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# Raising an isolated low HDL-C level: Why, how, and when?

## ABSTRACT

Treating patients with isolated low high-density lipoprotein cholesterol (HDL-C) remains daunting. The decision to treat depends on the individual patient's overall risk for coronary heart disease (CHD). Strategies for raising HDL-C levels can include various lifestyle and drug therapies, which should be tailored to individual patients. While no current therapy is optimal, many can yield modest increases that translate into reduced risk for CHD events.

## KEY POINTS

Low HDL-C is the most common lipoprotein abnormality in patients with CHD and is predictive of CHD events, even when total cholesterol levels are normal.

Among lifestyle interventions for raising HDL-C levels, aerobic exercise is probably the most important. Weight loss is valuable but is often inadequate. Moderate daily alcohol consumption raises HDL-C levels by 5% to 10%.

Statins, niacin, and fibrates are the mainstays of drug therapy for raising HDL-C levels. Niacin has the greatest potency but is less well tolerated than the other agents.

Clinical trials of lipid-lowering drugs show that modest (5% to 10%) increases in HDL-C levels can significantly reduce CHD event rates.

**T**REATING ISOLATED low levels of high-density lipoprotein cholesterol (HDL-C) continues to be a challenge, and whether and how to treat it remains a question to be answered on a patient-by-patient basis.

The success of methods for raising HDL-C levels is often interrelated with other variables, including body mass index, triglyceride levels, and associated metabolic abnormalities.

Additionally, raising HDL-C levels is neither a primary nor a secondary target in the third report of the National Cholesterol Education Program Adult Treatment Panel (ATP III), although it has finally emerged as a potential tertiary target.<sup>1</sup>

This article briefly reviews lifestyle and pharmacologic interventions for raising HDL-C levels. It also explores the mechanisms of action of HDL-C as they relate to reverse cholesterol transport, offers recommendations for managing patients with isolated low HDL-C, and previews investigational agents that may help better tackle the problem.

## HDL-C LEVELS CLOSELY LINKED TO CORONARY HEART DISEASE

The body of evidence showing an inverse relationship between HDL-C levels and risk for coronary heart disease (CHD) has grown large. Low HDL-C is the most common lipoprotein abnormality in patients with CHD and is predictive of subsequent CHD events, even when total cholesterol is within the desirable range.<sup>2,3</sup> The National Cholesterol Education Program's ATP III report clearly defines a serum HDL-C level less than 40 mg/dL as an independent risk factor for CHD.<sup>1</sup>

Several studies have shown CHD risk to be more strongly or consistently related to

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HDL-C levels than to low-density lipoprotein cholesterol (LDL-C) levels. In fact, the HDL-C level influences the risk of developing CHD across all LDL-C strata.<sup>4</sup>

Despite these findings, most physicians continue to underestimate the clinical significance of HDL-C levels.<sup>1</sup>

### ■ HDL IS KEY TO REVERSE CHOLESTEROL TRANSPORT

HDL is a protein-enriched lipoprotein that plays a pivotal role in reverse cholesterol transport, or the transfer of cholesterol from extrahepatic sites, including vascular macrophages, to the liver for biliary excretion.<sup>5</sup> Although “HDL” and “HDL-C” are often used interchangeably, “HDL” refers to the lipoprotein particle and its properties, whereas “HDL-C” refers to its measured levels.

#### The pivotal proteins

Several important proteins appear to regulate this process (FIGURE 1). The initial step of cholesterol egress is mediated by the ATP-binding cassette protein (ABCA1), which belongs to a family of proteins involved in the transfer of substrates across cell membranes.

The free cholesterol liberated from extrahepatic cells is then moved to the HDL core following esterification in plasma by lecithin-cholesterol acyltransferase. Apolipoprotein A-I, derived from both hepatic and intestinal sources, serves as a cofactor for this reaction. Cholesterol carried by HDL may be removed from the circulation by transfer to lower-density lipoproteins in exchange for triglycerides, a process mediated by the cholesteryl ester transfer protein or by direct uptake by the liver or steroidogenic tissues via scavenger receptor B1. Cholesterol entering the liver is converted to bile and bile acids and is ultimately excreted in feces.

#### HDL-C level the best gauge for reverse cholesterol transport

Genetic variants that lead to partial deficiency of cholesteryl ester transfer protein (commonly seen among the Japanese) invariably raise HDL-C to moderately high levels (~60 mg/dL), yet affected subjects may not necessarily receive the cardioprotection that these

high levels normally confer.<sup>6</sup> In contrast, upregulation of scavenger receptor B1 lowers HDL-C levels, but there is greater efficiency of reverse cholesterol transport and, in animal studies, reduced progression of atherosclerotic lesions.

Therefore, although elevated HDL-C levels seem to be inversely correlated with CHD risk, there is no direct correlation between HDL-C concentration and reverse cholesterol transport. However, until more sensitive biochemical parameters become available, the HDL-C level remains the primary gauge for estimating reverse cholesterol transport.

### ■ LIFESTYLE MEASURES FOR RAISING HDL-C

#### Weight loss and dietary strategies: Important but often not enough

To minimize CHD risk, the optimal body mass index should approximate 22.6 kg/m<sup>2</sup> for men and 21.1 kg/m<sup>2</sup> for women.<sup>7</sup> Higher indexes are associated with lipid abnormalities, including reduced HDL-C levels and elevated triglyceride levels.

The good news is that weight loss ultimately improves the lipoprotein profile, although there may be transient reductions in HDL-C levels during active dieting. Specifically, for each kilogram (2.2 pounds) of weight lost during active dieting, HDL-C levels fall by 8%. However, once weight is stabilized there is a surge in the HDL-C level of about 1 mg/dL for every 7 pounds lost.<sup>8</sup>

There are no magic dietary bullets that selectively raise HDL-C levels. However, replacing fat with carbohydrates (which may stimulate production of very-low-density lipoprotein) without reducing caloric intake may cause HDL-C levels to fall by as much as 20%.<sup>9</sup> With associated weight loss, however, HDL-C levels rise by 12.5% in obese adults.<sup>10</sup> However, patients with a predominance of small, dense LDL particles may be resistant to this effect.<sup>11</sup>

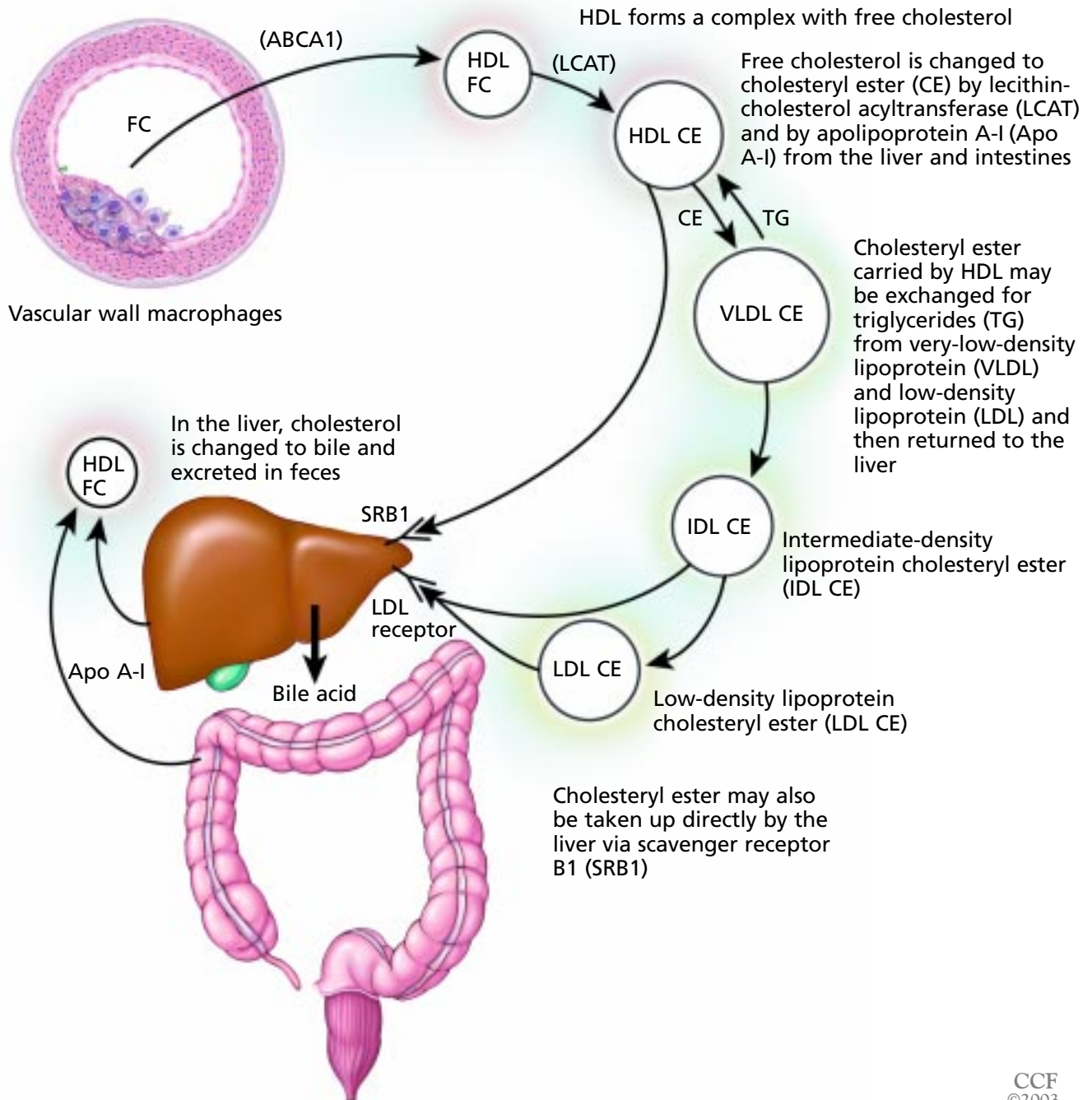
Controversy surrounds the question of whether monounsaturated fats such as olive oil may raise HDL-C levels.<sup>12</sup> However, in view of the increase in total calories consumed throughout our society, I would rather see the use of such fats in exchange for either saturated fats or carbohydrates.

**Low HDL-C is the most common lipoprotein abnormality in CHD patients**

## HDL's role in reverse cholesterol transport

High-density lipoprotein (HDL) exerts its “good” effect by helping to transport cholesterol to the liver for excretion.

Free cholesterol (FC) is liberated from vascular wall macrophages by ATP-binding cassette protein (ABCA1)



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**FIGURE 1**

Overall, while dietary and weight-loss measures are an important component of treatment for patients with low HDL-C levels, they are often insufficient for optimizing these levels.

### Aerobic exercise: Duration over intensity

Aerobic exercise is perhaps the most important nonpharmacologic method for raising a low HDL-C level. The average increase ranges from 10% to 20%, and a “dose-

response” relationship has been reported, with an approximate 1-mg/dL increase in HDL-C levels for every 4 to 5 miles run per week.<sup>13</sup>

The duration of aerobic exercise (eg, number of miles run), rather than the intensity, appears to have the biggest influence on HDL-C levels.<sup>14</sup> Earlier studies suggested that the threshold required to raise HDL-C levels was an energy expenditure of at least 1,200 cal/week, achieved by running or brisk walking (approximately 12 miles/week), swimming, or cycling. However, one recent study<sup>15</sup> reported only a modest 10% increase among subjects expending 2,000 calories after jogging 20 miles weekly and no increases in two groups (joggers and walkers) expending 1,200 calories weekly.

One caveat: aerobic conditioning is less likely to raise HDL-C levels in patients with a low baseline level (ie, < 40 mg/dL) than in those with a higher baseline level.<sup>16</sup> Still, the unlikelihood of such an effect in patients with a low baseline level should not stop us from encouraging these patients to participate in aerobic exercise, in view of other well-established potential cardiac benefits of this exercise.<sup>17</sup>

#### **Alcohol consumption: Half the benefit is from HDL-C effects**

Moderate daily alcohol consumption (1 to 2 oz/day) raises levels of HDL-C and apolipoprotein A-I by 5% to 10%.<sup>18</sup> This effect occurs whether the alcohol is in the form of wine (two 4-ounce glasses), beer (two 12-ounce bottles) or spirits (2 shots). This HDL-C effect appears to account for approximately half of the CHD benefit attributed to moderate alcohol intake.<sup>19</sup>

Other potential cardiovascular benefits augmented by moderate drinking include enhanced HDL-mediated antioxidant activity and reverse cholesterol transport.<sup>20</sup> Both large (HDL2) and smaller (HDL3) subfractions of HDL increase with alcohol consumption, although the clinical significance of raising a specific HDL subfraction, as opposed to total HDL, is uncertain. Moderate alcohol consumption is associated with additional cardiovascular benefits, including reduced platelet aggregability, enhanced fibrinolysis, and improved endothelial vasomotor activity.<sup>20</sup>

#### **Fish oil consumption: Modest effects**

Omega-3 fatty acids or “fish oil”—notably, eicosapentaenoic acid and docosahexaenoic acid—possess antiatherothrombotic properties, including inhibition of platelet aggregation, suppression of arrhythmogenesis, and significant lowering (by 25% to 30%) of very-low-density lipoprotein and triglyceride levels.<sup>21</sup>

However, the effect of omega-3 supplementation on HDL-C levels is modest: an increase of approximately 3% was noted in subjects with fasting triglyceride levels of less than 177 mg/dL, whereas no effect was seen in those with higher fasting triglyceride levels.<sup>21</sup> Nevertheless, a recent policy statement from the American Heart Association endorses omega-3 supplementation for CHD risk prevention.<sup>22</sup>

#### **■ DRUG THERAPY TO RAISE HDL-C LEVELS**

##### **Niacin: Potent but not always well tolerated**

Niacin or nicotinic acid (vitamin B<sub>3</sub>) is the most potent agent currently available for raising HDL-C levels, producing increases that often approach or exceed 30%, even in subjects with isolated low HDL-C.<sup>23</sup> Niacin reduces hepatic removal of HDL-apolipoprotein A-I and hepatic lipase activity, resulting in higher levels of total HDL-C and the HDL2 subfraction.<sup>24</sup> The nicotinic acid receptor was recently identified,<sup>25</sup> a finding that may lead to the development of novel and perhaps more potent compounds for raising HDL-C levels.

**Side effects.** Immediate-release niacin appears to have a higher incidence of side effects such as flushing (> 90% incidence) compared with sustained-release or extended-release preparations. Other common side effects of all niacin formulations include pruritus (~15% incidence) and rash (~10%).

Uncommon side effects include acanthosis nigricans (hyperpigmentation of the skin, primarily along the neck, axillary, and inguinal creases) and toxic amblyopia (toxicity in the orbital portion of the optic nerve resulting in impaired visual acuity).

The most concerning side effect, hepatotoxicity, appears to be related to the use of higher-than-recommended dosages of the sustained-release formulation or the substitution of the sustained-release formulation for the

**Niacin is the most potent agent now available for raising HDL-C**





immediate-release form, resulting in excessive daily dosing.<sup>26</sup>

**Dosage.** Niacin should be started at low dosage (100 to 250 mg for the immediate-release and sustained-release formulations, 500 mg for the extended-release form) and given with food with or without aspirin to minimize flushing. The flushing caused by prostaglandin-mediated cutaneous vasodilation may be intensified by concurrent use of other vasodilators, sun exposure, spicy foods, hot beverages, or aerobic activity. Aspirin given 30 minutes before niacin administration may reduce the incidence and severity of flushing.

Fortunately, niacin raises HDL-C levels at relatively low dosage (eg, 1,000 mg).<sup>27</sup> A “creeping” effect (continued increases in HDL-C levels over time) was recently identified in a 52-week study using the extended-release formulation.<sup>28</sup> This extended-release preparation has also been associated with a reduced incidence of hepatotoxicity.<sup>29</sup> Moreover, an excellent efficacy and safety profile has been demonstrated with the combination of niacin and a statin in subjects with low or average HDL-C levels.<sup>30</sup>

Niacin should be avoided in patients with active peptic ulcer disease or gout. However, it may be used successfully in diabetic patients with well-maintained glycemic control.<sup>31</sup>

Because over-the-counter niacin preparations are not tightly regulated, we prescribe the following niacin preparations at our preventive cardiology center:

- The immediate-release formulation, Niacor
- The sustained-release formulation, Slo-Niacin
- The extended-release formulation, Niaspan.

### **Fibrates: HDL-C effects depend on triglycerides**

The fibrates gemfibrozil (Lopid) and fenofibrate (Tricor) appear to raise HDL-C levels by activating peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), which in turn enhances expression of the HDL-regulating genes, apolipoproteins A-I and A-II, lipoprotein lipase, and ABCA1.<sup>32</sup> Fibrates raise HDL-C levels (predominantly the HDL3 subfraction) by an average of 5% to 20%.<sup>33</sup>

In subjects with an isolated low HDL-C, the effect appears to depend on fasting triglyc-

eride levels. For example, in one study, subjects with low median fasting triglyceride levels (< 95 mg/dL) had a mere 4% increase in HDL-C levels, compared with a 15% increase in subjects with higher fasting triglyceride levels (95 to 150 mg/dL).<sup>34</sup>

Two head-to-head studies have compared fibrates with niacin in subjects with low HDL-C levels.<sup>23,35</sup> Niacin showed superior effects in both trials, raising HDL-C levels by 26% to 35%, compared with 13% to 15% increases with fibrates.

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT)<sup>36</sup> is the only clinical trial to date designed to evaluate CHD patients with normal total cholesterol but low HDL-C. In this study, gemfibrozil was associated with reduced rates of myocardial infarction and stroke compared with placebo, an effect attributed in part to the 6% increase in HDL-C levels observed with gemfibrozil.<sup>36</sup>

Fibrates also reduce concentrations of atherogenic particles, normalize LDL composition, and reduce fibrinogen,<sup>36,37</sup> which may have also contributed to the benefits observed in VA-HIT.

### **Statins: Clinical impact despite modest HDL-C increases**

The HMG-CoA reductase inhibitors (statins) raise HDL-C levels by an average of approximately 5% to 10%, but clinical trials have shown that they have a larger impact on CHD risk than these relatively modest gains would imply. In each of these landmark randomized clinical end-point trials, patients with low HDL-C who received statins experienced cardiovascular event rates comparable to those of placebo recipients with higher HDL-C levels.<sup>38</sup>

A recent subgroup analysis from the Scandinavian Simvastatin Survival Study (4S) showed that CHD risk reduction was greatest among simvastatin recipients who had a combination of low HDL-C levels, high triglyceride levels, and high LDL-C levels at baseline compared with those who had high LDL-C levels alone.<sup>39</sup>

Plausible mechanisms that may account for these effects include the activation of PPAR $\alpha$  and apolipoprotein A-I.<sup>40</sup> Recent studies using high doses of simvastatin (eg, 80 mg) have shown particularly large increases in

**Limit doses of simvastatin to 10 mg/day in patients taking niacin or a fibrate**

HDL-C (15% to 21%) among subjects with low baseline HDL-C levels.<sup>41,42</sup> Moderate increases in HDL-C (10% to 15%) have also been reported with starting doses of the investigational agent rosuvastatin (Crestor).<sup>43</sup>

Notably, the US Food and Drug Administration (FDA) recently made a revision to the simvastatin package insert that is particularly pertinent to patients who may be receiving the drug to raise HDL-C levels. The label now warns that the dose of simvastatin should not exceed 10 mg daily in patients who are also receiving a fibrate or niacin, owing to a potentially increased risk of myopathy and rhabdomyolysis. However, published studies using higher doses of simvastatin with either niacin<sup>30</sup> or fibrates<sup>44</sup> found that this did not lead to myopathy.

### Estrogen therapy: Not recommended

Estrogen raises HDL-C levels by 10% to 20%.<sup>45</sup> The increases likely reflect reductions in hepatic lipase activity and enhanced apolipoprotein A-I production. In contrast, progestins reduce HDL-C levels, so the use of combined estrogen-progestin hormone therapies results in a modest net increase in HDL-C levels (~5%).<sup>46</sup> Overall, estrogen use (either singly or in combination with progestational agents) has not been shown to improve cardiovascular survival rates<sup>47</sup> and is not recommended for the treatment of low HDL-C or for CHD prevention.

### Miscellaneous therapies

Other therapies that have been shown to increase HDL-C levels include bile-acid resins, which raise levels by 5%, and beta<sub>2</sub>-agonists such as terbutaline, which raise them by 10%.<sup>48,49</sup> The currently available bile-acid resins are cholestyramine, colestipol (Colestid), and colestevlam (Welchol).

Two studies have demonstrated 10% to 15% increases among patients with low HDL-C who were randomized to phenytoin.<sup>50,51</sup> Another study found that chromium supplementation raised HDL-C levels by approximately 15% in patients receiving beta-blockers,<sup>52</sup> a group often resistant to increases in HDL-C levels.

The cholesterol absorption inhibitor ezetimibe (Zetia) has a minimal effect on HDL-C

(< 5% increase) but may potentiate increases in combination with statins.<sup>53</sup>

### RAISING HDL-C LEVELS: PRIMARY AND SECONDARY PREVENTION

The data showing an independent effect of raising HDL-C levels on CHD event rates are limited, in part because there are no agents that selectively raise HDL-C levels. However, while clinical end-point studies of lipid-lowering therapies have demonstrated only modest increases in HDL-C levels (5% to 10%), these trials have shown those increases to have considerable clinical impact.

For example, the Helsinki Heart Study, a primary prevention trial evaluating the use of gemfibrozil, suggested that a 1% rise in HDL-C levels was associated with a 2% to 3% reduction in the incidence of CHD events.<sup>54</sup> As noted above, the VA-HIT also found that raising levels of HDL-C was associated with an independent reduction in CHD event rates, even though only 23% of the benefit was attributable to higher HDL-C levels.<sup>36</sup>

Statins also have been shown to be particularly effective in people with low HDL-C. Both in primary prevention trials (eg, the West of Scotland Coronary Prevention Study [WOSCOPS] and the Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS]) and in secondary prevention trials (4S, the Cholesterol and Recurrent Events [CARE] study, the Long-term Intervention with Pravastatin in Ischemic Disease [LIPID] study), patients with low baseline levels who received a statin had no greater risk of CHD events than patients with higher baseline levels who received placebo. Additionally, studies of niacin-statin combination therapy have demonstrated reductions in arteriographic progression of CHD and improvement in clinical event rates,<sup>30,55</sup> and in one of these trials CHD regression was most closely correlated with increased HDL-C levels.<sup>55</sup>

### FUTURE PHARMACOLOGIC TARGETS

Pharmacologic targets for raising HDL-C levels include activators of apolipoprotein A-I (PPAR $\alpha$ ) and ABCA1 (LXR agonists).<sup>56</sup>

No available  
drugs  
selectively  
raise HDL-C



Inhibitors of cholesteryl ester transfer protein may also raise HDL-C levels by more than 30%, as demonstrated in one recent trial.<sup>57</sup> Other agents that may not raise HDL-C levels but may affect reverse cholesterol transport or lipoprotein oxidative modification are currently under investigation.<sup>58,59</sup> However, FDA approval and the subsequent utility of these novel therapies will likely depend on whether clinical data show reductions in CHD event rates.

## ■ RECOMMENDATIONS FOR MANAGING PATIENTS WITH LOW HDL-C

Treating isolated low HDL-C remains a daunting challenge because syndromes associated with low HDL-C (which are genetic or result from gene-environment interactions) are heterogeneous with regard to CHD risk, since the efficiency of reverse cholesterol transport does not necessarily correlate with HDL-C levels. Therefore, until more sensitive biochemical markers of reverse cholesterol transport are developed, therapies to raise low HDL-C levels should be individually tailored based on the patient's overall CHD risk.

Lifestyle measures are always recommended initially; depending on other factors, phar-

macologic therapies may also be endorsed.

While raising HDL-C levels is neither a primary nor a secondary target in the recent National Cholesterol Education Program ATP III report,<sup>1</sup> it has finally emerged as a potential tertiary target. This is an important step, considering that therapies to raise HDL-C levels were not recommended in previous ATP reports. Thus, statins remain the premier agents in treating low HDL-C in patients with vascular disease because of the benefits demonstrated in clinical end-point trials. However, fibrates, niacin, and omega-3 preparations may be used as adjunctive agents, especially if triglyceride levels remain elevated.

The decision to treat isolated low HDL-C in the absence of vascular disease or CHD risk equivalents depends on other factors, including cigarette smoking and history of hypertension. Both of these factors are strong predictors of primary CHD events in people with low HDL-C, and the prognosis of these persons does improve with treatment.<sup>60</sup> Finally, a strong family history of premature CHD (ie, occurring before age 50 years in a first-degree relative) is an important risk factor to consider when identifying patients with low HDL-C who are at high risk for CHD and who may also be candidates for drug therapy.

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