Low High-Density Lipoprotein Cholesterol as a Risk Factor in Coronary Heart Disease
A Working Group Report

Antonio M. Gotto, Jr, MD, DPhil

A working group meeting was convened from January 7 to 8, 2000, in Naples, Florida, to assess low HDL cholesterol (HDL-C) concentration as a risk factor for coronary heart disease (CHD). The 30 speakers and discussants at this 2-day meeting included specialists in epidemiology, endocrinology, molecular biology, public health, lipid metabolism, cardiovascular medicine, and preventive cardiology from the United States, Europe, and Australia (Appendix). The group’s wide-ranging presentations and discussions considered the latest knowledge on HDL metabolism and the effects of interventions for raising HDL-C levels on the development of atherosclerosis. It was generally accepted that low HDL-C may be a marker for the metabolic syndrome, an enhanced atherosclerotic disease state that is also associated with an impaired response to insulin, hypertriglyceridemia, and abdominal obesity. Therefore, beyond risk assessment based on LDL cholesterol (LDL-C) alone, the case has been made for considering HDL-C in tandem with triglycerides (TG) as synergistic coronary risk factors.1 The following article summarizes the participants’ discussion of low HDL-C as an independent CHD risk factor and identifies areas requiring further research.

Influence of Genetic Factors and Environment on the Atherogenicity of Low HDL-C

Although population studies indicate that a high level of HDL-C in general protects against CHD,2,3 a high HDL-C concentration in any given individual may not necessarily confer cardioprotection. The atherogenicity of low HDL-C seems to be influenced by an array of genetic and environmental factors.

Tangier disease, a disorder caused by mutations in the ATP-binding cassette transporter 1 (ABCI) gene,4 is characterized by the absence of normal HDL, with only a very small quantity of abnormal HDL present. However, early atherosclerosis (before 40 years) is not a consistent feature of this disorder.5 In men of Japanese ancestry in Hawaii, mutations in the gene for plasma cholesteryl ester transfer protein (CETP), which transfers cholesteryl ester from HDL to TG-rich lipoproteins, have been shown to result in elevated HDL-C levels.6 However, subjects carrying heterozygous CETP gene mutations had a moderately increased CHD risk, despite higher HDL-C levels. Elevated HDL-C caused by a common mutation in the CETP gene also increases the risk of ischemic heart disease in Danish women.7 This and other evidence indicates that both genetic and environmental factors influence the atherogenicity of low HDL-C and that an increase in HDL-C due to impaired CETP activity may be atherogenic.

New Insights Into HDL Metabolism

The HDL lipid-protein complex comprises 2 major subclasses in terms of density: the HDL2 particle is larger and less dense, whereas the HDL3 particle is smaller and more dense.8 In addition, HDL2 is richer in particles that contain apoA-I without apoA-II, whereas HDL3 is richer in particles that contain both apoA-I and apoA-II.9 Recent work suggests that the cardioprotective properties of HDL-C particles may be altered by their size and apolipoprotein composition.10 There is some controversy regarding whether this antiatherogenic effect is primarily associated with the A-I subclass alone or with the A-I/A-II subclass. In CHD patients, both types of particles seem to be reduced compared with controls.

The cardioprotective effect of HDL has been largely attributed to its role in reverse cholesterol transport (RCT), in which cholesterol that has been synthesized or deposited in peripheral tissues is returned to the liver (Figure). Analysis of various genetic causes of low HDL-C has provided insights into the multiple mechanisms involved in RCT and the relationships of these mechanisms to CHD risk.

ABCI has been identified by inference as the major apoA-I-mediated pathway for the efflux of cellular cholesterol.10 Mutations in the ABCI gene result in defective lipidation of pre-β-HDL, rapid catabolism of this poorly lipidated HDL, and low plasma HDL levels.

The cholesterol-esterifying enzyme lecithin:cholesterol acyltransferase (LCAT) plays a key role in the metabolism of HDL and cholesterol. Although both complete and partial
LCAT deficiencies markedly reduce HDL-C (to <10 mg/dL [<0.3 mmol/L]) and apoA-I concentrations, neither is commonly associated with premature CHD.

Several genetic causes of high HDL-C concentrations have been reported, including defects in the genes for CETP and hepatic lipase and polymorphism of lipoprotein lipase. CETP facilitates the transfer of cholesteryl esters among lipoproteins, and genetic CETP deficiency leads to delayed catabolism of both cholesteryl ester and apoA-I, resulting in marked increases in HDL-C and apoA-I concentrations.

Despite the expected protective effects of these elevations, evidence suggests that impaired cholesterol transport resulting from genetic CETP deficiency may be associated with an increased risk of premature CHD.

Another important component of the RCT process is phospholipid transfer protein (PLTP). PLTP facilitates the transfer of phospholipids between lipoproteins and induces HDL conversion, which remodels the homogeneous HDL fraction into populations of large and small particles similar to pre-β-HDL particles, the initial acceptors of membrane cholesterol.

By producing initial cholesterol acceptors, PLTP increases the capacity of the RCT process. Investigations in PLTP knockout mice have indicated that the transfer of phospholipids to HDL may play an essential role in HDL maturation and that when this process is absent, particles are catabolized at an increased rate. Therefore, it seems that 2 steps may be involved in HDL formation. The first involves catalyzation by ABC1 acting on apoA-I to form pre-β-HDL particles, and the second involves catalyzation by PLTP and LCAT acting on pre-β HDL to produce mature HDL.

Hepatic lipase, another key enzyme involved in HDL metabolism, is localized mainly to hepatocytes of the hepatic sinusoids, where it hydrolyses TG and the phospholipid of HDL, causing a reduction in HDL particle size. This in turn leads to an increase in HDL catabolism and the lowering of HDL levels.

In mice and rats, the scavenger receptor, class B, type I (SR-BI) has a role in determining plasma HDL-C and biliary cholesterol levels, in mediating the delivery of HDL-C to the liver and to steroidogenic tissues, and in maintaining oocyte development and female fertility. This cellular receptor may perform similar functions in humans. Hepatic overexpression of SR-BI has been shown to decrease atherosclerosis significantly in mice, suggesting that interventions that promote HDL-C transport and thus promote HDL-C turnover may suppress atherosclerosis. Such an effect would be associated paradoxically with a decrease in HDL-C due to enhanced clearance.

Other mechanisms besides RCT, such as inhibition of LDL oxidation (possibly mediated by paraoxonase) and stabilization of prostacyclin production, may also account for the cardioprotective effects of HDL. Although evidence indicates that paraoxonase, an HDL-associated, calcium-dependent enzyme, may be responsible for the antioxidant activity of HDL, antioxidant effects of HDL have also been observed under calcium-free conditions, suggesting that paraoxonase may not be the only mechanism by which HDL can inhibit LDL oxidation. HDL also seems to stabilize the production of prostacyclin by macrovascular endothelial cells in vitro, which may have some influence on vascular function in disease states such as atherosclerosis.

What Is the Optimal Strategy for Treating Patients With Low HDL-C?

Nonpharmacological Interventions for Raising HDL-C

The National Cholesterol Education Program (NCEP) guidelines emphasize lifestyle modifications (eg, exercise, moderate alcohol use, smoking cessation, and monounsaturated fat in the diet) as first-line therapy for low HDL-C. Moderate- and high-intensity cycle ergometer training has been shown to increase HDL2 levels significantly in hypercholesterolemic men, and moderate-intensity aerobic exercise significantly increased HDL2 levels in healthy women.

Recommendations to include alcohol consumption in a lifestyle program are controversial given the risks of overconsumption and abuse. Furthermore, no data from prospective, randomized, clinical trials have associated reductions in atherosclerotic events with alcohol consumption.

Many patients will not substantially increase their HDL-C levels or lower their LDL-C levels with nonpharmacological treatment alone.

Pharmacological Therapy in Patients With Low HDL-C

Four classes of lipid-lowering drugs are currently available for clinical use: bile acid sequestrants (resins), nicotinic acid (niacin), fibric acid derivatives (fibrates), and 3-hydroxy 3-methyl glutaryl coenzyme A reductase inhibitors (statins). The resins have only a marginal effect on HDL-C and will not be discussed here.

Niacin

Niacin is efficacious for raising HDL-C concentrations and for lowering TGs and LDL-C. However, no large, randomized, clinical trials have evaluated the use of niacin in the treatment of isolated low HDL-C. Dose-dependent hepatotoxicity occurs more often with sustained-release niacin preparations than with regular (crystalline) niacin, but a new intermediate-release form of niacin seems to be as safe as the regular form.
HDL-C concentrations

Nary Atherosclerosis Study involving fluvastatin, the greatest

patients with low HDL-C. In the small Lipoprotein and Coron-

Two recent reports provide information about statin therapy in

Statins

bezafibrate, however, significantly reduced ($P=0.002$), unstable angina ($P=0.32$), and revascularization ($P=0.001$). The greatest relative risk reduction with lovastatin was observed among participants in the lower 2 tertiles of baseline HDL-C, reinforcing the significance of low HDL-C in this cohort.

Estrogen

The Heart and Estrogen/Progestin Replacement Study, the first prospective investigation of hormone replacement for CHD prevention, has raised serious concerns about the use of such treatment. More than 2700 postmenopausal women with established CHD received either 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily or a placebo for an average follow-up period of 4.1 years. Primary CHD events occurred in 172 women (12%) in the group treated with hormone replacement therapy (33.1/1000 women per year) compared with 176 women (13%) in the placebo-treated group (33.6/1000 women per year; relative hazard, 0.99). The log rank $P$ value for primary CHD events was 0.91. Thus, in this population of postmenopausal women with established CHD (and an average age of 67 years), daily estrogen plus progestin did not reduce the incidence of primary CHD events compared with placebo. Moreover, in addition to providing no overall cardiovascular benefit, hormone replacement therapy increased the risk of venous thromboembolic events and gall bladder disease.

Implications for Therapy

When HDL-C is low, LDL-C is moderately elevated, and other CHD risk factors are present, the statins seem to be the agents of choice. Statins act primarily by reducing LDL-C, but they also have moderate effects on HDL-C. These agents are well tolerated, with adverse side effects that include elevated liver enzyme levels, dyspepsia, and myopathy. Statins have shown the most consistent benefits in patients with low HDL-C levels and average LDL-C levels (eg, AFCAPS/TexCAPS), as well as in post hoc subgroups of patients with low HDL-C and high LDL-C in the Scandinavian Simvastatin Survival Study and the West of Scotland Coronary Prevention Study. A statin may be used to achieve an LDL-C target $\leq 100$ mg/dL ($\leq 2.6$ mmol/L) and, if the HDL-C level remains low (with or without an elevated TG level), then niacin or a fibrate may be considered as adjunc-
tive therapy, taking into account the risks of combination therapy.

The HDL Atherosclerosis Treatment Study is currently evaluating lipid responses to simvastatin plus niacin in 160 subjects with CHD and low HDL-C levels (≥35 mg/dL [≥1 mmol/L] in men and ≥40 mg/dL [≥1 mmol/L] in women). In a 16-month interim analysis of 70 subjects, total cholesterol decreased by 35% (from 200 to 131 mg/dL [5.2 to 3.4 mmol/L]), LDL-C decreased by 45% (from 131 to 72 mg/dL [3.4 to 1.9 mmol/L]), HDL-C increased by 35% (from 31 to 42 mg/dL [0.8 to 1.1 mmol/L]), and TG decreased by 29% (from 210 to 150 mg/dL [2.4 to 1.7 mmol/L]) (B.G. Brown, MD, PhD, personal communication, 2000). The increase in HDL-C was almost entirely due to an increase in apoA-I and cholesterol in the apoA-I–only particle.

It is important to consider that no pharmacological intervention trial has specifically targeted HDL-C without yielding improvements in other lipid parameters associated with CHD risk. Therefore, it is difficult to determine how much of the clinical benefit, if any, in these trials is the result of HDL-C modification and how much may be attributed to other lipid and lipoprotein changes. Although both pharmacological and nonpharmacological therapies will raise HDL-C levels, their potential effects on CHD prevention may differ substantially. The biological effects and activities of HDL particles may vary according to the specific intervention applied, and each therapeutic approach, while increasing HDL-C, may have differing metabolic effects on, for example, CETP, ABC1, LCAT, SR-BI, and hepatic lipase.

**Threshold and Target for HDL-C Levels**

According to the NCEP guidelines, the decision to initiate treatment to raise HDL-C levels in patients without CHD should be based on the baseline LDL-C value and the number of CHD risk factors present. It is interesting to note that only 17% of the participants in AFCAPS/TexCAPS would have met NCEP criteria for consideration for drug therapy. The results of AFCAPS/TexCAPS may have important implications for the identification of individuals at risk of CHD, as well as for what the goals of treating such individuals should be. The use of below-average HDL-C (≤50 mg/dL [≤1.3 mmol/L]) as an entry criterion in AFCAPS/TexCAPS underscores its use as an important modifier of risk in CHD risk assessment, especially in individuals whose borderline LDL-C values (130 to 159 mg/dL [3.4 to 4.1 mmol/L]) do not necessarily suggest high risk.

The NCEP’s emphasis on LDL-C as the principal determinant of treatment intensity may discount the risk associated with low HDL-C and other major CHD risk factors, such as obesity, smoking, and diabetes. Harper and Jacobson have argued for increased use of multifactorial risk models, such as the Framingham risk-prediction chart, in the clinical setting to better identify individuals with isolated low HDL-C who may benefit from treatment.

Thus, low HDL-C as a risk factor for CHD should not be considered in isolation. The many established risk factors must be included in clinical decision-making for individual patients. Those with “low” HDL-C (<35 mg/dL, [<1 mmol/L], according to current NCEP guidelines) but without elevated LDL-C may not require HDL-C-raising therapy in the absence of concomitant risk factors. Furthermore, the ratio of LDL-C to HDL-C may be a more clinically relevant measurement than HDL-C alone, although there is some controversy regarding its use. Because a “target” HDL-C value has not been identified, it may be appropriate to match patients to populations enrolled in published clinical studies and to treat them accordingly.

**Conclusions**

Recent research has greatly expanded our knowledge of the complex genetic and molecular mechanisms involved in HDL-C metabolism. As the mechanisms involved in this process are further elucidated, investigators will be able to identify new targets for antiatherogenic treatments (Table). Increasing the expression of the ABC1 gene, for example, may offer the potential for raising HDL-C levels by enhancing both cholesterol efflux and plasma apoA-I. Elevating HDL-C levels by increasing the synthesis of apoA-I or by decreasing its metabolism also seems to hold promise, as does inhibiting hepatic lipase, which may decrease apoA-I catabolism without affecting HDL catabolism of cholesteryl ester.

On the basis of the available clinical data, CHD-free individuals with low HDL-C and ≥2 other risk factors and diabetic individuals with LDL-C ≥130 mg/dL (≥3.36 mmol/L) should be considered for LDL-C–lowering therapy. In these patients, the statins seem to be the agents of choice. For secondary prevention in patients with low HDL-C, statin or fibrate treatment may be used, with the fibrate being reserved for patients without concomitant LDL-C elevation.

HDL-C is an important modifier of CHD risk, but the goals of treating patients with low HDL-C have not yet been firmly established. When considering the potential benefits of raising plasma HDL-C with diet or drugs, clinicians must be aware of the complicated processes involved in lipid metabolism, the effects of such interventions on specific genes and metabolic pathways, and the importance of modifying concomitant risk factors.

**Appendix**

Dr Gotto chaired the Working Group Meeting “Assessing HDL as a Risk Factor in Coronary Heart Disease.” Guest speakers were Gerd Assmann, MD, Münster, Germany; Philip J. Barter, MD, PhD, Adelaide, Australia; Thomas P. Bersot, MD, PhD, San Francisco, California; H. Bryan Brewer, Jr, MD, Bethesda, Maryland; Eliot A.
Brinton, MD, Phoenix, Arizona; B. Greg Brown, MD, PhD, Seattle, Washington; John R. Crouse III, MD, Winston-Salem, North Carolina; Christian Ehnholm, MD, Helsinki, Finland; Jean-Charles Fruchart, MD, Lille, France; Steven M. Haffner, MD, MPH, San Antonio, Texas; Monty Krieger, PhD, Cambridge, Massachusetts; Hanna B. Rubins, MD, MPH, Minneapolis, Minnesota; Silvia Santamaria-Fojo, MD, PhD, Bethesda, Maryland; Ernst J. Schaefer, MD, Boston, Massachusetts; James Shephard, MD, Glasgow, United Kingdom; and Alan R. Tall, MD, New York, New York. Other participants were Luther T. Clark, MD, Brooklyn, New York; Michael Clearfield, DO, Fort Worth, Texas; Margo A. Denke, MD, Dallas, Texas; Robert H. Eckel, MD, Denver, Colorado; Kenneth R. Feingold, MD, San Francisco, California; Henry Ginsberg, MD, New York, New York; Ronald B. Goldberg, MD, Miami, Florida; William James Howard, MD, Washington, DC; D. Roger Illingworth, MD, PhD, Portland, Oregon; John C. LaRosa, MD, Brooklyn, New York; Maria L. F. Lopez-Virella, MD, Charleston, South Carolina; Trevor J. Orchard, MD, Pittsburgh, Pennsylvania; Daniel J. Rader, MD, Philadelphia, Pennsylvania; William Roberts, MD, Dallas, Texas; and Francine K. Welty, MD, PhD, Boston, Massachusetts.

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