

High-density lipoproteins: the next frontier in lipid management

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Combined with appropriate lifestyle modification and statin therapy, raising HDL levels may be an important strategy to reduce cardiovascular risk

In the past two decades, we have made significant advances in the management of cardiovascular disease (CVD), with a dramatic reduction in cardiovascular events occurring in parallel with the widespread use of statins to lower low-density lipoprotein (LDL) cholesterol levels. Nevertheless, despite intensive use of statin therapy, a significant patient cohort remains at high risk of cardiovascular events, paving the way for new strategies to reduce their residual cardiovascular risk.

One attractive target for such strategies is high-density lipoprotein (HDL) cholesterol. There is strong epidemiological evidence demonstrating the inverse relationship between the incidence of cardiovascular events in normal populations and serum HDL levels. Based on data from the Framingham Heart Study, the risk of myocardial infarction increases about 25% per 0.13 mmol/L decrement in serum HDL below median values.¹ HDL levels are also predictive of coronary events in patients with known CVD across a range of LDL levels, as demonstrated in the Treating to New Targets trial, in which nearly 10 000 patients with established CVD were treated with statins.² HDL levels were inversely predictive of time to first major cardiovascular event across the spectrum of LDL levels, including patients with treated LDL levels below 1.8 mmol/L, highlighting the predictive value of HDL levels independent of LDL levels.

The atheroprotective effects of HDL have been attributed to its ability to mediate “reverse cholesterol transport”, where cholesterol in peripheral tissues is transferred via plasma to the liver for either recycling or excretion. More recently, the antioxidant and anti-inflammatory properties of HDL have been explored. In particular, intravenous preparations of HDL have been shown to dramatically reduce acute vascular inflammation in animal models, improve endothelial function (an important surrogate of cardiovascular risk), and promote atheroma regression and stabilisation in human

studies.³ Moreover, because of the heterogeneity of human HDL, an appreciation of function as well as absolute concentration is becoming increasingly important. For example, HDL from subjects with diabetes has been shown to be less effective in its cholesterol-effluxing and anti-inflammatory capacity.⁴

Lifestyle modifications in the form of regular exercise, smoking cessation, weight loss and moderate alcohol consumption have each been shown to individually raise HDL levels by 5%–10%.⁵ Although statins are currently the cornerstone of lipid-modifying therapy, they raise HDL levels by only 5%–10%.⁶ On the other hand, fibrates have been shown to raise HDL levels by 10%–15%.⁷ Fibrates regulate HDL metabolism as ligands and activators of the nuclear transcription factor peroxisome proliferator-activated receptor- α .⁸ The benefits of using fibrates to raise HDL levels have been suggested by a number of randomised trials. For example, the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) included 2531 patients with CVD, with an LDL level \leq 3.6 mmol/L, HDL level \leq 1.0 mmol/L, and triglycerides \leq 3.4 mmol/L; patients were randomly assigned to receive treatment with gemfibrozil or placebo. At 5 years, the combined primary endpoint of cardiac death and non-fatal myocardial infarction occurred less often in the gemfibrozil-treated group, and the reduction in this endpoint correlated strongly with both serum HDL levels and degree of weight loss, but was independent of changes in LDL cholesterol or triglycerides concentration.^{7,9}

Nicotinic acid is another effective HDL-raising drug, with an ability to raise levels by up to 30%. The HDL-Atherosclerosis Treatment Study (HATS) reported the effects of combined therapy with a statin and niacin on 160 patients with CVD, with an HDL level $<$ 0.9 mmol/L and LDL level $<$ 3.75 mmol/L.¹⁰ Compared with placebo, patients receiving simvastatin plus niacin were signifi-

cantly less likely to experience a cardiovascular event. Furthermore, the magnitude of the reduction of clinical events with drug therapy was greater than that observed in studies of statins alone, suggesting that raising HDL levels provides additional protection beyond that attributable to simply lowering LDL levels.¹⁰ The side-effect profile remains problematic with this drug class, though development of extended-release preparations may overcome these issues.

Most recently, a novel class of HDL-raising medications, the cholesteryl ester transfer protein (CETP) inhibitors, which prevent the transfer of cholesteryl ester from HDL to triglyceride-rich lipoproteins in exchange for triglyceride, have been tested in large clinical trials. In particular, the CETP inhibitor torcetrapib was evaluated in the multicentre randomised Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, which compared torcetrapib with placebo in more than 15 000 patients receiving atorvastatin.¹¹ A significant increase in HDL levels (72%) and an additional decline in LDL levels (25%) below baseline after 12 months of torcetrapib therapy were seen. However, the trial was prematurely terminated due to a significant increase in cardiovascular events in the treatment arm; an “off target” effect on the aldosterone receptor leading to blood pressure elevations was postulated as a potential mechanism for this.¹¹

Despite the setback experienced with torcetrapib, further studies are underway to develop more target-specific CETP inhibitors. Intravenous reconstituted HDL preparations and apolipoprotein A-I mimetic compounds are also in development. In the future, these compounds may be used to regress atheroma or suppress the arterial inflammation that is the hallmark of the acute coronary syndromes. Thus, raising HDL levels, in combination with optimising LDL cholesterol levels, blood pressure and glycaemic control, as well as appropriate lifestyle modification, represent important strategies for reducing residual cardiovascular risk. Such measures should see further improvements in clinical outcomes for patients with CVD.

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