

# High-Density Lipoprotein Cholesterol as the Holy Grail

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FOR MORE THAN 3 DECADES, SINCE HIGH LEVELS OF HIGH-density lipoprotein cholesterol (HDL-C) were first linked to a lower risk of developing cardiovascular disease, the notion of raising HDL-C levels has been regarded as a potentially ideal treatment to prevent cardiovascular disease.<sup>1,2</sup> High-density lipoprotein cholesterol has generally been called the “good cholesterol” to distinguish it from low-density lipoprotein cholesterol (LDL-C), which has been clearly linked to increased risk of cardiovascular disease and mortality. Although multiple large randomized trials have shown that lowering LDL-C leads to a reduction in cardiovascular events and mortality,<sup>3</sup> for HDL-C, the translation from these observational studies to identifying a drug in randomized clinical trials that both increases HDL-C and reduces clinical events has been long and difficult. As such, the search for an HDL-C-raising, cardioprotective drug almost seems like the quest for the Holy Grail.

While the relationship from epidemiologic studies between HDL and cardiovascular disease has been robust and reproduced in multiple studies, the issue of confounding may be at play; that is, other factors such as obesity and glucose intolerance/diabetes also occur in patients with low HDL-C levels, and these conditions could potentially be the more important cause of the increased risk of cardiovascular disease than low HDL-C. As such, could HDL-C be just a marker of disease and not a mediator of the disease process?

However, there is strong biologic plausibility that HDL-C does have an important counterregulatory role in atherosclerosis. High-density lipoprotein cholesterol has numerous effects that would appear to be beneficial in atherosclerosis, including most notably its central role in reverse cholesterol transport.<sup>4</sup> This process transports excess cholesterol from the foam macrophages in the arterial wall onto HDL particles and then to the liver, bile, and feces.<sup>5</sup> Apolipoprotein A-I is lipid-free HDL, discoid HDL particles are lipid-poor, and more mature HDL particles include small,

dense, spherical HDL3 and large spherical HDL2.<sup>5</sup> The smaller HDL3 particles more efficiently promote cholesterol efflux through the adenosine triphosphate cassette-binding transporters (ABCA1) pathway, whereas the larger HDL2 particles do so via the ABCG1 pathway. High-density lipoprotein cholesterol also has anti-inflammatory and antioxidant effects, improves endothelial function by enhancing nitric oxide synthase, and has anticoagulant effects, all of which could contribute to a beneficial effect.<sup>4</sup>

To date, there have not been many drugs that increase HDL-C levels. Statins can increase HDL-C by just 5% to 10%, and in large trials, fibrates have been associated with very modest HDL-C changes. Niacin (vitamin B<sub>3</sub>) has been shown to increase HDL-C by 15% to 35% in a dose-dependent fashion and also lowers LDL-C and triglycerides. The clinical effects had been studied in only 1 outcomes trial, in which the incidence of nonfatal reinfarction was reduced by 27% over 5 years<sup>6</sup> and the incidence of all-cause mortality was reduced by 9% after 15 years.<sup>7</sup> However, because this study predated the use of statins, additional trials were needed to assess the effects of niacin when added to statins. The first trial, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM HIGH),<sup>8</sup> was stopped prematurely because of futility, whereby no benefit was seen. A second, much larger trial is ongoing (clinicaltrials.gov identifier: NCT00461630), and the final word on niacin awaits those results.

Interest now has focused on another class of agents that increase HDL-C levels much more substantially, the cholesteryl ester transfer protein (CETP) inhibitors. Cholesteryl ester transfer protein is a plasma protein that promotes transfer of cholesteryl esters from HDL-C to LDL-C and triglycerides.<sup>9</sup> Cholesteryl ester transfer protein inhibitors increase HDL-C levels, and some reduce LDL-C levels, with parallel changes in apolipoproteins A-I and B (TABLE). This class had a difficult start, however, with the first agent tested in large trials, torcetrapib, leading to an increase in

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See also p 2099.

**Table.** Lipid Changes Following Treatment With Cholesterol Ester Transfer Protein Inhibitors<sup>a</sup>

	Change From Baseline, %			
	Dalcetrapib, 600 mg/d	Torcetrapib, 60 mg/d	Anacetrapib, 100 mg/d	Evacetrapib, 500 mg/d <sup>b</sup>
High-density lipoprotein cholesterol	+31	+61	+138	+132
Apolipoprotein A-I	+11	+25	+45	+50
Low-density lipoprotein cholesterol	-2	-24	-40	-40
Apolipoprotein B	+4	-12	-21	-26
Triglycerides	-3	-9	-7	-20
Total cholesterol	+8	+4	+16	+11

<sup>a</sup>Data are adapted from Barter et al,<sup>10</sup> Cannon et al,<sup>15</sup> and Fayad et al.<sup>19</sup>

<sup>b</sup>As monotherapy.<sup>18</sup>

mortality and cardiovascular events.<sup>10</sup> Torcetrapib was also found to increase blood pressure, increase circulating aldosterone levels, and alter serum electrolytes.<sup>10</sup> Torcetrapib was later found to have an “off-target” effect, leading to induced synthesis of both aldosterone and cortisol in adrenal cortical cells.<sup>11,12</sup> In contrast, none of the other agents in this drug class alters blood pressure, electrolytes, or serum aldosterone.<sup>13-15</sup> A second question for this class was whether the larger, cholesterol-rich HDL particles formed by CETP inhibitors would function properly for reverse cholesterol transport. In vitro studies have demonstrated that following treatment with either torcetrapib or anacetrapib, the HDL particles had normal (or even enhanced) ability to promote the cholesterol efflux from macrophages in vitro.<sup>16,17</sup>

In this issue of *JAMA*, Nicholls and colleagues<sup>18</sup> report the results of a clinical trial evaluating evacetrapib, another agent in the class. This drug was tested in a trial involving approximately 400 patients with dyslipidemia. The investigators studied various dosages, ranging from 30 mg/d to 500 mg/d, either as monotherapy or in combination with one of the commonly used statins. The effects on lipids at the highest dosage were quite substantial, with a 132% relative increase in HDL-C and a 40% decrease in LDL-C (Table). No safety issues were identified, including no changes in blood pressure, aldosterone levels, or liver function tests. However, several limitations of this study should be acknowledged: only 40 patients were treated with the 500-mg/d dosage, without a concomitant statin, for just 12 weeks. Longer-term safety data are not available at present; thus, these data represent early experience with this agent. With dalcetrapib, several reports of phase 2 studies have been published or presented,<sup>13,19,20</sup> and a large phase 3 trial (clinicaltrials.gov identifier: NCT00658515) has been ongoing with a data and safety monitoring board overseeing it.<sup>21</sup> For anacetrapib, there have been lipid efficacy studies<sup>14,22</sup> similar to the report by Nicholls et al and a formal safety study of 1600 patients,<sup>15</sup> while the large phase 3 trial is just beginning (clinicaltrials.gov identifier: NCT01252953).

Current approaches to patients with low HDL-C levels are, first, institution of therapeutic lifestyle changes with diet and exercise and, if relevant, cessation of cigarette smoking. Each of these approaches has been shown to increase HDL-C and is associated with improved outcomes. The next step is to lower LDL-C. The current guidelines emphasize lowering LDL-C as the primary approach for patients with low HDL-C because it is a proven strategy, and the benefits of lowering LDL-C are present regardless of HDL-C levels (high or low).<sup>23</sup> Next, in selected patients, some lipid experts use currently available therapies including niacin to increase HDL-C levels, although the evidence base for this approach is limited. Further interventions await data from the large randomized trials of current therapies (eg, niacin) and emerging therapies like the CETP inhibitors, including dalcetrapib,<sup>20</sup> anacetrapib, and, likely, evacetrapib. As such, the quest for the Holy Grail in coronary disease has many worthy knights on the trail.

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