Editorial

Strategies to promote HDL-C: an emerging therapeutic target

Stephen J. Nicholls and Steven E. Nissen*

The Cleveland Clinic Foundation, Department of Cardiovascular Medicine/F15, 9500 Euclid Avenue, Cleveland OH 44195, USA

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This editorial refers to ‘High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial’† by A.G. Olsson et al., on page 890

Hydroxy-methyl glutaryl coenzyme A reductase inhibitors (statins) have accumulated an extraordinary record of successful randomized clinical trials, transforming the practice of preventive cardiology. However, most placebo-controlled statin trials have reported not more than 25–35% reduction in morbidity/mortality during 5 year follow-up. Thus, despite their established benefits in primary and secondary prevention, statin drugs fail to prevent the majority of clinical events. In acute coronary syndromes (ACS), despite aggressive use of statins, the prognosis is even less favourable. In a recent trial of lipid lowering in ACS, the 2 year event rate was still 22% in the most aggressively treated patients. These findings highlight the need to develop new strategies to compliment statins in reducing cardiovascular risk.

Emerging therapeutic targets include C-reactive protein, recently shown to have a strong link to outcomes during statin administration. However, few therapies other than statins have been shown to reduce C-reactive protein. A particularly inviting therapeutic target is high-density lipoprotein cholesterol (HDL-C), a lipoprotein with well-established protective properties in epidemiological studies.

Olsson et al.3 present data from the MIRAcl study describing the ability of plasma lipoproteins to predict recurrent clinical events. Surprisingly, the incidence of clinical events could not be predicted by the plasma LDL-C concentration at baseline. Further, the reduction in clinical events with high dose atorvastatin did not correlate with the degree of LDL-C lowering. This finding adds further evidence to support the concept that the benefit of commencing statins early in the setting of ACS may result from their pleiotropic properties. A pivotal finding of this analysis was the association of plasma concentration of HDL-C at baseline with the incidence of subsequent clinical events. These observations provide important support for the concept that HDL-C is atheroprotective.

It has been >50 years since the initial report that patients with a history of myocardial infarction had lower plasma levels of HDL-C. However, it took several decades for the concept of the protective properties of HDL-C to gain popularity. The key observation was the finding in large population studies that the plasma HDL-C concentration was inversely correlated with the incidence of cardiovascular disease (CVD). HDL was the strongest biochemical predictor of CVD in the Framingham cohort. It was further demonstrated that elevating plasma HDL by either the transgenic expression of apolipoprotein A-I (apoA-I) or the infusion of native HDL, reconstituted HDL (rHDL), or lipid-free apoA-I reduced lesion size in animal models of atherosclerosis. These findings have stimulated considerable interest to further understand the mechanisms underlying these beneficial properties.

The best characterized functional property of HDL-C is its role in the promotion of reverse cholesterol transport. A key factor in this process involves the interaction between lipid depleted apoA-I and the transmembrane protein ABCA1, which results in cellular cholesterol efflux. However, it has become apparent that HDL-C possesses other functional properties that may contribute to its beneficial impact on the arterial wall. HDL-C exerts a favourable impact on vascular reactivity, via the promotion of nitric oxide bioavailability. HDL-C exerts antioxidant effects, inhibiting LDL-C oxidation and improving the balance of nitric oxide to superoxide.
HDL-C has prominent anti-inflammatory properties, inhibiting the expression of adhesion molecules and monocyte chemotaxis, both early events in atherogenesis. In addition, elevation of HDL-C in the setting of established atheroma leads to a reduction in macrophage infiltration. Furthermore, HDL-C has been demonstrated to have anti-thrombotic effects. In combination, these functional properties of HDL-C have the potential to modify many stages of the atherosclerotic process.

There currently exist a limited number of therapeutic options to promote HDL-C. However, several exciting therapeutic strategies have recently emerged and currently are the focus of intense research interest. Some of the benefits of fibric acid derivatives (fibrates) have been attributed to their modest ability to elevate plasma HDL-C. In fact, the greatest clinical benefit in fibrate prevention studies was observed in subjects with low plasma HDL-C levels at baseline. Fibrates are relatively weak agonists of the nuclear receptor PPAR-α, now recognized as playing a major role in the regulation of lipid homeostasis and the inflammatory cascade. These agonists stimulate production of the major HDL-C associated lipoproteins. A new generation of PPAR-α agonists with greater activity is likely to have more profound effects on HDL-C levels. Other experimental agents act as agonists of both PPAR-α and PPAR-γ receptors. PPAR-γ regulates insulin sensitivity and the inflammatory cascade. Because of the increasing prevalence of the metabolic syndrome, characterized by insulin resistance, a proinflammatory state, and low levels of HDL-C, the ability to target all of these cardiovascular risks with a single agent is highly desirable.

The most effective therapeutic option currently available to clinicians to elevate plasma HDL-C remains niacin. Niacin has been reported to elevate HDL-C via several mechanisms that increase its production and inhibit its metabolism. However, side effects such as flushing and dermatological reactions limit the utility of this drug. When tolerated, niacin effectively elevates HDL-C by 30%. In combination with statins, niacin has been demonstrated to halt progression of carotid intimal medial thickness and to promote plaque regression in an angiographic study. These results strongly support the notion that raising HDL-C in the presence of concomitant statin administration can have additional benefits on cardiovascular prevention.

Factors that influence HDL-C metabolism represent ideal targets to develop strategies to elevate HDL-C. Cholesteryl ester transfer protein (CETP), in particular, has stimulated major scientific interest. CETP facilitates the transfer of esterified cholesterol from HDL-C to apolipoprotein B containing lipoproteins, in exchange for triglyceride. Following transfer, LDL-C may transport cholesterol to the liver, where it is taken up by the LDL receptor, providing an alternative pathway for reverse cholesterol transport. Alternatively, the esterified cholesterol may be deposited in peripheral tissues such as the arterial wall. The net effect of CETP on atherogenesis remains uncertain. By lowering LDL and raising HDL, CETP inhibition promotes an antiatherogenic lipoprotein phenotype. Population studies have reported variable effects of CETP deficiency on the incidence of CVD. Certain populations with a high incidence of CETP deficiency are associated with lower rates of CVD and increased longevity. Functional polymorphisms that result in a reduction in CETP activity are associated with reduced clinical events. Several experimental approaches that inhibit CETP activity have been demonstrated to be atheroprotective in animal models. Oral chemical inhibitors of CETP have been developed. In early human studies, they raise HDL and lower LDL in a dose-dependent fashion. Their effect on clinical events and plaque burden remains to be determined.

The direct administration of HDL or its components has received considerable interest. Synthetic or rHDL particles comprising apoA-I complexed with phospholipid can be easily prepared in the laboratory setting. These particles have been demonstrated to possess similar functional properties and metabolic disposition as native forms of HDL-C. Single infusions of high dose rHDL have been demonstrated to rapidly improve endothelial function in human subjects with hypercholesterolemia or low plasma HDL-C concentrations, in the setting of heterozygous ABCA1 deficiency. Further, weekly infusions of rHDL-C containing the recombinant mutant apolipoprotein, apoA-I Milano, for 5 weeks promoted regression of coronary atherosclerotic plaque, as determined by intravascular ultrasound, in humans following ACS. In addition, strategies that involve the administration of phospholipid vesicles, apoA-I like mimetics, or selectively delipidated plasma are each being developed as a potential approach to promote HDL-C and its functional properties.

The ongoing development of these strategies will be accompanied by calls to establish target goals for HDL-C elevation. However, it remains to be determined whether it is the quantity or quality of HDL-C that is of greater importance. It has not been established whether wild-type apoA-I and its mutant form apoA-I Milano differ with regard to their influence on atheroma. Several groups have proposed that HDL-C can circulate in a dysfunctional form, with a loss of its established protective properties. HDL-C isolated from patients with high plasma levels and established CVD have been demonstrated to promote in vitro monocyte chemotaxis, suggesting that HDL-C in these subjects is proinflammatory. Further, it has recently been reported that apoA-I is a selective target for oxidative modification by the enzyme myeloperoxidase (MPO). Following modification by MPO catalyzed chlorination, the ability of apoA-I to promote ABCA1-dependent cholesterol efflux from macrophages is impaired. It remains possible that the most clinically important benefit of each of the HDL-C promoting strategies results from improving the functional quality of HDL-C. Regardless, with an increasing arsenal of therapeutic options, the time has arrived to test the hypothesis that directly targeting HDL-C will result in further reductions in cardiovascular risk.
References


