# The Importance of Recognizing and Treating Low Levels of High-Density Lipoprotein Cholesterol: A New Era in Atherosclerosis Management

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*Low levels of high-density lipoprotein cholesterol (HDL-C) represent a major cardiovascular risk factor, with a stronger relationship to coronary heart disease than that seen with elevated levels of low-density lipoprotein cholesterol (LDL-C). HDL-C has important antiatherogenic effects, including reverse cholesterol transport, inhibition of LDL-C oxidation, and antiplatelet and anti-inflammatory actions. Patients with low HDL-C are also at an amplified risk of coronary heart disease due to the common coexistence of other risk factors, including excess adiposity, metabolic syndrome, type 2 diabetes mellitus, hypertriglyceridemia, and the atherogenic dyslipidemia characterized by small dense LDL-C. First-line therapy of low HDL-C generally consists of nonpharmacologic measures such as improved fitness and weight loss. Current pharmaceutical options include statins, fibrates, and nicotinic acid. A host of novel approaches involving HDL-C and reverse cholesterol transport hold the promise of fundamentally changing the natural history of atherosclerosis, the most common and important chronic disease in humans.*
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**Key words:** Atherosclerosis • High-density lipoprotein cholesterol • Dyslipidemia • Reverse cholesterol transport system • Cholesteryl ester transfer protein • Niacin • Nicotinic acid • Laropiprant • Fibrate

The National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) guidelines recommend focusing on low-density lipoprotein cholesterol (LDL-C) as the primary target for lipid therapy to prevent development and progression of atherosclerotic vascular disease,[1] a goal that generally can be achieved in compliant patients with available lipid-lowering therapies. However, many coronary heart disease (CHD) events still occur in

patients (about 15%[2,3]) whose LDL-C levels and other major risk factors appear to be adequately controlled (Figure 1). In major trials of patients treated with hydroxy-methylglutaryl-coenzyme A reductase inhibitors (statins), up to 70% of cardiovascular (CV) events were not prevented.[4] It has been suggested that either the established target LDL-C levels are still too high, and thereby obscure the maximum benefit attainable by treating high levels of this lipoprotein, or that other risk factors, particularly low levels of high-density lipoprotein cholesterol (HDL-C), also must be controlled to achieve better outcomes. In addition, the fact that in the United States more than one-fourth of adults and more than one-half of patients with CHD have low levels of HDL-C[5] has led to increased interest in the physiology, abnormalities, and treatment of problems related to HDL. Lately, there has been great success in developing more potent therapies to raise HDL-C that will likely usher in a new era in the primary and secondary prevention of atherosclerosis.[6]

Although the terms *HDL* and *HDL-C* are often used interchangeably, *HDL* refers to the lipoprotein and its properties, and *HDL-C* refers to the measured value (mg/dL) on laboratory testing. Low HDL-C is an important risk factor; it is highly prevalent and strongly associated with atherosclerotic vascular disease.[7] Low HDL-C has been detected in 35% of men and 15% of women among the general population, according to data from the National Health and Nutrition Examination Surveys (NHANES).[8] Several epidemiological and clinical studies have demonstrated that low levels of HDL-C are an independent risk factor for CHD (Figure 2).[9,10] Some of these studies have also shown that low HDL-C may be even more strongly related to CHD events than high LDL-C: for every increase in HDL-C of 1 mg/dL, the risk of major CHD events decreases by 2% to 3% and the risk of CHD mortality decreases by 4% to 5% (Figure 3).[11,12] The highest risk of CHD occurs when low HDL-C coexists with high LDL-C.[12,13]

There is evidence that low HDL-C increases the risk of CHD independently of other lipid abnormalities.[14] However, in many cases the association of low HDL-C with CHD may not be isolated from other CHD risk factors that frequently coexist in these patients, including excess adiposity, metabolic syndrome, type 2 diabetes mellitus (DM), hypertriglyceridemia, and the atherogenic dyslipidemia characterized by small dense LDL-C. This association also helps explain the growing incidence of low HDL-C in patients afflicted in the worldwide obesity pandemic.[13,15,16]

The elucidated mechanism of low HDL-C in patients with the metabolic syndrome includes increased hepatic production of very low-density lipoprotein (VLDL) molecules from free fatty acids that are released by the abdominal fat (which is greater in obese patients) into the portal circulation, and then into the peripheral bloodstream. The larger the number of VLDL molecules, the greater the chances that cholesteryl ester transfer protein (CETP) can transfer cholesterol from HDL or LDL

**Figure 1.** *In these data from the Framingham study, low HDL-C levels (< 40 mg/dL) were associated with an increased risk of CHD, even when the total-C level was less than 200 mg/dL. This figure shows the CHD incidence for a 14-year period among Framingham study subjects who were aged 48 to 83 years at baseline. Among those with HDL-C levels less than 40 mg/dL and total-C less than 200 mg/dL, 11.24% experienced a CHD event. This incidence was virtually the same as that for subjects with HDL-C levels between 40 to 49 mg/dL and total-C at or greater than 260 mg/dL (11.91%). HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; C, cholesterol. Reprinted with permission from Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study.* JAMA. *1986;256:2835-2838.*[10] *Copyright © American Medical Association. All rights reserved.* www.medreviews.com

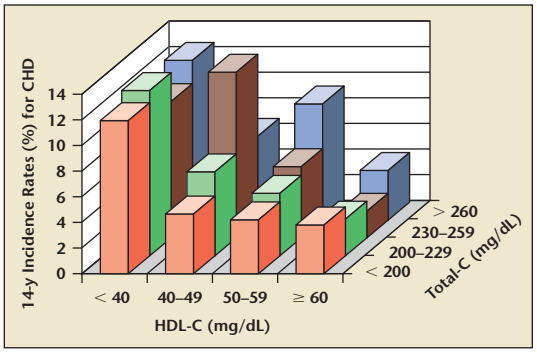
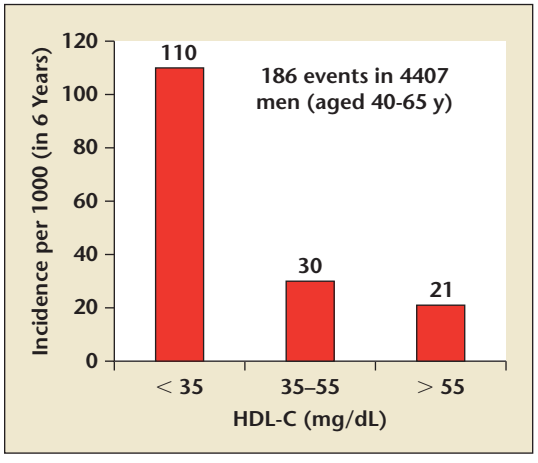



**Figure 2.** *Results of the Prospective Cardiovascular Münster (PROCAM) study confirmed the Framingham data. PROCAM showed that the incidence of coronary heart disease decreased with increasing HDL-C levels among a group of 4407 German men, aged 40 to 65 years, followed for 6 years. HDL-C, high-density lipoprotein cholesterol. Reprinted with permission from Assmann G and Schulte H.*[116] www.medreviews.com



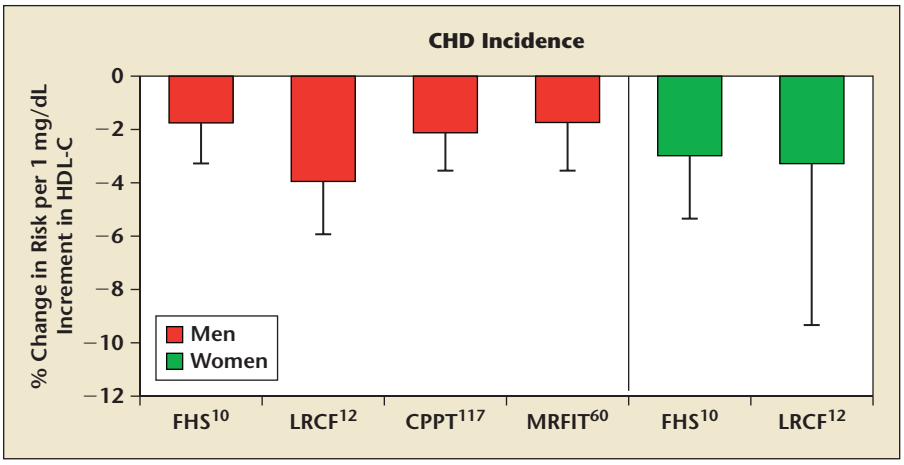
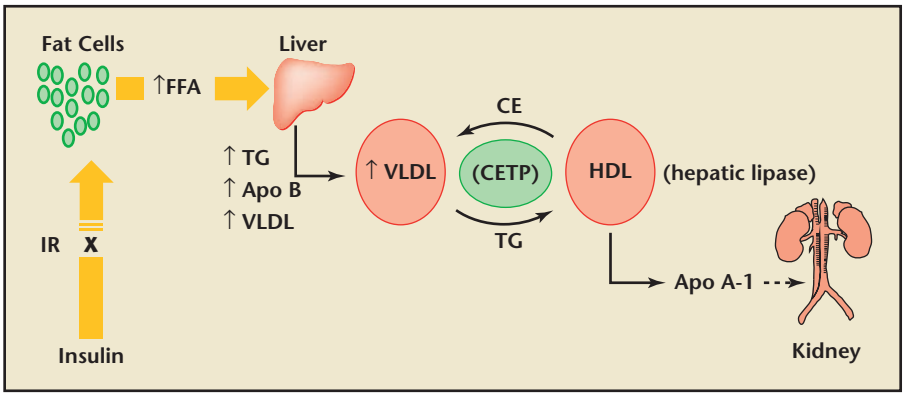



**Figure 3.** *Several studies suggest that low HDL-C may be even more strongly related to CHD events than high LDL-C: for every increase in HDL-C of 1 mg/dL, the risk of major CHD events decreases by 2% to 3% and the risk of CHD mortality decreases by 4% to 5%. The 95% confidence intervals shown were adjusted for proportional hazards regression coefficients. HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; FHS, Framingham Heart Study; LRCF, Lipid Research Clinics Prevalence Mortality Follow-up Study; CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; MRFIT, Multiple Risk Factor Intervention Trial. Adapted with permission from Gordon DJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies.* Circulation. *1989;79:8-15.*[12] www.medreviews.com

to VLDL in exchange for triglycerides (TGs). This process also results in large, cholesterol-rich atherogenic VLDL particles and in small-LDL (which is very atherogenic because it carries cholesterol into the endothelium) and small-HDL particles. Finally, the kidneys more easily clear the small TG-rich HDL, reducing its plasma concentration (Figure 4).

In terms of treatment, clinical trials have shown that increasing low HDL-C levels further reduces the risk of CHD, beyond the success achieved by LDL-lowering therapy. Furthermore, certain therapies for low HDL-C levels may not only slow or arrest the atherogenic process, but in some cases they may also cause existent lesions to revert, thus promoting true regression of atherosclerosis.[17,18] However, supporting evidence of many studied therapies is not strong or is inconsistent and not infrequently limited by the fact that some of their clinical effects cannot be isolated from comodification of other lipid abnormalities.

**Figure 4.** *In patients with IR, hepatic production of VLDL is increased due to elevated levels of FFA in the portal circulation, released by the abdominal fat. High levels of VLDL molecules enhance the transfer of CE from HDL to VLDL in exchange for TG, causing production of large cholesterol-rich atherogenic VLDL and small HDL that can be more easily cleared by the kidneys (reducing HDL-C levels). IR, insulin resistance; FFA, free fatty acids; TG, triglycerides; Apo, apolipoprotein; VLDL, very low-density lipoprotein; CE, cholesteryl esters; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein.* www.medreviews.com




## Metabolism and Mechanisms of Action of HDL

The anti-atherogenic properties of HDL are a result of at least 4 major antiatherogenic effects. First, HDL is a major participant in the reverse cholesterol transport system that brings cholesterol from peripheral tissues back to the liver to be removed (Figure 5). This system is a multistep process through which HDL removes excess cholesterol from extrahepatic peripheral cells, especially cholesterol-loaded macrophages in the arterial walls, and transfers it to the liver for biliary excretion.[19] Second, HDL inhibits LDL-C oxidation via paraoxonase, an enzyme that appears to be upregulated with exercise.[20,21] Third, HDL inhibits the expression of cellular adhesion molecules and monocyte recruitment and, thus, has an anti-inflammatory effect.[22,23] Fourth, HDL inhibits platelet activation and aggregation with platelet-activating factor acetylhydrolase and, thus, reduces the risk of atherothrombosis.[23] However, the traditional belief that the main antiatherogenic effect of HDL is related to its reverse transport mechanism has been questioned recently, and more direct protective effects of HDL are being considered.

HDL is a lipoprotein composed mainly of phospholipids and apolipoproteins (apo A-I, apo A-II, apo C) that are synthesized in the liver and intestinal mucosa as nascent HDL particles, which are small, spherical, and lipid-poor (Figure 6).[24] After being released to the circulation, the nascent lipid-poor HDL promotes the transfer of excess extrahepatic cellular-free cholesterol, mainly from lipid-rich macrophages in arterial walls and other peripheral tissues, to HDL apo A-I particles. This process is mediated by molecular

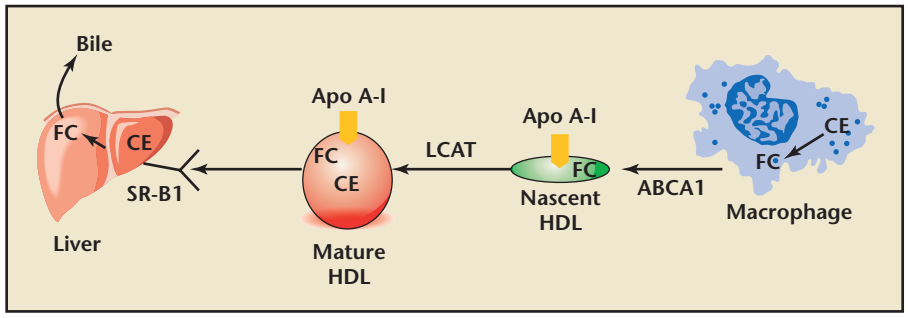



**Figure 5.** *Nascent lipid-poor HDL promotes the transfer of excess extrahepatic cellular-FC, mainly from lipid-rich macrophages in arterial walls, to HDL apo A-I particles. This process is mediated by molecular interaction with ABCA1 in these cells, and results in formation of discoid HDL particles. Plasma LCAT converts the cholesterol in these growing HDL particles into cholesteryl esters, mediated by apo A-I protein on the surface of HDL. The hydrophobic cholesteryl esters are withdrawn into the core of HDL, allowing new cholesterol molecules to be translocated onto the surface of HDL. The result is the maturation of HDL that acquires a spherical configuration and is brought to the liver for final fecal excretion in the bile. FC, free cholesterol; CE, cholesteryl ester; SR-B1, scavenger receptor B1; Apo A-I, apolipoprotein A-I; HDL, high-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; ABCA1, adenosine 5′-triphosphate–binding cassette transporter A1.* www.medreviews.com

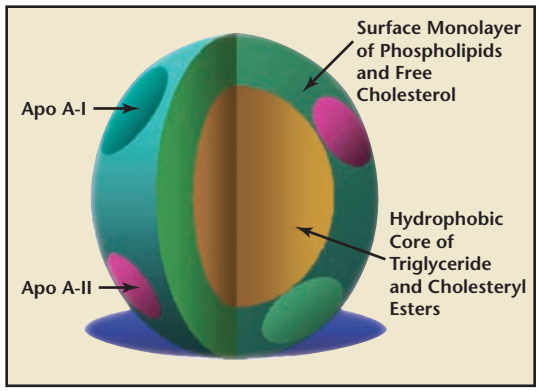



**Figure 6.** *Structure of high-density lipoprotein. Apo, apolipoprotein. Adapted from* Atherosclerosis, *Vol 145, Rye KA, Clay MA, Barter PJ. Remodelling of high density lipoproteins by plasma factors, pages 227-238,*[118] *Copyright 1999, with permission from Elsevier.* www.medreviews.com

interaction with the adenosine 5′-triphosphate–binding cassette transporter A1 (ABCA1) present in these cells, which is the cholesterol efflux regulatory protein that interacts with newly synthesized lipid-poor apo A-I and results in formation of discoid HDL particles.[19,25,26] Then, plasma lecithin-cholesterol acyltransferase (LCAT) converts the cholesterol in these growing HDL particles into cholesteryl esters, a step that is mediated by apo A-I protein on the surface of HDL. The hydrophobic cholesteryl esters are withdrawn into the core of HDL, allowing new cholesterol molecules to be translocated onto the surface of HDL. The result is the maturation of HDL that acquires a spherical configuration and is ready to be brought to the liver for final excretion (Figure 7).[25]

Once HDL has recovered cholesterol particles from the peripheral tissues, it can transport them back to the liver by 2 alternative mechanisms. First, it can transfer the esterified cholesterol to apo B–containing lipoproteins, such as VLDL and LDL, in exchange for TG, a process that is mediated by CETP.[27] These lipoproteins can subsequently deliver the esterified cholesterol for clearance back to the liver through the hepatic LDL receptor. Second, the esterified cholesterol within the TG-rich HDL-molecules that is generated following the CETP effect is directly removed by the liver through a scavenger receptor B1. This step occurs after the TG component in HDL undergoes hydrolysis by a hepatic lipase and results in the generation of lipid-depleted HDL particles that can be excreted or catabolized. In the liver, the extracted cholesterol is then converted to bile and excreted in the feces.[19,25]

Both of these hepatic delivery steps lead to a drop in the lipid content of HDL and, thus, promote HDL catabolism.[25] The catabolic rate of apo A-I (the main protein in HDL) is a key determinant of the circulating levels of HDL-C and is inversely related to the lipid content in HDL (and at the same time proportional to HDL's molecular size). The higher the lipid content of HDL, the larger the molecule and the slower the catabolic rate of apo A-I, thus maintaining the elevation of HDL-C levels. Factors that are involved in the reverse cholesterol transport system and regulate the lipid content of HDL, such as lipid transfer proteins or enzymes, also control the levels of circulating HDL-C. As shown in Table 1, different mutations and interactions of these enzymes cause a variety of effects on the levels of HDL-C, revealing the complexity of the reverse cholesterol transport system. Some of the components of the reverse cholesterol transport system have also become of interest in preventive cardiology due to their value as markers of vascular disease or their influence on HDL-C metabolism. For example, low levels of apo A-I have been consistently demonstrated to be independently related to coronary artery disease,[25] leading some authors to advocate their use as a more accurate risk factor for atherosclerotic vascular disease than total cholesterol or HDL-C.

## Factors Associated With Low and High HDL-C

In addition to the different physiologic and metabolic factors that influence HDL-C levels by altering the

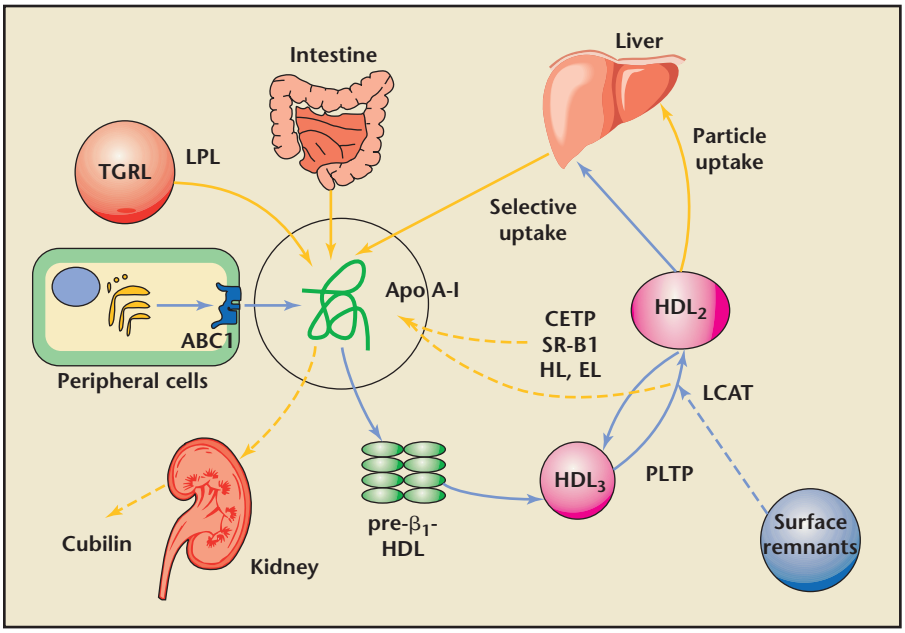



**Figure 7.** *These are some of the pathways involved in the generation and conversion of HDL: Mature $HDL_3$ and $HDL_2$ are generated from precursors (lipid-free apo A-I or lipid-poor pre-$\beta_1$-HDL), which are produced as nascent HDL by the liver or intestine, or from lipolysed very low-density lipoprotein and chylomicrons. ABC1 mediates lipid efflux from cells; LCAT mediates esterification of cholesterol, generating spherical particles that continue to grow on ongoing cholesterol esterification. Larger $HDL_2$ particles are converted into smaller $HDL_3$ particles during the CETP-mediated export of cholesteryl esters from HDL onto: apo B–containing lipoproteins, SR-B1–mediated selective uptake of cholesteryl esters into the liver, and HL- and EL-mediated hydrolysis of phospholipids. HDL lipids are catabolized either separately from HDL proteins (ie, by selective uptake or via CETP transfer) or together with HDL proteins. The conversion of $HDL_2$ into $HDL_3$ and the PLTP-mediated conversion of $HDL_3$ into $HDL_2$ liberates lipid-free or poorly lipidated apo A-I. A portion of lipid-free apo A-I undergoes glomerular filtration in the kidney and tubular reabsorption through cubilin. HDL, high-density lipoprotein; TGRL, triglycerides; LPL, lipoprotein lipase; ABC1, ATP-binding cassette transporter 1; apo A-I, apolipoprotein A-I; CETP, cholesteryl ester transfer protein; SR-B1, scavenger receptor B1; HL, hepatic lipase; EL, endothelial lipase; LCAT, lecithin-cholesterol acyltransferase; PLTP, phospholipid transfer protein. Adapted with permission from von Eckardstein A and Assmann G.*[119] www.medreviews.com

lipid content of HDL-C and thereby modulating the catabolic rate of apo A-I, there are several other genetic and acquired factors that contribute to the concentration of plasma HDL-C. These factors are directly or indirectly related to the reverse cholesterol transport system and magnify the effects of metabolic factors that alter HDL-C levels. In fact, about 50% of the variability in HDL-C among the population is due to genetic mutations that affect the structure of the apolipoproteins in HDL or the enzymes involved in the reverse cholesterol transport system.[28] The most commonly recognized genetic causes of low HDL-C include familial hypoalphalipoproteinemia (apo A-I gene mutations), familial HDL deficiency and Tangier disease (ABCA1 mutations), lipoprotein lipase deficiency, elevated hepatic TG lipase activity, and LCAT deficiency (Table 2). Alternatively, there are other factors that are associated with elevated levels of HDL-C by different mechanisms (Table 3).

**Table 1**
**Conditions and Genetic Factors That Change HDL-C Levels**

| Effect | Condition | Mechanism |
|---|---|---|
| ↓ HDL-C | Mutation of ABCA1 | ↓ Cellular cholesterol efflux → ↑ clearance of apo A-I |
| | Senescent, very small HDL particle | Renal glomerular filtration |
| | Hypertriglyceridemia | ↑ Catabolic rate of apo A-I |
| | Mutations of apo A-I gene | Eg, apo A-I Milano → ↑ HDL size → enhances reverse cholesterol transport<br>Eg, ↓ ability of LCAT to catalyze cholesterol esterification, increasing lipid-poor apo A-I catabolism |
| | Overexpression of SR-B1 | Enhances reverse cholesterol transport |
| | Complete inhibition of CETP | ↑ Cholesterol-rich HDL → decreases reverse cholesterol transport |
| ↑ HDL-C | Alcohol, estrogens | ↑ Transport rate of apo A-I |
| | Overexpression of ABCA1 | ↑ Cellular cholesterol efflux → ↓ clearance of apo A-I |
| | Mutation of other plasma factors | ↑ Response to certain medications |
| | Partial inhibition of CETP | ↑ HDL-C → enhances reverse cholesterol transport |

HDL-C, high-density lipoprotein cholesterol; ABCA1, adenosine 5′-triphosphate–binding cassette transporter A1; apo, apolipoprotein; LCAT, lecithin-cholesterol acyltransferase; SR-B1, scavenger receptor B1; CETP, cholesteryl ester transfer protein.

**Table 2**
**Causes of Low HDL-C**

| |
|---|
| Genetic factors/familial disorders |
| Familial hypoalphalipoproteinemia |
| Familial high-density lipoprotein deficiency |
| Tangier disease |
| Overweight/obesity |
| Physical inactivity |
| Elevated triglycerides |
| Cigarette smoking |
| Metabolic syndrome |
| Type 2 diabetes mellitus |
| Atherogenic dyslipidemia |
| Very low-fat/carbohydrate-rich diet |
| Medications |
| Antihypertensives |
| Loop and thiazide diuretics |
| β-blockers without intrinsic sympathomimetic activity |
| Steroids |
| Anabolic |
| Progestins |
| Lipid-lowering agents |
| Probucol |
| Benzodiazepines |

HDL-C, high-density lipoprotein cholesterol.

**Table 3**
**Causes of High HDL-C**

| |
|---|
| Genetic factors |
| Exercise |
| Weight loss |
| Smoking cessation |
| Moderate daily alcohol intake |
| Very high-fat diet |
| Medications |
| Lipid-lowering agents |
| Nicotinic acid |
| Fibrates |
| Statins |
| Estrogen |
| Corticosteroids |
| Anticonvulsants |
| Phenobarbital |
| Phenytoin |
| Carbamazepine |

HDL-C, high-density lipoprotein cholesterol.

There are some conditions in which there is no direct proportional relationship between the HDL-C level and the expected effect on CHD protection, indicating that other factors, including particle function, are important. Some patients have CETP deficiency that is associated with high HDL-C levels. However, these high levels do not seem to provide any protection against CHD.[29] Conversely, some polymorphisms of the CETP gene can cause higher CETP levels and lower levels of HDL-C, which has been found to be associated with reduced risk of CHD.[30] A recent large study demonstrated that certain ABCA1 mutations are related to lower HDL-C levels. However, lower plasma HDL-C was not associated with increased risk of CHD.[31]

HDL particles differ in size, structure, and function,[32] allowing them to be subcategorized based on their density into $HDL_2$ (density range, 1.063-1.125 g/mL) and $HDL_3$ (density range, 1.125-1.21 g/mL), subspecies that seem to be inversely associated with a lower incidence of CHD.[33,34] The $HDL_2$ particles contain apo A-I, whereas the $HDL_3$ particles are composed of apo A-I and apo A-II.[35] (The HDL particles containing only apo A-I are strongly participate in cholesterol efflux from peripheral cells, whereas the particles containing both apoproteins are less effective in cholesterol mobilization from nonhepatic cells and appear to have other functions that are not antiatherogenic.) However, the clinical importance of the different HDL subfractions is still uncertain. Many case control and prospective studies have demonstrated that the $HDL_2$ subfraction and plasma apo A-I concentration are better predictors of coronary atherosclerosis than total HDL-C or $HDL_3$.[36] In contrast, the Physicians' Health Study and some other reports have shown similar CHD risk between levels of total HDL-C and $HDL_3$ compared with $HDL_2$ and apo A-I.[34,37] This finding may reflect the participation of both $HDL_2$ and $HDL_3$ in the reverse cholesterol transport system.

## Treatment of Low HDL-C

The NCEP/ATP III guidelines have designated an HDL-C level of less than 40 mg/dL as a major risk factor for CHD, in both men and women.[1] Conversely, an HDL-C level of 60 mg/dL or higher is a protective factor because it eliminates one of the major risk factors used to calculate CV risk. Although the absolute parameters of normalcy mentioned above have been established, HDL-C correlates inversely with CHD as a continuous variable, with a wide spectrum of effects.[38]

Importantly, HDL-C levels are also predictive of major CV events in patients treated with statins to low LDL-C levels. A recent analysis of the Treating to New Targets (TNT) study found an inverse relationship between HDL-C and CV events among patients treated with statins, including those with LDL-C less than 70 mg/dL (Figure 8).[39] Furthermore, another observational study recently demonstrated the importance of low HDL-C levels in patients who have LDL-C well below current guidelines (< 60 mg/dL), achieved either spontaneously or with pharmacotherapy. In this study, among patients on statin therapy and with an LDL-C level less than 60 mg/dL (~50%), the inverse relationship between HDL-C and CHD risk persisted.[40] In patients

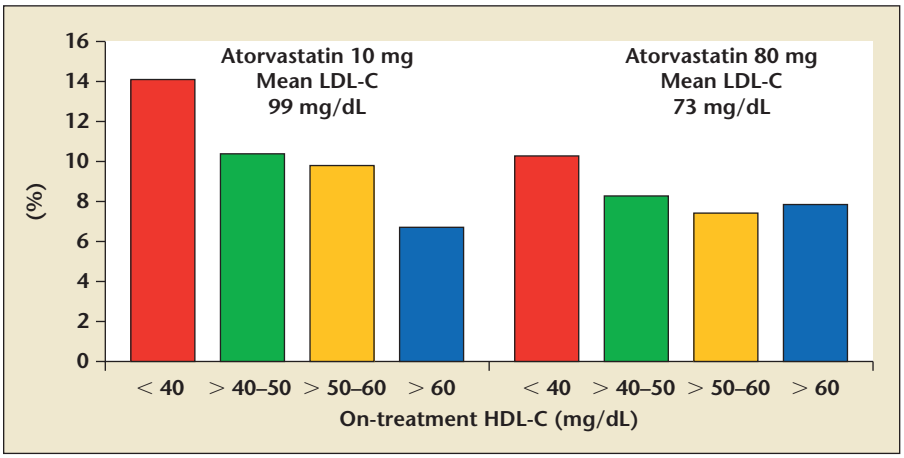



**Figure 8.** *Major cardiovascular events according to on-treatment HDL-C: results from the TNT trial. The TNT trial demonstrated that atorvastatin 80 mg with an on-treatment LDL-C of 73 mg/dL was superior to atorvastatin 10 mg with an on-treatment LDL-C of 99 mg/dL at decreasing coronary events in a coronary heart disease patient population. Low HDL-C (< 40 mg/dL) was associated with a higher residual risk, even in patients with a low LDL-C. HDL-C, high-density lipoprotein cholesterol; TNT, Treating to New Targets; LDL-C, low-density lipoprotein cholesterol. Data from Barter PJ and Kastelein JJ[101] and Waters DD et al.[120]* www.medreviews.com

with CHD, achievement of an LDL-C level of less than 70 mg/dL with statin therapy may need to be followed by efforts to raise the HDL-C level. These patients will likely benefit from a significant further reduction in event rates compared with patients managed according to the common current practice standards of treating only LDL-C.

Despite a comparable effect of high LDL-C and low HDL-C on the incidence of CHD as demonstrated in several epidemiologic studies, evidence proving the benefits of therapies that increase HDL-C is more limited than evidence showing LDL-C reduction with statin therapy. It is also still uncertain if raising HDL-C levels per se, independently of other lipid and nonlipid abnormalities, reduces CHD. Therefore, the NCEP/ATP III guidelines did not establish specific treatment goals for HDL-C except for the use of therapies that raise HDL-C when used for treatment of other lipid and nonlipid disorders. The guidelines recommend a stepwise approach to patients with dyslipidemia, in which LDL-C continues to be the primary target of therapy. Once LDL-C has been controlled (based on the Framingham risk score criteria), the secondary target is non–HDL-C, which consists of the sum of VLDL-C, LDL-C, and remnant particles (all atherogenic lipid particles). VLDL is a TG-rich lipoprotein that contains 10% to 15% of the total cholesterol apo B-100 and is associated with atherogenic remnant lipoproteins. Therefore, non-HDL cholesterol combines these atherogenic particles with LDL-C (all apo B–containing lipoproteins), improving the CHD risk prediction, particularly when TG levels are greater than 200 mg/dL—in which case VLDL-C begins to substantially increase. Non–HDL-C is calculated by subtracting HDL-C from total cholesterol. The recommended plasma value is less than 30 mg/dL higher than the LDL-C goal. Considering that non–HDL-C seems to provide additional predictive power and overlaps with HDL-C, the guidelines focus on TG instead of HDL-C as a secondary therapeutic target. However, many experts recommend that HDL-C be considered as a treatment target.[1,41]

Treatment of low HDL-C consists of both nonpharmacologic and pharmacologic measures. Pharmacologic agents that raise HDL-C are generally used when the nonpharmacologic measures are insufficient. However, they are also used as a tertiary prevention strategy for very high-risk patients (after LDL-C and non-HDL have been controlled), or as a primary prevention strategy for those patients in whom HDL-C is particularly important (those who are overweight/obese or who have the metabolic syndrome or DM). Selection of a pharmacologic agent depends on the presence and type of coexistent lipid abnormalities. In the presence of elevated TGs, treatment usually focuses on reduction of TG levels with fibrates, which frequently leads to significant increases in HDL-C.

Disadvantages and limitations of treating low HDL-C are:

- Less than 3% of the general population is physically fit enough to complete 3 miles of running; therefore, almost all patients have suboptimal or poor fitness.
- Substantial increases in or high levels of physical conditioning are needed to substantially raise HDL-C.
- More than 80% of adults are experiencing a steadily increasing waistline and growing stores of excess adipose tissue, which work to lower levels of HDL-C.
- Because many of the available and most-studied medications to raise HDL-C have additional molecular effects, it is difficult to attribute their benefits only to their effect on HDL-C.
- Niacin, the most effective agent currently available to raise HDL-C, is the most poorly tolerated medication in preventive cardiology.

## Nonpharmacologic Management of Low HDL-C

Nonpharmacologic measures that raise HDL-C are the first step in the management of patients in any risk category with this lipid abnormality. Although low HDL-C levels of patients with concomitant hypertriglyceridemia seem to respond better to nonpharmacologic interventions,[42] some studies have demonstrated the opposite effect, that is, that patients with isolated low HDL-C and normal TGs have a better response.[43,44] Nonpharmacologic strategies include increased physical activity and conditioning, weight loss, reduction of cholesterol-raising foods, smoking cessation, moderate daily alcohol consumption, and discontinuation of HDL-lowering medications.[26,45] These measures, such as increased exercise and fitness combined with weight reduction, can not only raise HDL-C but may also improve its function.

*Weight Reduction*

There is good evidence that obesity is associated with low HDL-C levels and elevated TGs.[46] Weight loss is a main component of the management of overweight and obese patients with low HDL-C. Although caloric restriction may be associated with slight decreases in HDL-C, $HDL_2$-C, and apo A-I, as weight loss occurs, these levels increase again and remain improved with sustained normalization of body weight. Estimates from meta-analyses suggest that for every 4.5 kg of weight reduction, HDL-C increases by 2 mg/dL and TG levels decrease by 6 mg/dL.[47] Some authorities recommend gradual, controlled weight loss with an average of 1 pound per week and a goal body-mass index of less than 25 $kg/m^2$.[26] More importantly, reduction of abdominal adiposity with the return of a scaphoid abdominal profile and normal/small waist circumference should be a prime goal for those who are overweight or obese.

*Diet*

Caloric restriction with resulting weight loss has been shown to raise HDL-C. Additionally, because diets rich in simple carbohydrate (starch) content (> 60% of total calories) tend to raise TG levels and to lower HDL-C, they should be avoided.[1,45] Thus, patients with low HDL-C should be counseled to reduce or eliminate sugars and starch sources including candy; desserts; most baked goods, including breads and pasta; potatoes; and rice. However, low-fat diets (especially those low in saturated fat and cholesterol, such as the Dietary Approaches to Stop Hypertension [DASH] diet) usually decrease both LDL-C and HDL-C.[48] Therefore, it is recommended that the undesired decline of HDL-C that often occurs with these diets be offset or compensated by exercise and reduction of visceral adiposity.[49]

Replacing diets rich in sugar, starch, and saturated fat for diets that are rich in high-quality sources of protein, fresh fruits and vegetables, and monounsaturated fatty acids (eg, olive oil) lowers LDL-C and may prevent a reduction in HDL-C.[50] Increased intake of monounsaturated fatty acids (even without any energy restriction, like in a Mediterranean-type diet) has been shown to produce comparable effects.[51] Diets rich in n-3 polyunsaturated fatty acids also seem to have a beneficial effect on HDL-C. Some studies have shown that communities in which people eat diets rich in n-3 polyunsaturated fatty acids have higher HDL-C levels.[52] Therefore, we generally recommend a modified Mediterranean-type diet that eliminates or markedly reduces sugar, starch, and saturated fat and emphasizes high-quality sources of protein (seafood, lean meats, beans, nuts, legumes) that are relatively rich in monounsaturated fats, fish oils, and n-3 polyunsaturated fatty acids (eg, olive and canola oils). Fresh fruits and vegetables complement this approach by providing soluble and insoluble fiber and important micronutrients. This dietary approach leads to loss of adiposity in the overweight and obese, maintenance of ideal weight in those who are fit, improvement in the overall lipid profile, maintenance/increase in HDL-C, and prevention of CHD and some forms of cancer.[26,53]

*Exercise*

A meta-analysis of 4700 subjects that included 52 trials of exercise training programs lasting more than 12 weeks demonstrated an average increase in HDL-C of 4.6%, reduction in TG of 3.7%, and reduction in LDL-C of 5.0%.[54] Data from the Ochsner Clinic Foundation in New Orleans, Louisiana, showed that patients with CHD, including elderly people, achieved 6% to 16% elevation in HDL-C when undergoing cardiac rehabilitation and taking part in exercise training programs. In this study, greater improvements were noted in patients with lower initial levels of HDL-C.[42,43,55] Likewise, in a study of healthy military recruits who were free of CHD, Rubinstein and colleagues[56] reported 10% improvement in HDL-C after 6 weeks of intensive exercise training and 33% improvement after 12 weeks of training. In summary, it is accepted that regular aerobic exercise increases HDL-C levels by 3% to 9% in healthy people and probably also in CHD patients, especially if they have a sedentary lifestyle.[26]

*Smoking Cessation*

It has been shown that cigarette smoking is associated with low levels of HDL-C[57] and apo A-I, as well as with reduced CETP and LCAT activity,[58,59] both of which interfere with

the adequate functioning of the reverse cholesterol transport system. HDL-C levels seem to be particularly low in the postprandial state, contributing to the fat intolerance condition in patients who smoke.[58] Therefore, smoking cessation is a main component of the management of low HDL-C, besides being a therapeutic target in prevention of CHD, because it is a recognized independent risk factor.[60,61]

*Alcohol Consumption*

Alcohol (ethanol) consumption in moderate amounts raises HDL-C levels. This effect seems to be related to an elevation in apo A-I, by increasing its transport rate in the liver, in a dose-dependent fashion.[62] A meta-analysis of studies that assessed the effects of moderate alcohol intake on lipids and hemostatic factors showed that consumption of 30 g of ethanol per day (2 servings of ethanol, beer, wine, or spirits) raised HDL-C levels by an average of 4 mg/dL.[63] Data from other studies show that people who consume 1 to 3 drinks a day have higher HDL-C levels and a lower risk of CHD events than those who drink less.[26] The effect on HDL-C seems to explain, at least in part, the inverse association of moderate alcohol intake with the lower risk of CHD events.[64] Approximately 80% of the US population consumes alcohol, and promoting alcohol use in nondrinkers is not advised due to the recognized and well-established medical and social risks associated with such practice (alcoholism, violence, accidents, violation of religious practices, etc).[65]

*Estrogen Replacement Therapy*

Oral estrogen replacement therapy is known to cause favorable effects on the lipid profile. It elevates levels of HDL-C (from 12% to 22%, depending on the dose) and decreases levels of LDL-C (from 11% to 23%)[66] and lipoprotein (a) (Lp[a]). However, estrogens also increase TG levels (which are usually associated with small dense LDL particles),[67] increase inflammatory markers, and cause coagulation abnormalities that adversely affect the incidence of CHD events.[68] Therefore, initiation or continuation of estrogen therapy is not recommended for the treatment of low HDL-C. Clinically, results of several studies do not support this practice either. Results from the Women's Health Initiative trial and the Heart and Estrogen/Progestin Replacement Study (HERS) did not confirm a net beneficial effect on CHD and suggested that estrogen-progestin therapy might cause harm when used for either primary or secondary prevention of CHD.[68,69] In the HERS trial, women with elevated Lp(a) (> 25 mg/dL) had a significant mortality benefit with hormone replacement therapy.[70] For this reason, estrogen therapy could be considered in the management of women with CHD who have elevated Lp(a) levels, especially if the HDL-C is low and TGs are not significantly elevated.

Multimodality intervention on HDL-C in patients with CHD was assessed in a study performed in 2 major institutions with cardiac rehabilitation units.[43,55] Strict hygienic interventions (American Heart Association/National Cholesterol Education Program [AHA/NCEP] phase I diet, directly supervised exercise program, weight loss, and smoking cessation program) were applied, and their effects on HDL-C and LDL-C were evaluated according to the presence of isolated and nonisolated low HDL-C levels (without and with elevated TGs, respectively). There were no differences in achieving control of major risk factors between both patient groups, but the ability to raise HDL-C was significantly stronger in patients who had isolated low HDL-C compared with patients who had nonisolated low HDL-C (+17% vs +2%; $P < .001$). Patients with isolated low HDL-C also had a nonsignificant decline in LDL-C. Results from this study suggested that patients with isolated low HDL-C are more sensitive than patients with nonisolated low HDL-C to therapeutic lifestyle measures that can improve the lipid profile and are more likely to gain important benefits from this approach.

## Pharmacologic Treatment of Low HDL-C

In our experience, many patients with low HDL-C levels have an inadequate response to lifestyle changes. A high level of dedication and effort is required for the normalization of body weight and for achievement of physical fitness. Unfortunately, this is a difficult task that is rarely carried out by the average adult. Therefore, pharmacologic therapy is generally required, especially for CHD or CHD-equivalent conditions. However, this approach differs from the NCEP/ATP III guidelines, which do not recommend treating HDL-C pharmacologically, except as part of the management of other lipid and nonlipid risk conditions.[71] On the other hand, certain expert groups, such as the American Diabetes Association and the Expert Group on HDL, are more explicit in recommending the addition of pharmacologic agents to raise HDL in specific patient populations, including those with isolated low HDL-C and subclinical coronary or systemic atherosclerosis, metabolic syndromes, DM, or atherogenic dyslipidemia, as well as elderly patients. They recommend the use of pharmacologic therapy as part of primary or secondary prevention, especially after other established risk factors are controlled.

Available drugs include fibric acid and nicotinic acid derivatives, statins, estrogens, and the combination of an LDL-lowering drug with

**Table 4**
**Pharmacological Management of Low HDL-C**

| Agent | Percentage HDL-C Increase* |
|---|---|
| Nicotinic acid | 20%-40% |
| Gemfibrozil | 5%-20% |
| Fenofibrate | 10%-25% |
| Statins† | 0%-15% |
| Apo A-I Milano | NA |
| CETP inhibitors | 46%-106% |

*See text for percentage increase of HDL-C with different combinations of agents.
†See text for possible differences between statins at various dosages.
HDL-C, high-density lipoprotein cholesterol; Apo, apolipoprotein; NA, not applicable; CETP, cholesteryl ester transfer protein.

**Table 5**
**Studies Supporting Benefit of Pharmacological Treatment of Low HDL-C**

| Study | Prevention Category | Medication |
|---|---|---|
| Helsinki Heart Study[87] | Primary | Gemfibrozil |
| Fenofibrate Intervention and Event Lowering Diabetes (FIELD)[92] | Primary | Fenofibrate |
| VA-HDL Intervention Trial (VA-HIT)[90] | Secondary | Gemfibrozil |
| Bezafibrate Infarction Prevention Trial (BIP)[91] | Secondary | Bezafibrate |
| Coronary Drug Project[77] | Secondary | Niacin |
| HDL Atherosclerosis Treatment Study (HATS)[78] | Secondary | Niacin + Simvastatin |
| Arterial Biology of Reducing Cholesterol (ARBITER)[79] | Secondary | Niacin + Statin |

HDL-C, high-density lipoprotein cholesterol.

either a fibrate or a nicotinic acid derivative. In current clinical practice, these agents are still commonly used despite their modest effect on HDL-C levels (Tables 4 and 5) because they have acceptable clinical evidence from different trials to support their use. However, contrary to the strong evidence from epidemiological studies demonstrating the inverse relationship between HDL-C level and CHD risk, available evidence showing the benefit of raising HDL-C on improvement of CHD outcomes, independent of other lipid and nonlipid effects, is not as robust. Observational studies have questioned the inverse correlation between HDL-C and CHD risk in the setting of pharmacotherapy. Although some trials have suggested that raising HDL-C (mainly by using monotherapy with niacin or fibrates) is associated with improved CHD outcomes, in most of these trials, levels of several other lipoproteins and serologic risk factors (LDL-C, remnant lipoproteins, TGs, fibrinogen, etc) have also been modified. Therefore, it has been difficult to specifically determine how much of the clinical benefits of those medications are related to raising HDL-C per se.

*Niacin*

Niacin inhibits the hepatic synthesis of VLDL, delays HDL-C clearance by reducing the hepatic removal of apo A-I particles without impairing hepatic uptake of their cholesteryl esters, and reduces the transfer of cholesterol from HDL-C to VLDL.[25,72]

Niacin or nicotinic acid remains the most effective medication to raise HDL-C that is currently available for clinical use (Figure 9). It typically increases HDL-C levels by about 25% in patients with isolated low HDL-C, but it may raise it by more than 35%, especially in patients with combined hypertriglyceridemia (Table 6) (2- to 3-fold higher than the increase noted with fibrates).[73] In a study that enrolled

**Figure 9.** *Results from randomized, placebo-controlled trials of agents that increase HDL-C in patients with isolated low HDL-C. HDL-C, high-density lipoprotein cholesterol.* www.medreviews.com

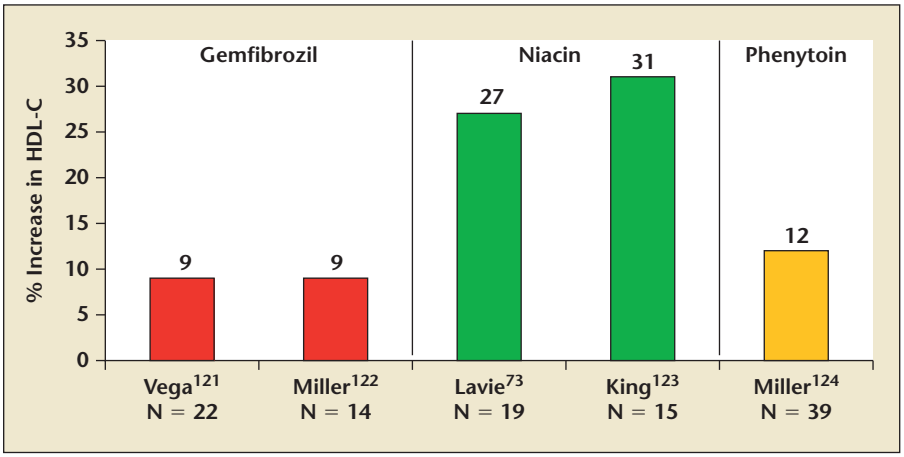


**Table 6**
**Pharmacologic Agents to Raise HDL-C: Mechanisms and Effects on Lipoproteins**

| Medication | Mechanism of Action | Lipoprotein Effect |
|---|---|---|
| Niacin | ↓ Hepatic removal of apo A-I (not cholesteryl esters)<br>↓ Synthesis of VLDL<br>↓ Transfer of cholesteryl esters from HDL-C to VLDL | ↑↑ HDL-C (20%-40%)<br>↓ LDL-C (5%-25%)<br>↓ TG (20%-50%)<br>↓ Lp(a) ≤ 30% |
| Fibrates | ↑ Production of apo A-I by PPAR-α activation | ↑ HDL-C (5%-25%)<br>↓/−/↑ LDL-C (0%-20%)<br>↓ TG (20%-50%) |
| Statins | ↑ Production of apo A-I by PPAR-α activation | ↑ HDL-C (0%-15%)<br>↓ LDL-C (18%-55%) |
| r-Apo A-I Milano | Direct ↑ levels of highly active apo A-I variant | ↑ HDL-C (short-term) |
| CETP inhibitors | ↓ CETP activity: ↓ transfer of cholesteryl esters to apo B–containing lipoproteins (VLDL, LDL) | ↑ HDL-C (long-term)<br>↓ LDL-C |

HDL-C, high-density lipoprotein cholesterol; apo, apolipoprotein; VLDL, very low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein (a); PPAR, peroxisome proliferator activated receptor; CETP, cholesteryl ester transfer protein.

37 patients with isolated low HDL-C, nicotinic acid (mean dose of 4.5 g/d) raised serum HDL-C by 30%, whereas gemfibrozil raised it by only 10%.[74] In another multicenter, randomized, double-blind trial, an extended-release niacin preparation at its higher doses (1 to 2 g at bedtime) provided up to a 2-fold greater HDL-C increase than gemfibrozil (600 mg twice a day). In addition, it caused greater reduction of Lp(a) and fibrinogen levels, as well as greater improvements in HDL-C/cholesterol ratios ($P < .001$ to $P < .02$). Gemfibrozil was more effective in reducing the TG level ($P < .001$ to $P = .06$; −40% for gemfibrozil vs −16% to −29% for extended-release niacin), but it also increased LDL-C.[75] Similar findings were reported in another study, in which extended-release niacin (1 to 2 g at bedtime) was more effective than gemfibrozil (1.2 g/d) in increasing HDL-C and apo A-I levels.[72] We also reported the substantial benefit of using sustained-release niacin in patients with isolated low HDL-C, and the comparably superior effect in patients with concomitant hypertriglyceridemia.[73]

The Coronary Drug Project, a secondary prevention trial of patients with previous myocardial infarction (MI), showed that despite a compliance of only 30%, short-acting niacin significantly reduced the incidence of recurrent nonfatal MI by about 30% compared with placebo, and produced a nonsignificant trend toward decreased mortality.[76] A 15-year follow-up study (10 years after the trial ended) reported a significant 11% mortality reduction in patients treated with niacin.[76] More recent analyses have also shown that patients with DM or the metabolic syndrome who are treated with niacin seem to have at least the same and probably greater reductions in CHD events and total mortality than other patient populations.[77]

The combination of niacin plus simvastatin was evaluated in CHD patients with low HDL-C and normal LDL-C in the HDL-Atherosclerosis Treatment Study (HATS) (Figure 10). Patients who were treated with the combination therapy had marked reduction of LDL-C (–42%) and elevation of HDL-C (+26%), accompanied by a 60% to 90% reduction of CV events (death, MI, stroke, or revascularization) and by angiographic regression of coronary lesions.[78]

The Arterial Biology of Reducing Cholesterol (ARBITER) 2 trial assessed the effect of extended-release niacin (1 g/d) on change in carotid intima-media thickness (CIMT) in patients with CHD who were already receiving statins (usually simvastatin).[79] When niacin was added, HDL-C levels increased by 21%, and LDL-C levels remained unchanged (the baseline LDL-C was only 89 mg/dL). Patients taking statin-only treatment continued to show progression of carotid lesions (0.044 ± 0.1 mm; $P < .001$), whereas patients taking the combination treatment had no progression of CIMT (0.014 ± 0.1; $P = .23$). Although the overall difference in CIMT progression between niacin and placebo was not statistically significant ($P = .08$), niacin significantly reduced the rate of CIMT progression in patients with no insulin resistance and showed a nonsignificant trend toward decreased incidence of CV events (9.6% vs 3.8%; $P = .2$).

The most troublesome side effect of niacin is the development of flushing,

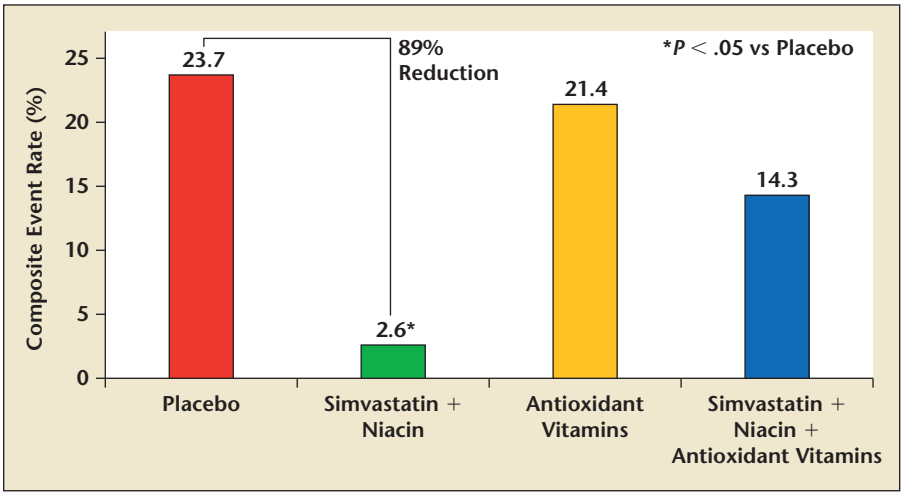



**Figure 10.** *Results from the HATS niacin and statin outcome trial. In this placebo-controlled secondary prevention study, 160 patients with CHD, low HDL-C (average, 31 mg/dL), and "normal" LDL-C levels (average, 125 mg/dL) were administered either niacin (slow-release or immediate-release, mean dose 2.4 g/d) plus simvastatin (mean dose 13 mg/d) or placebo with or without antioxidant vitamins for 3 years. In the group receiving niacin plus simvastatin without antioxidants, LDL-C levels were lowered by 42%; the LDL-C levels in the placebo groups were unaltered. HDL-C was increased by 26% in the niacin plus simvastatin group. The combination of niacin and simvastatin reduced CHD events (coronary death, MI, stroke, or revascularization) by 60% to 90%, with about a 90% reduction seen in those subjects who did not take antioxidants, possibly because the treatment-induced increase in HDL particle size was blunted by antioxidants. HATS, HDL-Atherosclerosis Treatment Study; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction. Data from Brown BG et al.*[78] www.medreviews.com

which limits its clinical use. Flushing can only be partially controlled by premedicating patients with aspirin, starting with a lower dose that is gradually increased, or by using a sustained-release (many of which are associated with higher rates of liver enzyme abnormalities) or an intermediate-release preparation. The mechanism of niacin-induced flushing, which consists of cutaneous vasodilation with associated discomfort, has been partially established. It is mediated by prostaglandins, which exert an effect on a G protein-coupled receptor, $PGD_2$ receptor 1 or DP1.[80] This discovery has led to the development of an investigational drug that is being tested for clinical use, laropiprant (MK-0524), which is a potent, selective, and orally active DP1 antagonist. Other potential side effects of niacin include dyspepsia, liver enzyme abnormalities (which are more likely with sustained-release preparations), and modest increases in blood glucose and uric acid, which have also limited the widespread use of this important therapy. However, 2 recent studies have demonstrated that niacin therapy markedly improves the lipid profile without adversely affecting glucose control in DM patients,[81,82] suggesting that the reduction in CHD risk seems to far outweigh the theoretically negative consequences of a hyperglycemic effect.

*Fibric Acid Derivatives*

Fibric acid compounds are the first-line therapy in patients who require pharmacologic treatment for low HDL-C associated with hypertriglyceridemia, and they are an alternative to niacin in patients with isolated low HDL-C. Fibrates belong to a class of synthetic peroxisome proliferator activated receptor (PPAR)-α activators. PPAR activators are direct or indirect ligand-activated nuclear transcription factors that regulate a wide range of genes, some of which induce synthesis of apo A-I and apo A-II. Fibric acid derivatives (eg, gemfibrozil, fenofibrate) generally increase HDL-C by less than 10% in patients with isolated low HDL-C but by 15% to 25% in patients who have low HDL-C combined with hypertriglyceridemia (Table 6).[83] These drugs are very effective in reducing TG levels by up to 60%, but they may also raise LDL-C.[74] However, this effect on LDL-C is minimal in the presence of significant hypertriglyceridemia. Slow-release fibrates (eg, fenofibrate) have been found to be more effective than gemfibrozil in raising HDL-C and are effective even in those patients who do not respond to gemfibrozil. The main advantage of fenofibrate, however, is the lower risk of drug interactions and myopathy when it is used in combination with statins. Finally, in patients with very low levels of HDL-C or patients who do not respond to a single-agent therapy, the combination of gemfibrozil and nicotinic acid has been shown to be more effective than each agent alone, raising HDL-C by as much as 45%.[84] Unfortunately, compared with other drugs, there is not enough evidence proving superior clinical event reduction from primary or secondary prevention studies,[85] and the incidence of side effects may be higher.

The Helsinki Heart Study (HHS) examined the benefit of using gemfibrozil 600 mg twice daily for primary CHD prevention in patients with non–HDL-C levels above 200 mg/dL. This study suggested that an 8% increase in HDL-C would be expected to result in a 23% reduction in major CHD events. It also showed a more prominent elevation in HDL-C in those patients at greatest CV risk. A subgroup analysis found that gemfibrozil was particularly effective in

preventing CHD in patients with high serum TGs plus either low HDL-C or a high LDL/HDL cholesterol ratio (> 5.0). In these patients, CHD events were reduced by 70% compared with 34% in the entire trial population.[86] Recently, the 18-year follow-up of the HHS was published, showing a significant mortality reduction in the subgroup with the most obese patients and the worst levels of TG and HDL-C.[87]

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) was a secondary prevention study that included 2531 patients with CHD who had an LDL-C of 140 mg/dL or less, an HDL-C of 40 mg/dL or less, and TGs of 300 mg/dL or less.[88] The patients were randomly assigned to treatment with gemfibrozil (1200 mg/d) or placebo. At 5 years, in the gemfibrozil group, HDL-C rose by 6%, and the combined primary endpoint (CHD and nonfatal MI) was modestly reduced compared with the group receiving placebo (17.3% vs 21.7%, with absolute and relative risk reductions of 4.4% and 22%; $P = .006$).[88] Further analysis showed that gemfibrozil was associated with reduction of primary endpoints in patients both with and without DM. (Among patients without diabetes, gemfibrozil was particularly effective in those with the highest fasting plasma insulin levels.[89]) Furthermore, another study suggested that the occurrence of CV events and the benefit of fibrate therapy was less dependent on levels of HDL-C or TGs than on the presence or absence of insulin resistance.[90]

Another secondary prevention study, the Bezafibrate Infarction Prevention Trial (BIP), evaluated patients with CHD and low HDL-C who were randomly treated with either bezafibrate (400 mg/d) or placebo. In the fibrate-treated group, TG levels decreased by 21% and HDL-C levels increased by 18%. However, after 6.2 years, the reduction in the cumulative probability of the primary endpoint (MI or sudden death) was not significantly different compared with placebo (7.3%; $P = .24$). But, in a post hoc analysis, patients in the bezafibrate group who had high baseline TGs (≥ 200 mg/dL) experienced a significant reduction in the cumulative probability of the primary endpoint (39.5%; $P = .02$).[91] Diabetic dyslipidemia (small and dense LDL-C, low HDL-C, and high TGs) can be treated with fibrates, and most available trials have suggested greater benefit in patients with DM or insulin resistance. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was designed to evaluate this hypothesis. This study assessed the effects of long-term treatment with fenofibrate (200 mg/d) on CHD morbidity and mortality in patients with type 2 DM and total cholesterol levels of less than 250 mg/dL, who were not taking statins.[92] Fenofibrate did not significantly reduce the risk of primary outcome of CHD, death, or nonfatal MI. However, further analysis showed that fenofibrate reduced the number of total CHD events, mainly due to fewer nonfatal MIs and revascularizations. During the 5 years of the study, more patients in the placebo group than in the fenofibrate group started using statins, which might have masked a more significant treatment benefit of fenofibrate. Certainly, after adjusting for the use of statins, fenofibrate therapy was associated with a statistically significant reduction in major CHD events.

Finally, in a recently published meta-analysis of all randomized controlled trials using monotherapy with either fibric acid or nicotinic acid derivatives, it was demonstrated that fibrates reduced major CHD events and increased HDL-C without significant toxicity. In contrast, niacin, despite a more potent effect on HDL-C levels, lacked data supporting its effect on CHD outcome reduction.[93]

*Statins*

Statins also have PPAR-α activator activity, which helps explain their beneficial effect on HDL-C.[94] However, statins are generally less effective in raising HDL-C than niacin or fibrates. They modestly increase HDL-C levels, by about 4% to 7%, independently of TG levels.[83] Starting doses of statins usually increase HDL-C by 5% to 7%. There is evidence that simvastatin at a high dose (40 to 80 mg/d) may be more effective than atorvastatin (20 to 40 mg/d) in raising concentrations of HDL-C (9.1% vs 6.8%; $P < .001$) and apo A-I (5.6% vs 2.6%; $P < .001$).[95] Among different statins, the greatest effect on HDL-C is achieved with rosuvastatin, which increases HDL-C by 10% to 15% (Table 6).[96] In a study comparing rosuvastatin and atorvastatin, increases of HDL-C were larger with rosuvastatin 5 mg (13%) and 10 mg (12%) than with atorvastatin (8%; $P < .01$ and $P < .05$, respectively).[97] In addition, a greater effect on LDL-C reduction was seen with rosuvastatin 5 mg (−40%) and 10 mg (−43%) than with atorvastatin 10 mg (−35%; $P < .01$ and $P < .001$, respectively).[97] Furthermore, apo A-I increments were also greater with rosuvastatin. TG reductions were similar.

*Combination Treatments*

Small but important studies, including HATS (niacin plus simvastatin) and ARBITER-2 (extended-release niacin plus a statin) have shown that combining niacin and statins is not only efficacious in normalizing lipid values but also in achieving better clinical outcomes than monotherapy

with statins alone. Furthermore, a recent randomized clinical trial of patients with angiographic evidence of coronary atherosclerosis and low HDL-C assessed the angiographic and clinical effects of dietary and lifestyle interventions to increase HDL-C along with an aggressive pharmacologic strategy (using gemfibrozil plus niacin and cholestyramine) or placebo. Compared to placebo, the combination regimen improved lipid profiles and showed a trend towards a reduction in angiographic progression of coronary atherosclerosis and major CV events. Pharmacologically treated patients experienced an increase in HDL-C of 36% (95% confidence interval [CI], 28.4%–43.5%), a decrease in LDL-C of 26% (95% CI, 19.1%–33.7%), and reduction in TGs of 50% (95% CI, 40.5%–59.2%). Focal coronary stenoses decreased by 0.8% in the treatment group and increased by 1.4% in the placebo group (difference, −2.2% [95% CI, −4.2% to −0.1%]). The incidence of the composite CHD event endpoint was 50% lower in the active treatment group compared with the placebo group (13% vs 26% [95% CI, 0.9%–26.5%]).[98]

## New and Investigational Treatments

The development of strategies to treat low HDL-C has been stimulated by several factors: the recognition of low HDL-C as an important contributor to CV risk, including in patients with CHD and controlled traditional risk factors; controversial data from different epidemiologic studies suggesting a clinical benefit of treating low HDL-C; and better understanding of the different processes involved in HDL metabolism. Some pharmacologic studies have failed to show that increased HDL-C levels correlate with improved clinical outcomes. This finding has led to the acknowledgment that functionality of HDL particles is critical and may not correlate with the serum HDL mass. Mechanisms are being developed to determine HDL's effectiveness in removing cholesterol from peripheral cells and to identify the nature of the anti-inflammatory, antioxidant, antithrombotic, and endothelial functions that promote beneficial effects.[99] Understanding of the importance of HDL's metabolism and insights into the mechanisms of operation have also facilitated the development of more focused therapies that target the different components of the reverse cholesterol transport system and enhance the antiatherogenic effect. Some of these therapies could improve HDL function without necessarily increasing HDL-C levels but by making the reverse cholesterol transport system more effective.

The therapeutic approach to raising HDL-C can target 1 or more mechanisms, including increased production of apo A-I, primarily by the liver and/or the intestine, and alteration of intravascular remodeling of HDL particles, by mechanisms such as inhibition of CETP. The new treatments that are being investigated can be divided into oral and intravenous agents (Table 7).

*Oral Agents*

**CETP inhibitors: torcetrapib and anacetrapib.** Understanding the role of CETP in HDL metabolism and identification of clinical implications of CETP gene mutations in certain populations have converted CETP into a pivotal target for the development of new treatments of atherosclerosis. CETP is a glycoprotein secreted by the liver that circulates mainly bound to HDL molecules. Its main role is to facilitate the transfer of cholesteryl esters from HDL to apo B–containing lipoproteins in exchange for TGs, theoretically enhancing the antiatherogenic effect of reverse cholesterol transport (Figure 11). However, by facilitating transfer of cholesteryl esters from HDL to VLDL and LDL, which brings them back to the liver, CETP also causes a reduction in the concentration of antiatherogenic HDL and increases the concentration of LDL-C.[100] This process makes HDL particles rich in TGs and susceptible to hydrolysis by hepatic TG lipases. The final products are small-dense HDLs, devoid of atheroprotective effect, and lipid-poor apo A-I particles that can be excreted by the kidneys. This process is important in metabolic diseases like type 2 DM and the metabolic syndrome, in which there is high CETP activity. On the other hand, CETP deficiency causes

Table 7
Novel Agents for Treatment of Low HDL-C

| Oral Agents | Intravenous Agents |
|---|---|
| CETP inhibitors: torcetrapib, anacetrapib | Apo A-I Milano |
| Niacin with DP1 receptor blocker (ER niacin/laropiprant) | Parenterally administered human HDL, apo A-I |
| Apo A-I mimetic peptides (D4F) | |

HDL-C, high-density lipoprotein cholesterol; CETP, cholesteryl ester transfer protein; Apo, apolipoprotein; ER, extended release.

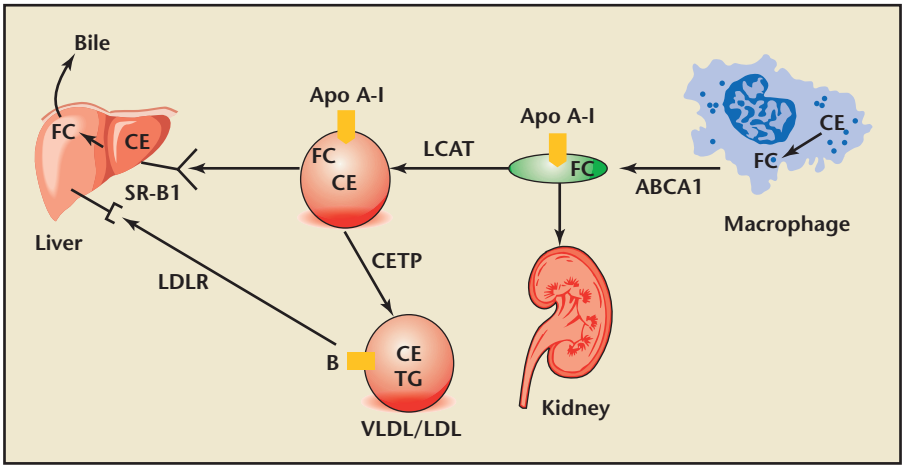



**Figure 11.** *CETP is secreted by the liver and circulates mainly bound to HDL molecules. It facilitates the transfer of CE from HDL to apo B–containing lipoproteins (ie, VLDL and LDL) in exchange for TGs. However, by facilitating this process, CETP also causes a reduction in the concentration of antiatherogenic HDL and increases the concentration of atherogenic LDL-C. This process makes HDL particles rich in TGs and susceptible to hydrolysis by hepatic TG lipases. The final products are small-dense HDLs, devoid of atheroprotective effect, and lipid-poor apo A-I particles that can be excreted by the kidneys. HDL, high-density lipoprotein; CETP, cholesteryl ester transfer protein; FC, free cholesterol; CE, cholesteryl ester; SR-B1, scavenger receptor B1; LDLR, low-density lipoprotein receptor; apo A-I, apolipoprotein A-I; TG, triglycerides; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; ABCA1, adenosine 5′-triphosphate–binding cassette transporter A1.*
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accumulation of cholesteryl esters in HDL, with increased amounts of apo A-I, phospholipids, nonesterified cholesterol, and large HDL particles.[101] The role of CETP in HDL metabolism is also highlighted by the discovery that genetic CETP deficiency is the main cause of high HDL-C levels in Asian populations.

CETP may have both pro- and anti-atherogenic properties depending on the lipid environment, the mechanism that caused the alteration of CETP levels, and the degree to which CETP activity is changed.[102] In humans, the first CETP inhibitor was shown to be capable of raising HDL-C by up to 100%.[103] However, this agent, torcetrapib, failed to reduce CHD events in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial (Figure 12).[104] The study was terminated prematurely due to increased mortality in the torcetrapib group. Torcetrapib increased HDL-C, apo A-I, and apo E levels, as well as HDL particle size. However, it was also believed to increase aldosterone levels, cause electrolyte abnormalities, and raise blood pressure, which may account for the excess in major CV events. It has also been hypothesized that CETP inhibition could stimulate production of nonfunctional HDL, according to the findings of 2 major trials that have failed to show significant effects of torcetrapib on coronary or carotid atherosclerosis.[105]

A newer CETP inhibitor, anacetrapib, is also being investigated. It increases HDL-C levels to a higher extent than torcetrapib—up to 129% with the highest dose of 300 mg/d. It also decreases LDL-C by up to 38% and raises apo A-I by 47%.[106] Anacetrapib has not been shown to change blood pressure. These findings indicate that those adverse effects seem to be specific to torcetrapib and cannot be attributed to a class effect.[107]

**Niacin with a DP1 receptor blocker (extended-release [ER] niacin/laropiprant).** In spite of all the beneficial effects of niacin on LDL-C, TGs, Lp(a), HDL-C, and apo A-I, its widespread use has been limited by flushing, its main side effect. Flushing is associated with cutaneous vasodilation of the face, neck, and

**Figure 12.** *Data from the ILLUMINATE trial shown in Kaplan-Meier curves for the primary composite outcome, which was the time to the first occurrence of a major cardiovascular event, a composite that included 4 components: death from coronary heart disease, nonfatal myocardial infarction (excluding procedure-related events), stroke, and hospitalization for unstable angina. These data show the between-group comparison of patients who had the primary composite outcome: 373 patients in the atorvastatin-only group and 464 patients in the torcetrapib group. The hazard ratio for the primary outcome was 1.25 in the torcetrapib group, as compared with the atorvastatin-only group (95% confidence interval, 1.09–1.44; P = .001). ILLUMINATE, Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events. Adapted with permission from Barter PJ et al.*[107]

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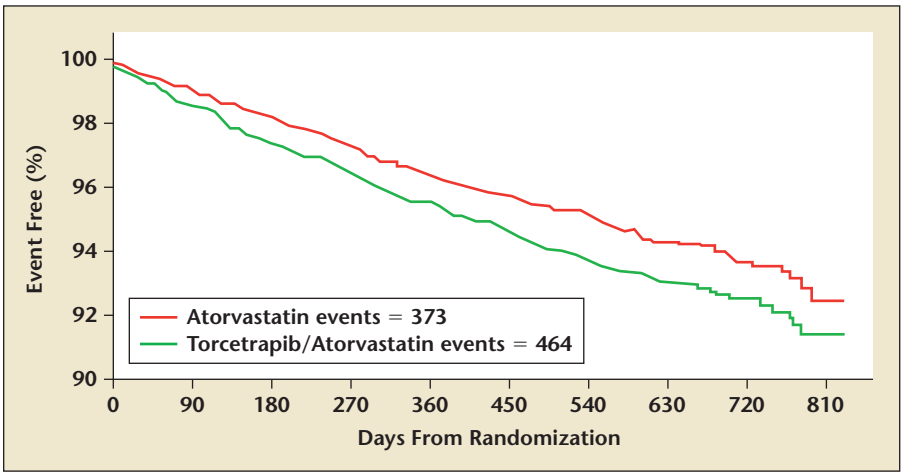

torso. It causes significant discomfort and is related to elevated levels of vasodilatory prostaglandin D2 (PGD2), whose major source is the skin. Flushing can be partially attenuated by pretreatment with high doses of aspirin and other cyclooxygenase inhibitors. However, because niacin is also associated with elevated levels of other prostanoids, further investigations have focused on potential involved receptors. One of the receptors for PGD2, receptor DP1, has been found to mediate niacin-induced vasodilation. Treatment with a DP1 antagonist has also been shown to partially reduce flushing.[80] Preliminary studies have been performed with a combination drug, ER niacin/laropiprant, formerly known as *MK-0524A*. Unfortunately, the positive results of the combination drug have been modest. Trials presented on March 31, 2008, at the annual Scientific Sessions of the American College of Cardiology showed that 78% of patients taking ER niacin alone had episodes of moderate to very severe flushing, compared with 53.3% of patients taking ER niacin/laropiprant. Twelve percent of those on niacin alone stopped taking the drug because of the side effect, compared with 7% of subjects on niacin/laropiprant. In many of the study subjects, aspirin therapy, which is utilized in most patients with CHD, seemed to prevent flushing almost as well as the combination therapy. Therefore, due to these findings and the lack of information about long-term effects, ER niacin/laropiprant received a "Not Approvable" action letter from the US Food and Drug Administration.

**Apo A-I mimetic peptides (eg, peptides synthesized from D-amino acids or D-4F).** Apo A-I is the main protein in HDL, and when it is forming part of lipid-poor particles, it becomes an important acceptor of cholesterol from macrophages. This process is mediated by the cellular transporter ABCA1. Apo A-I has been found to be an independent risk factor for CHD, and its levels seem to have a stronger inverse relationship to CHD than levels of HDL-C. Therefore, several approaches to increase apo A-I levels are being studied, including intravenous infusion of delipidated HDL (rich in lipid-poor apo A-I), apo A-I–like peptides, or a genetic variant of apo A-I; oral administration of apo A-I mimetic peptide; and upregulation of apo A-I gene expression. According to some animal studies, D-4F, a synthetic apo A-I mimetic peptide that can be administered orally, markedly reduced atherosclerosis in mice. These agents are being evaluated in humans, following demonstration of their anti-inflammatory and anti-atherosclerotic effects.[108] In mice, administration of D-4F did not raise HDL-C concentrations but promoted formation of pre-β HDL, increasing paraoxonase activity, which results in significant improvements in the HDL's anti-inflammatory properties and ability to promote cholesterol efflux from macrophages in vitro. Oral D-4F also promotes reverse cholesterol efflux from macrophages in vivo. These findings further confirm that the quality of HDL may be more important than the actual levels of HDL-C, and that apo A-I and apo A-I mimetic peptides appear to have significant therapeutic potential in atherosclerosis.[109] In systemic inflammatory states like acute coronary syndrome (ACS) or certain infections, HDL-C loses its anti-inflammatory properties and may even become pro-inflammatory.[105] It has been shown in mice models infected with influenza that in this inflammatory setting, the loss of the anti-inflammatory properties of HDL is associated with increased arterial macrophage traffic, and it can be prevented by administration of D-4F.[110,111] Apo A-I mimetic peptides, like D-4F, remove oxidation products from lipoproteins and cell membranes and help HDL return to its normal structure and function.

An important mechanism that may increase the production of apo A-I is the enhancement of apo A-I gene expression. New and more potent PPAR-α agonists, which have this effect, are being investigated. These agents seem to enhance the macrophage ABCA1 enzyme that facilitates the transfer of cholesterol to apo A-I.[26,112]

*Intravenous Agents*

**Apo A-I Milano.** Genetic variants of apo A-I have also been seen as potential therapeutic approaches to low HDL-C. Apo A-I Milano was discovered in a small population in northern Italy that has low HDL-C levels and low incidence of CHD. Animal studies have also shown that apo A-I Milano is associated with reduced atherosclerosis.[113] In addition, preclinical studies have demonstrated that intravenous infusions of recombinant apo A-I Milano inhibit progression and induce regression of atherosclerosis. In a clinical trial that enrolled 57 patients with ACS, administration of 5 weekly injections of synthetic HDL that contained recombinant apo A-I Milano complexed with phospholipids was associated with significant regression of coronary atherosclerosis as measured by intravascular ultrasound.[17] Furthermore, acute plaque regression after short-term administration of apo A-I Milano also seems to be associated with plaque stabilization. Production of large quantities of apo A-I Milano has proved to be difficult, and therefore larger trials have not been performed.

**Parenterally administered HDL and apo A-I.** Other therapies based on infusion of plasma-derived human HDL and apo A-I are being studied. These treatments have the potential to be useful in patients with ACS, as induction therapy, for rapid plaque stabilization and/or regression. However, evaluation of short-term infusions of reconstituted HDL, which contains delipidated apo A-I from human plasma combined with soybean phosphatidylcholine and that (chemically and biologically) resembles native HDL, has not been associated with any significant reduction in the volume of coronary lesions measured by intravascular ultrasound. Unpublished data also show controversial results regarding beneficial effects of human-derived HDL infusion.

**Other therapies.** Other promising therapies that are being evaluated include a vaccine that induces autoantibodies that specifically bind and inhibit the activity of endogenous CETP. In addition, endothelial lipase inhibitors hold the promise of inhibiting apo A-I catabolism and remodeling HDL particles.[114]

*Current Treatment Strategies*

Selection of optimal drug therapy for low HDL-C is determined in part by the presence or absence of other lipid abnormalities. Our recommendations are as follows:

1. The LDL-C goal should be reached before low HDL-C is treated. The goal can be achieved with a statin (simvastatin at a high dose of 40 to 80 mg/d or rosuvastatin seems to produce the largest effects on HDL-C) or with a statin/ezetimibe combination. If HDL-C remains low, it can be effectively treated with the addition of either nicotinic acid or fibrates. The combination of a statin with fenofibrate is suggested, given the lower risk of myopathy. In this situation, pravastatin or fluvastatin may be the statins of choice because they have fewer drug interactions and perhaps less intrinsic muscle toxicity than other statins (which are more lipophilic and undergo more metabolism by the cytochrome P450 3A4 system).[85,115] Statins can also be combined with niacin as shown in a recent meta-analysis,[93] given the low rates of significant drug interactions.[85,115]
2. In patients with goal or minimally elevated LDL-C levels, according to their Framingham risk score, low HDL-C along with hypertriglyceridemia (with or without elevated non–HDL-C level) may be corrected using monotherapy with fibrates or nicotinic acid. In this setting, nicotinic acid and fenofibrate usually lower LDL-C considerably better than gemfibrozil. If LDL-C levels are still minimally elevated after the hypertriglyceridemia is controlled, a statin can be added.
3. For patients with goal or minimally elevated LDL-C and isolated low HDL-C levels requiring pharmacologic treatment (but without any other lipid abnormality), nicotinic acid is the most effective therapy. And for those patients who cannot tolerate nicotinic acid, statin therapy can be considered in order to increase HDL-C and, in particular, to improve the LDL/DHL ratio.

## Conclusion

Substantial data support the importance of considering HDL-C as a major CV risk factor and primary target for therapy. Nonpharmacologic approaches (especially weight loss and aerobic exercise) and pharmacologic agents (niacin, fibrates, and statins) that increase levels of HDL-C or enhance the effects of the reverse

### Main Points

- Low high-density lipoprotein cholesterol (HDL-C) may be even more strongly related to coronary heart disease (CHD) events than high low-density lipoprotein cholesterol (LDL-C): for every increase in HDL-C of 1 mg/dL, the risk of major CHD events decreases by 2% to 3%, and the risk of CHD mortality decreases by 4% to 5%.
- There is evidence that low HDL-C increases the risk of CHD independently of other lipid abnormalities, but in many cases the association of low HDL-C with CHD may not be entirely explained by impairment of the reverse cholesterol transport system.
- Increased exercise and fitness combined with weight reduction can raise HDL-C and may improve its function.
- To raise HDL-C levels, available drugs include fibric acid and nicotinic acid derivatives, statins, estrogens, and the combination of an LDL-lowering drug with either a fibrate or a nicotinic acid derivative. These agents are commonly used despite their modest effect on HDL-C levels.
- Understanding of the importance of HDL's metabolism and insights into the mechanisms of operation have facilitated the development of more focused therapies that target the different components of the reverse cholesterol transport system and enhance the antiatherogenic effect.

cholesterol transport system should routinely be considered for most at-risk patients to prevent development, slow progression, or even promote regression of atherosclerotic lesions. New therapies that directly or indirectly enhance the effects of the reverse cholesterol transport system are being developed and appear promising, with the potential to change the natural history of atherosclerosis and bring the risk of future CHD events to minimally acceptable levels. ■

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