A low serum high-density lipoprotein cholesterol (HDL-C) level is a potent predictor of premature coronary heart disease (CHD). It has been estimated that 11% of US men have isolated low HDL-C levels, and there is uncertainty regarding the management of these patients. A cause-and-effect relationship between low HDL-C levels and CHD is supported by epidemiological, animal, and human clinical studies. We reviewed the structure and function of HDL-C and its role in preventing atherosclerosis. We then suggested an approach to the patient with isolated low HDL-C that may be useful to the primary care physician. An algorithm was proposed for use in patients with existing CHD, while the decision to treat patients without CHD was based on their score on the Framingham Heart Study risk prediction chart.

**EPIDEMIOLOGY**

Although there is strong epidemiological evidence that HDL-C protects against CHD, a cause-and-effect relationship has not been proven. The Framingham Heart Study was one of the first epidemiological studies to show the relationship between CHD and low HDL-C levels (Figure 1). Of note, a low LDL-C level did not completely remove the risk imparted by a low HDL-C level, while a high HDL-C level seemed to offset some of the risk of a high LDL-C level. Finally, an aggregate analysis of 4 of the largest US epidemiological studies (Framingham Heart Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Lipid Research Clinics Primary Prevention Trial, and Multiple Risk Factor Intervention Trial) suggested that for each 1-mg/dL (0.02-mmol/L) increase in HDL-C, a 2% decrease in CHD risk in men and a 3% decrease in women may occur.

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PREVALENCE OF LOW HDL-C LEVELS

A review of the National Health and Nutrition Examination Survey III data, a population-based survey of noninstitutionalized US adults, revealed that 11% of US men older than 20 years have ILHDL-C. In Canada, the Quebec Cardiovascular Study, which measured lipoprotein levels in more than 2000 men free of CHD, also found a similar frequency of ILHDL-C in 13% of adult men. When examining higher-risk populations, such as men with CHD, the incidence of patients with ILHDL-C is much greater. The prevalence of ILHDL-C in CHD populations has been found to range from 17% to 36%.

ANIMAL STUDIES

In addition to epidemiological evidence, rodent studies suggest raising HDL-C levels may inhibit atherosclerosis. Mice that are genetically manipulated to overproduce HDL-C apolipoprotein A-I were protected against diet-induced atherosclerosis. In a second experiment, a different strain of mice with premature atherosclerosis were genetically altered to express the "human" HDL-C apolipoprotein A-I gene. These mice had a marked decrease in the development of atherosclerosis. Finally, in another animal model, rabbits intravenously infused with HDL-C exhibited regression of atherosclerotic lesions. Although animal models provide presumptive evidence that genetically altering HDL-C may be useful in slowing atherosclerosis, they do not necessarily generalize to humans or replace the need for human interventional trials.

INTERVENTIONAL TRIAL EVIDENCE

In addition to the data in animal studies, there is clinical trial evidence in humans that therapy directed at raising HDL-C levels may decrease CHD risk. The Helsinki Heart Study was a randomized, placebo-controlled primary prevention trial using gemfibrozil therapy in more than 4000 high-risk men with dyslipidemia. The treatment group received gemfibrozil, 600 mg twice daily. During a 5-year interval, the intervention group demonstrated a decrease in LDL-C and triglyceride levels by 11% and 35%, respectively, while the HDL-C levels increased by 11%. Although this was a primary prevention study designed to reduce CHD risk in men with high LDL-C levels, the study demonstrated that for every 1-mg/dL (0.02-mmol/L) increase in HDL-C, there was a 2% to 3% decrease in CHD risk, independent of changes in LDL-C level. These numbers are based on a post hoc subgroup analysis, since the Helsinki Heart Study was not specifically designed to look at therapy directed toward raising HDL-C levels. Fibrates may have other beneficial effects besides raising HDL-C levels, such as reducing atherogenic remnants of triglyceride-rich lipoproteins or changing LDL-C particle size. It was shown, however, that patients with low HDL-C levels and high LDL-C levels had significantly greater risk reduction than any other subset.

HDL-C BIOCHEMISTRY AND Atherosclerosis

The HDL-C subfractions are small, dense, spherical lipid-protein complexes synthesized in the liver and small intestine. The lipids that make up this complex include phospholipid, cholesterol, cholesterol esters, and triglycerides. The proteins are apoproteins A-I, A-II, E, and C. The HDL-C lipid protein complex is built around a hydrophobic core that contains cholesterol ester and triglycerides. The surface is hydrophilic and consists of phospholipids, unesterified cholesterol, and apolipoproteins.
There are 3 events that are key to the formation of early atherosclerotic lesions. The first is infiltration of native LDL-C particles through the endothelium into the intimal layer of the arterial wall. It is thought that these LDL-C particles are then oxidized. Macrophages in the intima can ingest a limited number of native LDL-C particles. Once LDL-C is oxidized, however, macrophage uptake is increased and leads to foam cell formation. Foam cells are a major component of the early atherosclerotic lesion. The factors that result in the proliferation of monocytes and macrophages include hypothyroidism, diabetes, uremia, and liver disease. Elevated triglyceride level is one of the leading causes of depressed HDL-C levels, and thus a fasting lipid profile, a thyroid-stimulating hormone level, blood glucose level, creatinine level, and liver enzyme levels are necessary to first rule out these secondary causes. In addition, certain commonly prescribed drugs also may lower HDL-C levels. Diuretics, progestins, androgens, and β-adrenergic blocking agents without intrinsic sympathomimetic activity are commonly prescribed drugs that decrease HDL-C levels. However, the use of these drugs may have other benefits that outweigh their risk of lowering HDL-C levels. The contribution of other dyslipoproteinemias that result in low HDL-C levels. Most of these genetic disorders are quite uncommon and are not always associated with premature atherosclerosis in affected families.

NONPHARMACOLOGIC THERAPY

Numerous studies have documented the value of lifestyle modification in improving HDL-C levels. The patient’s weight, diet, exercise habits, and use of cigarettes should be addressed. Weight loss in obese men has been found to increase HDL-C levels. This is clearly depicted in a Dutch study of 315 men followed up for 10 years. The data from this study revealed that HDL-C...
levels increased 0.8 mg/dL (0.02 mmol/L) for every unit decrease in body mass index (a measure of weight in kilograms divided by the square of height in meters). The Framingham Offspring Study demonstrated a similar relationship. These studies indicate even modest weight loss can have a significant impact on HDL-C levels. The most important consideration in diet is energy (caloric) restriction with subsequent weight loss. Also, certain types of fats, called trans fatty acids, have been shown to lower HDL-C levels, whereas monounsaturated fats are thought to have a neutral effect on HDL-C. In recommending a diet to a patient with IHLDL-C not only should the total energy be restricted if the patient is overweight but so should the consumption of energy-dense saturated and polyunsaturated fats. Saturated fats and trans fatty acids may be substituted with unhydrogenated monounsaturated fats, such as olive oil or canola oil. These recommendations are based on studies that show that saturated fat raises LDL-C levels, whereas trans fatty acids lower HDL-C levels. Although some studies have shown that low-fat diets may lower HDL-C levels, total fat reduction is still thought to be overwhelmingly cardioprotective through mechanisms involving the lowering of LDL-C and its oxidation as well as possible effects on thrombosis.

Exercise in sedentary men increases HDL-C levels, but there is a threshold effect. It appears that moderate exercise is needed to result in a significant increase of HDL-C levels. Joggers who ran 16 km per week for 10 months showed a 10% increase in HDL-C levels. Exercise might not have as large an impact on HDL-C in women. Although a mechanism of HDL-C modulation has been proposed, it is still difficult to ascertain how much of the HDL-C response to exercise is derived from weight loss.

In addition to diet and exercise, cigarette and alcohol use significantly affect HDL-C levels. Cigarette smoking has a "dose-dependent" negative effect on HDL-C even with consumption of less than 1 pack per day. After adjusting for other variables, including alcohol intake, cigarette smoking caused a 5- to 9-mg/dL (0.13- to 0.23-mmol/L) reduction in HDL-C when compared with matched controls. Moderate use of alcohol can increase HDL-C levels. Multiple epidemiological studies have demonstrated that CHD is lower in moderate daily drinkers. Fifty percent of the cardioprotective effect of alcohol may be attributed to HDL-C. Other contributors to alcohol's cardioprotective effect include LDL-C lowering, inhibition of platelet aggregation, decrease in fibrinogen, and enhancement of prostacyclin formation. It appears that men who consume 1 drink per day (12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor) or less do not experience an increase in HDL-C level. Women, however, can consume 1 drink per day or less and still experience an increase in HDL-C level.

**PHARMACOLOGIC THERAPY**

Many patients will not achieve an adequate HDL-C level with nonpharmacologic therapy. There are several classes of drugs available for physicians to use in patients who do not respond to nonpharmacologic therapy. These classes include niacin, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, fibric acids, and estrogens.

**Niacin**

Niacin is the most efficacious drug for raising HDL-C levels. Its mechanism of action is not completely understood, but it is thought that niacin decreases hepatic production of very low-density lipoprotein levels and leads to an increase in HDL-C levels. Significantly lower doses of niacin are required to raise HDL-C levels than those required to lower LDL-C levels. Studies have shown that an increase in HDL-C of greater than 20% can be expected from doses of 1000 to 1500 mg/d. At higher doses niacin has been shown to lower triglyceride, LDL-C, and lipoprotein(a) levels. Full-dose niacin has been shown to decrease LDL-C levels 10% to 25%, increase HDL-C levels 15% to 35%, and decrease triglyceride levels 20% to 50%.

The crystalline niacin is less expensive and appears to be more effective at increasing HDL-C levels than the sustained-release niacin. Sustained-release niacin is better tolerated and more effective at lowering LDL-C levels. An increased frequency of hepatotoxicity has been reported with sustained-release preparations. Niacin can be purchased at health food stores without a prescription, and there can be great variation in the quality of the preparations. Once a patient’s dose and lipid level have been maintained, the patient should be instructed to avoid changing brands. Once-a-day, prescription-based niacin preparations (Niaspan; KOS Pharmaceuticals) have recently been approved by the Food and Drug Administration and may improve patient tolerance and lower the number of adverse effects.

Although niacin has a desirable effect on several lipoprotein subfractions, it has several unpleasant but benign side effects. In the Coronary Drug Project, 1119 men were randomized to 3 g/d of niacin or placebo, and there was a 66% adherence rate at the end of 5 years. Flushing and vasomotor symptoms were common and the most frequent reason for discontinuance. Gastrointestinal complaints include dyspepsia, nausea, abdominal pain, and activation of peptic ulcer. Niacin can result in dose-dependent hyperuricemia and hyperglycemia and should be used with greater caution or not at all in patients with uncontrolled diabetes, gout, or peptic ulcer disease. Dose-dependent hepatotoxicity has occurred but is more common with sustained-release preparations. Less common adverse effects include acanthosis nigricans and retinal edema. These adverse effects are less severe and less common at doses needed to increase HDL-C.

Crystalline niacin can be given 3 to 4 times per day. Patients can take 325 mg of enteric-coated aspirin 30 minutes before the morning dose to reduce the prostaglandin-mediated flushing. Patients can begin treatment with 100 mg of niacin 3 times daily. The dose can be increased to 200 mg 3 times daily after 1 week and then increased by 100 mg.
mg weekly until a daily dose of 1500 mg (500 mg 3 times daily) is reached. The patient's HDL-C level should be measured after 1 month at the 1500-mg dose and then increased slowly if needed. Niacin should be taken with food to reduce dyspepsia or nausea. Serum transaminase levels should be measured before treatment and then every 3 months during the first year. Niacin is absolutely contraindicated in patients with chronic active liver disease. There are no large randomized clinical event trials that have examined the use of niacin in the treatment of ILHDL-C. The Coronary Drug Project, however, which used niacin in 1119 men with moderate hyperlipidemia after myocardial infarction, showed a 27% reduction in nonfatal myocardial infarction at the end of 5 years and a total mortality reduction of 11% at the end of 15 years.

Fibrates

Gemfibrozil, 600 mg twice a day, increases HDL-C levels by an average of 11%. This drug is generally well tolerated; however, reported adverse effects include cholesterol gallstones, myopathy, liver enzyme elevations, dyspepsia, and leukopenia. There is increasing angiographic evidence that the fibrates may play a role in secondary prevention in patients with ILHDL-C. The Bezafibrate Coronary Atherosclerosis Intervention Trial study involved young survivors of myocardial infarctions with low HDL-C levels randomized to either bezafibrate or placebo. Ninety-two patients were followed up for 5 years. Treatment reduced triglyceride levels by 36% and increased HDL-C levels by 9%, whereas LDL-C levels did not change significantly. In addition to treatment that reduced triglyceride levels and increased HDL-C levels, there was a significant reduction in fibrinogen and remnant lipoproteins as well, which may account for the slowing of the atherosclerotic disease process. Treatment with bezafibrate not only slowed the progression of atherosclerosis, but also reduced coronary events. The Lipid Coronary Angiography Trial, a Finnish angiographic study, examined 372 patients after coronary artery bypass graft surgery who had ILHDL-C. Treatment with gemfibrozil decreased progression of CHD in native vessels and decreased graft lesions after an average of 32 months of therapy. VLDL triglyceride levels decreased by 40%, HDL-C levels increased by 15%, and LDL-C levels decreased by 10%. Although these angiographic trials have suggested some benefit for patients with CHD and ILHDL-C, the long-term follow-up of the secondary prevention component of the Helsinki Heart Study did not show clinical CHD event reduction with gemfibrozil. In addition, long-term follow-up of the primary prevention component of the Helsinki Heart Study showed that all-cause mortality was 20% higher in the gemfibrozil group when compared with placebo. This finding raises questions about the role of fibrates in CHD prevention.

Two new trials using fibrates in patients with CHD and ILHDL-C will report their results in the next year. In the Veterans Affairs HDL-C Intervention Trial (VA HIT), 2500 men with CHD and HDL-C levels less than 40 mg/dL (1.03 mmol/L), LDL-C levels less than 140 mg/dL (3.62 mmol/L), and triglyceride levels less than 300 mg/dL (3.39 mmol/L) were recruited from 20 Veterans Affairs medical centers. These men were randomized to either gemfibrozil or placebo. The Bezafibrate Infarction Prevention Trial examined 3000 patients after myocardial infarction from 19 cardiac departments in Israel who had HDL-C levels less than 45 mg/dL (1.16 mmol/L), triglyceride levels less than 300 mg/dL (3.39 mmol/L), and LDL-C levels less than 180 mg/dL (4.65 mmol/L). The subjects were randomized to bezafibrate, 400 mg/d, or placebo, and will be followed up for 5 years. A new more potent fibrate, fenofibrate, has recently become FDA approved, with clinical event data pending.

Hormone Replacement Therapy

Randomized control trials are also needed to further delineate the role of hormone replacement therapy in the management of women with ILHDL-C. Estrogen is thought to reduce coronary risk by a variety of mechanisms, including raising HDL-C levels, lowering LDL-C levels, decreasing lipoprotein(a) levels, and decreasing fibrinogen levels and through beneficial effects on the arterial wall. Progestogens, however, typically decrease HDL-C levels. A recent, small, randomized, crossover trial demonstrated that in postmenopausal women treatment with the combination of estrogen and medroxyprogesterone acetate resulted in a 7% increase in HDL-C, a decrease in lipoprotein(a) levels, and a reduction in LDL-C. In the Coronary Drug Project, which used conjugated estrogen in men who had survived myocardial infarctions, the estrogen arm was discontinued because of unacceptable thrombotic complications. The doses of estrogen used in this study were 2.5 and 5.0 mg, which are much higher than those used for hormone replacement therapy today (0.625 mg). The recent Heart and Estrogen/Progestin Replacement Study (HERS) trial in postmenopausal women with CHD found that conjugated equine estrogen, 0.625 mg, combined with medroxyprogesterone acetate, 2.5 mg, had no effect on CHD end points and resulted in an increased incidence of thromboembolic complications. Preliminary results of VA-HIT suggest a modest benefit with gemfibrozil with CHD event rates reduced by 22%.

HMG-CoA Reductase Inhibitors

The HMG-CoA reductase inhibitors act by inhibiting the conversion of HMG-CoA to mevalonic acid. This conversion is the rate-limiting step in cholesterol production and requires the enzyme HMG-CoA reductase. The HMG-CoA reductase inhibitors act in the liver by inhibiting HMG-CoA reductase, which reduces the cholesterol level in the liver cell. The reduced hepatocyte cholesterol levels result in an increase in the synthesis of LDL-C receptors. The HMG-CoA reductase inhibitors act predominantly by reducing LDL-C, but also have moderate effects on HDL-C and endothelial function. A study with lovastatin in patients with ILHDL-C...
sia, and myopathy.25 The HMG-CoA reductase inhibitors are well tolerated by patients. Adverse effects include increased liver enzyme levels, dyspepsia, and myopathy.25

Preliminary data from several primary and secondary CHD prevention trials suggest that HMG-CoA reductase inhibitors may reduce the adverse consequences of low HDL-C levels and result in significant morbidity and mortality reductions. For example, in the landmark HMG-CoA reductase inhibitor trials, such as the Scandinavian Simvastatin Survival Study, the West of Scotland Coronary Prevention Study, and the Cholesterol and Recurrent Events study, subgroup analysis of those with low HDL-C levels but with elevated LDL-C levels demonstrated similar CHD risk reductions compared with those with normal HDL-C levels.35-37

In the recently published Air Force/Texas Coronary Atherosclerosis Prevention Study, a random-
y. If the patient has an LDL-C level of less than 100 mg/dL (2.59 mmol/L) after nonpharmacologic therapy and the HDL-C level remains less than 35 mg/dL (0.90 mmol/L), then monotherapy with niacin may be considered (Figure 4).

**Primary Prevention**

In patients without established CHD, nonlipid risk factors should be accounted for, and only the patients at the highest absolute risk of CHD should be treated with drugs. For primary prevention, an improved risk prediction tool other than the NCEP II guidelines (Table 1) may assist the provider in determining which patients are at high enough risk to start pharmacotherapy. Although more cumbersome, the Framingham risk prediction chart (Figure 5) is a more inclusive assessment of CHD risk than the NCEP II guidelines. The risk prediction chart is derived from the Framingham population and more precisely estimates CHD risk based on the interrelationship of other CHD risk factors (age, sex, smoking, hypertension, and diabetes) with lipoprotein levels, including total cholesterol and HDL-C. The risk prediction chart will assign the patient an absolute risk of CHD during a 10-year period. Based on international guidelines, such as those of the European Atherosclerosis Society, patients with a greater than 20% risk of CHD during a 10-year period should then be considered for treatment.

The utility of the risk prediction chart is illustrated by the following cases of 2 patients free of CHD but with low HDL-C levels (Table 2). Patient 1 is a 46-year-old man with a total cholesterol level of 260 mg/dL (2.72 mmol/L), an LDL-C level of 190 mg/dL (4.91 mmol/L), an HDL-C level of 34 mg/dL (0.88 mmol/L), and a triglyceride level of 180 mg/dL (2.03 mmol/L). The patient has no other CHD risk factors. Patient 2 is a 55-year-old man who smokes and has diabetes and hypertension (average systolic blood pressure, 139 mm Hg), and who has a total cholesterol level of 191 mg/dL (4.94 mmol/L), an LDL-C level of 131 mg/dL (3.39 mmol/L), an HDL-C level of 34 mg/dL (0.88 mmol/L), and a triglyceride level of 130 mg/dL (1.47 mmol/L).

In case 1, the patient would be treated by the NCEP II guidelines by virtue of having an LDL-C level

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**Table 2. Comparison of CHD Risk for 2 Sample Patients With Low HDL-C Levels**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Total cholesterol, mg/dL (mmol/L)</th>
<th>HDL-C, mg/dL (mmol/L)</th>
<th>LDL-C, mg/dL (mmol/L)</th>
<th>Triglycerides, mg/dL (mmol/L)</th>
<th>CHD risk factors</th>
<th>10-Year CHD risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>46</td>
<td>260 (6.72)</td>
<td>304 (7.89)</td>
<td>100 (3.67)</td>
<td>Male</td>
<td>45</td>
</tr>
<tr>
<td>Patient 2</td>
<td>55</td>
<td>191 (4.94)</td>
<td>366 (9.40)</td>
<td>131 (3.39)</td>
<td>Male</td>
<td>25</td>
</tr>
</tbody>
</table>

*CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; ECG, electrocardiogram; +, positive; and −, negative.
greater than 160 mg/dL (4.14 mmol/L) and 2 CHD risk factors. His 10-year risk for CHD derived from the risk prediction chart is 10%. In case 2, the patient would not meet NCEP II criteria for drug therapy, since his LDL-C level is less than 160 mg/dL (4.14 mmol/L) but his 10-year risk is 27% when using the risk prediction chart. Thus, despite patient 2 having a much lower LDL cholesterol level than patient 1, patient 2 remains at 3 times greater absolute risk of CHD than patient 1 given the multitude and intensity of other CHD risk factors. When applying these numbers to the European Atherosclerosis Society Guidelines based on the patient’s absolute risk of CHD, patient 2 would be considered for drug therapy while patient 1 would not. These 2 cases illustrate that patients with ILHDL-C may not have their true CHD risk adequately expressed when using the NCEP II guidelines. The risk prediction chart allows the primary care physician to make a more informed decision about starting drug therapy in patients with ILHDL-C. A newer, more simplified Framingham risk prediction chart has recently been published.62

Another way to assess CHD risk aside from the Framingham Heart Study risk prediction tool is to use additional lipid and nonlipid CHD risk markers. Other markers if available, such as lipoprotein(a), apolipoprotein B, and dense LDL-C, may help identify higher-risk patients for treatment. In addition, nonlipid risk factors that may identify higher-risk patients include homocysteine, fibrinogen, or C-reactive protein.63 However, at present, their utility in the primary care setting has not been demonstrated and they can only be considered as research tools. Finally, another important nonlipid risk factor in treating patients with ILHDL-C is the presence of premature familial atherosclerosis in parents or siblings who also have relatively normal lipid levels or risk factor profiles. Since CHD is a multifactorial disease, members of high-risk families should be targeted more aggressively by either raising HDL-C levels or lowering LDL-C levels.

CONCLUSIONS

The existing evidence from epidemiological studies, transgenic animal studies, and subgroup analysis of human intervention trials supports the treatment of patients with ILHDL-C. The physician should determine the patient’s absolute risk for CHD. In those without existing CHD, the Framingham Heart Study risk prediction chart is suggested as a possible tool for improved risk prediction in the patient with ILHDL-C. Separate approaches for both primary and secondary CHD prevention have been proposed. Large randomized controlled trials evaluating the treatment of ILHDL-C in patients with CHD are still pending. Although no interventional trial to date has demonstrated that modulating HDL-C in patients with ILHDL-C will result in CHD risk reduction, the available clinical, epidemiological, and animal evidence supports a role for intervention in those deemed at high risk for CHD events. The approach suggested in this review may help physicians treat this common lipid abnormality.

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