Treating patients with low HDL cholesterol levels

By Charles A. Reasner, MD

When treating patients with dyslipidemia, physicians tend to focus almost exclusively on elevated low-density lipoprotein cholesterol (LDL-C) levels as a risk factor for heart disease. Today, a patient’s low level of high-density lipoprotein (HDL-C) must also be considered as a risk factor.

In a study of 7,692 patients with type 2 diabetes mellitus, 50% had low levels of high-density lipoprotein cholesterol (HDL-C). While 63% of these patients were being treated with a statin, only 7.9% were being given a nonstatin HDL-raising medication.

A low HDL-C level is an independent risk factor for heart disease. Increasing patients’ HDL-C levels has been shown to slow progression of atherosclerotic disease and reduce cardiovascular events.

Role of HDL-C in preventing atherosclerotic disease

The main action of HDL is in “reverse cholesterol transport”—the process that removes cholesterol from peripheral tissues and delivers it to the liver, where it is metabolized. In addition to reverse cholesterol transport, HDL has antioxidant properties and anti-inflammatory properties and it has been shown to stabilize the endothelium.

Usually, low HDL-C levels are seen in combination with high triglyceride levels and an increased number of small, dense LDL-C particles. This triad of lipid abnormalities is often referred to as “atherogenic dyslipidemia.” It is particularly common among individuals with central obesity.

Fibric acid derivatives and niacin preparations are commonly used to treat patients for these lipid abnormalities. Several prospective studies have examined the effect of raising HDL-C with these preparations. The results of a few key studies are summarized below:

Veterans Administration HDL Intervention Trial (VA-HIT)
The VA-HIT enrolled 2,531 men with known coronary heart disease (CHD), low HDL-C levels, and normal LDL-C levels. Treatment with gemfibrozil reduced triglyceride levels by 31%, reduced LDL-C levels by 2%, and raised HDL-C levels by 6% from baseline. Major coronary events were reduced 22% more with gemfibrozil than with placebo during a five-year period. The benefit tended to be greater among patients with diabetes than among those without diabetes (35% vs 18%; P = 0.07).

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

The FIELD study was designed to assess the effect of fenofibrate on cardiovascular disease among patients with diabetes both with and without known heart disease. A total of 9,795 subjects from 63 centers in Australia, New Zealand and Finland were studied for five years, making this by far the largest study ever completed in a diabetic population.

At the end of the trial, researchers reported a nonsignificant 11% reduction (P = 0.16) in the primary outcome of first myocardial infarction or coronary heart death in the treatment group. Prior to the FIELD study, the VA-HIT provided the largest sample of diabetic patients treated with a fibric acid derivative.

In the VA-HIT, 769 subjects with diabetes and with known heart disease were randomized to receive either gemfibrozil 1,200 mg daily or placebo for five years. Baseline LDL-C and triglyceride levels were similar to those seen in the FIELD study while HDL-C levels were significantly lower at 31 mg/dl. In the VA-HIT, subjects with diabetes who were treated with gemfibrozil had a 32% lower level of cardiovascular events compared with those who received placebo (P = .004). The lower level was due to 22% fewer myocardial infarctions and 41% fewer cardiovascular deaths.

The most likely explanation for the disappointing effect of fenofibrate on cardiovascular events in the FIELD trial was the lack of treatment to increase HDL-C.

Table 1: Lifestyle modifications and expected HDL-C changes

<table>
<thead>
<tr>
<th>Lifestyle Modification</th>
<th>Expected HDL increase,%</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Exercise</td>
<td>3% to 6%</td>
<td>Greater increases seen with increased intensity</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>1% for each 1kg lost</td>
<td>Inverse relationship between BMI and HDL</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>3% to 6%</td>
<td>HDL levels are 6% higher in nonsmokers vs smokers</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>8%</td>
<td>30 grams/day of alcohol increases HDL 8%</td>
</tr>
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In the FIELD study, the initial increase in HDL-C was not sustained. By the end of the study, the increase in HDL-C was only 1%. Analysis of the lipid values of subjects in VA-HIT demonstrated that only concentrations of HDL-C significantly predicted a reduction in cardiovascular endpoints.4

Change in triglyceride levels with gemfibrozil therapy was not predictive of a reduction in cardiovascular risk. Similarly in the FIELD study, the 29% reduction in triglyceride levels with fenofibrate therapy did not result in a significant reduction in the primary endpoint of nonfatal myocardial infarction or coronary death.

Niacin is the most effective pharmacologic agent currently available for increasing HDL-C levels. Niacin raises HDL-C levels 20% to 25%. In the HDL-Atherosclerosis Treatment Study (HATS),4 160 patients with CHD were randomized to receive simvastatin-niacin treatment or placebo. After three years of therapy, the composite cardiovascular endpoint (CHD death, myocardial infarction, stroke or revascularization) was almost 50% lower in the individuals randomized to the simvastatin-niacin combination than in the subjects who received placebo. The investigators concluded that the magnitude of cardiovascular event reduction was greater than would have been predicted from statin therapy alone.

**Treatment options**

Unlike treatment targets for LDL-C levels, firm targets for HDL-C have not been established from large clinical trials. However, most guidelines suggest that men with HDL-C levels below 40 mg/dl and women with levels below 50 mg/dl are at high risk. The expected increases in HDL-C with Lifestyle Modifications are listed in Table 1 and Pharmacologic Interventions Table 2.

All patients with low HDL-C levels should be encouraged to maintain an ideal body weight and exercise regularly. Smokers should quit. Fibrates, statins and thiazolidenediones are generally well-tolerated.

Unfortunately, the most effective therapy for low HDL-C levels, niacin, is the most difficult for most individuals to take.

Tips to reduce flushing with niacin are outlined below:

- Have patients take each dose with an adult strength (325 mg), nonenteric-coated aspirin. Aspirin blocks the prostaglandin release that causes the flushing. Small doses of aspirin do not work and enteric coating delays the release of aspirin until the flushing is over.

- Have your patients avoid taking niacin with alcohol, hot liquids or spicy foods.

- Have your patients use the niaspan preparation at a dose of 1000 mg daily. Higher doses result in minimal further increases in HDL-C.

- Encourage patients to take the medication for at least two weeks. During this period, tolerance to the flushing usually develops.

**References:**


**Table 2:** Pharmacologic interventions and expected HDL-C changes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Expected HDL-increase, %</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Niacin</td>
<td>15%-30%</td>
<td>1 gram daily</td>
</tr>
<tr>
<td>Fibrates</td>
<td>5%-20%</td>
<td>600 mg bid</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td></td>
<td>100-200 mg daily</td>
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<tr>
<td>Fenofibrate</td>
<td></td>
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<tr>
<td>Statins</td>
<td>2%-15% (Greatest with Rosuvastatin)</td>
<td>Varies by Agent</td>
</tr>
<tr>
<td>Thiazolidenediones</td>
<td>10%-20% (Greatest with Pioglitazone)</td>
<td></td>
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<tr>
<td>Pioglitazone</td>
<td></td>
<td>45 mg daily</td>
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<tr>
<td>Rosiglitazone</td>
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<td>8 mg daily</td>
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