsinki Heart Study of 4081 asymptomatic middle-aged men,\(^ {49}\) gemfibrozil increased HDL-C levels by more than 10% from baseline. Overall, there was a 34% reduction in coronary risk compared with placebo (\(P<0.05\)). Despite decreases of 10% and 43% in LDL-C and triglyceride levels, respectively, the association between the change in triglyceride levels and the risk for CHD was not statistically significant in the gemfibrozil group.\(^ {50}\) This implies that the reduction in CHD risk was mediated by changes in HDL-C and LDL-C. Both the increase in HDL-C and in the HDL-C/total cholesterol ratio with gemfibrozil were inversely associated with CHD risk (\(P<0.01\)).\(^ {50}\)

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) compared the effect of gemfibrozil versus placebo on coronary risk in 2531 middle-aged men with CHD and a primary lipid abnormality of low HDL-C.\(^ {51}\) After 1 year, there was a 6% increase in HDL-C levels, accompanied by a significant 22% reduction (\(P=0.006\)) in CHD death or nonfatal myocardial infarction.\(^ {51}\) Further analysis found a strong correlation between CHD event reduction and treatment levels of HDL-C, but not of triglycerides or LDL-C.\(^ {52}\) Moreover, during treatment HDL-C was the only major lipid to predict a significant reduction in CHD events based on both univariate and multivariate analyses. Despite the independent inverse association between HDL-C levels and CHD events, regression analysis revealed that lipid concentrations achieved with gemfibrozil accounted for just 23% of the treatment benefit. This suggests that other effects of fibrates are partly responsible for their clinical benefit, and that similar increases in HDL-C with other types of drugs might not produce the same reduction in risk.\(^ {52}\)

In the Bezafibrate Infarction Prevention (BIP) study, 3039 men and women with CHD were randomized to the study drug or placebo.\(^ {53}\) Despite an increase of 18% in HDL-C and a decrease of 21% in triglycerides, the reduction of 9.4% in coronary end points was not significant (\(P=0.26\)). One explanation for this unexpected outcome may be the possibility that an HDL-C increase from a lower baseline level (as in VA-HIT) may be more cardioprotective than a similar increase from a higher initial level.\(^ {54}\)

**Refinement of Risk Assessment and Treatment Strategies**

Although 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are primarily used to lower LDL-C levels, the 6 available drugs in this class also raise HDL-C levels by 5% to 15%.\(^ {42,55}\) Moreover, HDL-C
levels have been found to predict response to statin therapy. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)\textsuperscript{56,57} was the first primary-prevention trial in a population (N=6605) with average total cholesterol (mean, 221 mg/dL) and LDL-C (mean, 150 mg/dL) and below-average HDL-C (mean, 36 mg/dL for men, 40 mg/dL for women). After a mean 5.2 years of follow-up, treatment with lovastatin reduced the risk for a first acute major coronary event by 37% versus placebo.\textsuperscript{57} Participants in the 2 lowest tertiles of baseline HDL-C showed the greatest relative risk reduction with lovastatin therapy, and apo A-I was the only significant predictor of risk for the 3 categories of level at baseline, level at year 1, and percent change from baseline at year 1.\textsuperscript{56} These data suggest that HDL-C and apo A-I may help refine CHD risk assessment in primary-prevention patients with average LDL-C levels.

Low HDL-C may also predict the benefit of therapy, as evaluated angiographically, in CHD patients with LDL-C levels traditionally deemed mildly to moderately elevated. The Lipoprotein and Coronary Atherosclerosis Study (LCAS) of fluvastatin enrolled men and postmenopausal women aged 35 to 75 years with LDL-C levels of 115 to 190 mg/dL and angiographic evidence of CAD.\textsuperscript{58} One fifth of the 339 evaluable subjects also had HDL-C levels <35 mg/dL. According to a post hoc analysis, placebo patients with low baseline HDL-C had significantly more angiographic progression than those with higher HDL-C, and the effect of fluvastatin versus placebo on angiographic progression was significantly greater in patients with low HDL-C. With fluvastatin, HDL-C levels increased by 15.9% and 7.4% in the low and high HDL-C groups, respectively. Although LCAS was not designed to evaluate clinical outcomes, there was a significant trend toward improved event-free survival in the fluvastatin-treated low-HDL-C patients, compared with no benefit of fluvastatin in the higher HDL-C group. Lipid lowering alone cannot explain the difference in benefit between HDL-C categories, because the LDL-C reduction was similar in all patients.\textsuperscript{58} These results suggest that treatment of CAD patients with low HDL-C levels, and LDL-C levels traditionally regarded as mildly to moderately elevated, should address both lipid abnormalities.

Although niacin is considered to be the most effective pharmacological agent for raising HDL-C,\textsuperscript{42} few trials have evaluated its effect on clinical outcomes. Recently, a new formulation combining extended-release (ER) niacin and lovastatin was evaluated in a 28-week, double-blind, multicenter trial that randomized 237 patients to 1 of 4 treatment groups: niacin ER 1000 mg/lovastatin 20 mg, niacin ER 2000 mg/lovastatin 40 mg, niacin ER 2000 mg, or lovastatin 40 mg. In this study, both of the combination regimens were significantly more effective than lovastatin alone in raising HDL-C levels.\textsuperscript{59} There was also a strong dose–response relationship between niacin ER/lovastatin and improvements in LDL-C and HDL-C.

**Treatment Strategies: Present and Future**

As low HDL-C levels are often associated with the presence of other risk factors for atherosclerosis, it is difficult to assess the impact of raising HDL-C on CAD. Pharmacological interventions that increase HDL-C levels usually improve other lipid parameters as well. For example, the contribution of increased HDL-C levels is not easily distinguishable from that of decreased LDL-C and/or triglyceride levels.\textsuperscript{43}

Strategies for increasing low HDL-C levels include therapeutic lifestyle changes such as exercise, smoking cessation, weight loss, and reduction of saturated fat and cholesterol in the diet.\textsuperscript{42} Of the 4 classes of pharmacological agents currently approved for lipid-modifying therapy (resins [bile-acid sequestrants], nicotinic acid [niacin], fibric acid derivatives [fibrates], and statins), resins have little effect on HDL-C levels\textsuperscript{42,43} and are not discussed further in this review. Treatment with estrogen plus progesterin (medroxyprogesterone) as hormone replacement therapy is no longer recommended for the prevention of CHD. Pharmacological strategies that may be developed in the future include agents designed specifically to inhibit CETP, peroxisome proliferator-activated receptor (PPAR) agonists, and exogenous HDL mimetics.

**Niacin**

In addition to raising HDL-C, niacin lowers both LDL-C and triglycerides. No large, randomized clinical trials have evaluated the treatment of isolated low HDL-C with niacin. Side effects include potential hepatotoxicity; flushing, which is very prevalent; hyperglycemia; hyperuricemia; and upper gastrointestinal distress.\textsuperscript{42,43} When a switch is made from immediate-release niacin to ER formulations, equivalent doses should not be substituted; rather, the ER regimen should be initiated at a low dose and titrated to the desired therapeutic response.\textsuperscript{60}

**Fibrates**

Fibrates raise HDL-C by 10% to 20%, modestly lower LDL-C, and substantially lower triglycerides.\textsuperscript{42} These agents are absolutely contraindicated in patients with severe renal or hepatic disease.\textsuperscript{42,43} Moreover, because of the risk for myotoxicity, including rhabdomyolysis, the combination of a fibrate, particularly gemfibrozil, with a statin requires extreme caution and monitoring of creatine kinase levels.\textsuperscript{61}

**Fibrates as PPAR Agonists.** PPARs are a subfamily of nuclear receptors that act as transcription factors, altering the expression of target genes by binding to peroxisome proliferator response elements. Through activation of PPAR-\(\alpha\), fibrates influence the expression of 5 key gene-encoding proteins involved in HDL-C metabolism: apo A-I, apo A-II, lipoprotein lipase, SR-B1, and ABCA1. PPAR-\(\alpha\) thereby increases HDL synthesis and affects reverse cholesterol transport by accelerating the efflux of cholesterol from peripheral cells and its uptake by the liver.\textsuperscript{62} Further understanding of the mechanism of action of PPAR agonists may lead to the design of more specific agents with fewer side effects.

**Statins**

In addition to decreasing LDL-C concentrations through inhibition of HMG-CoA reductase, the enzyme involved in the rate-limiting step of cholesterol biosynthesis, statins lower triglycerides and modestly increase HDL-C. Compared with fibrates, statins as a class have a slightly lesser effect on HDL-C, decrease LDL-C levels to a much greater extent, and, in some patient populations, may be less effective in decreasing triglyceride levels.\textsuperscript{42,63}
Depending on the dose, all statins produce similar increases in HDL-C. The effect of statins on HDL level, composition, and functionality is not well understood, but appears to involve multiple mechanisms. For example, atorvastatin at a daily dose of 10 mg can beneficially shift the HDL subspecies profile and induce changes in CETP activity.\(^6^3\) Statins are contraindicated in patients with active or chronic liver disease.\(^6^2\)

**CETP Inhibition**

Because CETP enriches the cholesterol content of LDL and depletes that of HDL, it was originally considered to be a proatherogenic modulator of HDL metabolism. However, the generation of pre-\(\beta\)-HDL and the involvement in reverse cholesterol transport suggest antiatherogenic properties. Data from genetic studies show that CETP polymorphisms can be associated either with increased or decreased CAD risk. It seems, therefore, that CETP can be either proatherogenic or antiatherogenic depending on the metabolic setting. Inhibition of CETP would be expected to impair reverse cholesterol transport but at the same time to extend the biological lifetime of mature HDL particles and thereby to increase the bioavailability of antioxidants and lysosphingolipids associated with HDL particles. Animal models suggest that long-term inhibition of CETP reduces susceptibility to atherosclerosis, although the effect of such action in humans is not known.\(^3\) Specific statins affect CETP activity in different ways.

Atorvastatin and simvastatin both reduce CETP mass; however, the major effect of atorvastatin on CETP is to decrease CETP Inhibition of CETP reduces susceptibility to atherosclerosis, despite the absence of such action in humans.\(^3\) Specific statins affect CETP activity in different ways. Atorvastatin and simvastatin both reduce CETP mass; however, the major effect of atorvastatin on CETP is to decrease CETP activity through a reduction in the number of cholesteryl ester acceptor particles.\(^6^3\) It is possible that long-term inhibition of CETP may be accomplished in the future by use of vaccines or small-molecule inhibitors as a means of altering the metabolism and concentration of HDL and other lipoproteins to prevent coronary disease.\(^3\)

**Exogenous HDL Mimetic**

Apo A-I Milano is a naturally occurring variant of apo A-I. Found in a small number of inhabitants of a rural Italian village, it appears to be atheroprotective. Carriers have very low HDL-C levels, but are noted for their longevity and low incidence of atherosclerosis.\(^6^4\) In a recent randomized, double-blind study, recombinant apo A-I Milano (ETC-216) was administered weekly to 123 patients via intravenous infusion after an acute coronary syndrome. Results showed a significant decrease of 1.06% (SD = 3.17%) in mean atheroma volume, as evaluated by intravascular ultrasound, over 5 weeks. These results require confirmation in a larger population with a longer follow-up, as well as evaluation of the effect of therapy on clinical outcomes.\(^6^4\)

**Conclusions**

Reducing LDL-C levels can lower the incidence of CHD by up to one third. Although impressive, these results also raise the question of how to decrease the 65% to 70% of major cardiac events that still occur. Therefore, investigators are seeking other modifiable CHD risk factors.

HDL is one important target of investigation. The cardioprotective effect of HDL has been recognized since 1950,\(^6^5\) and low levels of HDL are now identified as a major independent risk factor for CHD. Although epidemiological data show an inverse relation between HDL-C levels and CHD risk, the outcomes of clinical trials evaluating HDL-C-raising therapies lack the strength and consistency of the statin trial data. Nevertheless, observational, biological, and clinical evidence strongly suggests that HDL is a promising target of therapeutic intervention. In the future, a more complete understanding of HDL metabolism could lead to the development of drugs that enhance atheroprotection by robustly increasing levels of HDL and/or enhancing its functionality.

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