



Review

HDL-C as a new therapeutic target in the treatment of dyslipidemia

Ibrahim Sahin

Inonu University, School of Medicine, Department of Endocrinology and Metabolism, Malatya, Turkey

Abstract

Clinical and epidemiological studies have suggested that low plasma levels of high-density lipoproteins cholesterol (HDL-C) are independently associated with an increased risk of cardiovascular diseases (CVD). Accumulated data from epidemiologic, animal models and clinical studies support the view that raising HDL may be an effective new target to decrease cardiovascular risks. New insights in the understanding of the physiology, mechanisms and pathways by which HDL may reduce atherosclerosis allow new promising agents for increasing plasma HDL-C. In this regards, apo-AI analogs, acute HDL-C infusions therapies and new cholesteryl ester transfer protein CETP inhibitors have opened new expectations in the treatment of CVD.

Keywords: HDL, cardiovascular risks, treatment

Corresponding Address: Ibrahim Sahin MD, Professor of Internal Medicine, Inonu University, School of Medicine, Department of Endocrinology and Metabolism, Malatya, Turkey.

E-mail: ibrahim.sahin@inonu.edu.tr

Elevated low-density lipoprotein cholesterol (LDL-C) levels are a well-documented risk factor for cardio-vascular disease (CVD). Thus, current best treatment including lifestyle changes and drugs aimed at lowering plasma levels low-density-lipoprotein cholesterol (LDL-C). According to the NCEP ATP III guidelines, elevated LDL-C is the primary therapeutic target for interventions to decrease cardiovascular risk [1].

However, despite the lowered LDL levels, many high-risk patients continue to have cardiac events [2]. This implies that other CV risk factors beyond LDL-C may deserve attention.

Epidemiological studies have demonstrated that beside the LDL-C, high-density lipoprotein cholesterol (HDL-C) is also independent risk factors for the development of CVD [3,4]. In the Framingham Heart Study, HDL-C level was even more potent as a risk factor for coronary heart disease than was the level of LDL-C [5].

Elevated TG and low HDL-C levels also make significant contributions to increased cardiovascular risk even after LDL-C treatment target have been reached. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trail that showed an increase of cardiovascular events in diabetic patients with persistently low HDL-C and high triglyceride levels, despite a mean LDL-C less than 80 mg/dl compared with those with normal TG and HDL-C levels [6].

Similarly, post hoc analysis of treating to new target (TNT) study showed that HDL-C levels were predictive of major cardiovascular events in patients treated with statins. This relationship was also observed among patients with LDL cholesterol levels below 70 mg per deciliter [2].

The incidence of CVD in a normal population seems to be inversely related to the HDL-cholesterol levels and low levels being associated with increased coronary risk [7,8], Almost 25% of patients with known CVD have decreased HDL-C levels (<35 mg/ dl) without high LDL-C levels [9].

According to data from the Framingham Heart Study, the risk for myocardial infarction increases by 25 percent for every 5mg/dL decrease in serum HDL-cholesterol levels in men and women. Likewise, 43% to 44% of coronary events happened in patients with low HDL-C levels (<40 mg/dl) that constitute 22% of the total study population [10]. Patients with HDL-C levels less

than 35 mg/dL had 8-fold higher incidence of CVD compared with those with HDL-C levels of more than 65 mg/dL [11]. An analysis of data from large trials demonstrated that each increase of 1 mg per deciliter in HDL-C is associated with a decrease of 2 to 3% in the risk of future coronary heart disease [12].

Anti-atherosclerotic effects of HDL

HDL-C have several physiological properties that may explain their anti-atherosclerotic effects; the best well-known is the ability of HDL-C to promote the efflux of excess cholesterol from peripheral tissues to the liver for excretion HDL-C [13,14]. Anti-atherogenic properties may be independent of their involvement in cholesterol homeostasis. In this regard, HDL-C may also have role in modulating immune system and other potent biological activities, including anti-oxidative, anti-inflammatory, anti-infectious and vasodilatory actions. Moreover, it improves endothelial function, promote endothelial repair and increase insulin sensitivity [15-17].

Benefit of increasing HDL-C

The inverse relationship between HDL-C levels and cardiovascular risk led to the development of new therapies that increase HDL-C to decrease cardiovascular disease. Among currently available compounds, statins do not seems to have a sufficient effect on HDL-C profile.

Benefit of increasing HDL-C levels was evaluated by two randomized trials and multivariate analyses that in which the primary target was lowering LDL-C. VA-HIT trial designed evaluate effect of rising HDL for secondary prevention of CHD: 2531 patients with CHD who had an LDL-cholesterol ≤ 140 mg/dL, HDL-cholesterol ≤ 40 mg/dL, and triglycerides ≤ 300 mg/dL were included. They were randomly assigned to treatment with *gemfibrozil* or placebo [18]. After one year, the following differences were seen in the *gemfibrozil* group: mean HDL-cholesterol level was 6 percent higher, the mean total cholesterol and mean triglyceride concentration was lower (4 and 31 percent respectively). These differences persisted throughout the study. At five years, the combined primary end point of cardio-vascular death and nonfatal myocardial infarction seen less often in the *gemfibrozil* using group. Patients using *gemfibrozil* also had a lower rate of stroke

(4.6 versus 6 percent for placebo), transient ischemic attacks (1.7 versus 4.2 percent), and carotid endarterectomy (1.3 versus 3.5 percent) [19]. Further analysis of the VA-HIT trial indicated that the decrease in nonfatal myocardial infarction and CVD death was correlated with the serum HDL-C concentration achieved with gemfibrozil therapy, but was independent of changes in LDL-C or TG [20].

A second study aimed to evaluate additional benefits of combining statin with niacin, which increases HDL-C, in patients with low HDL-C. 160 patients with clinical and angiographic evidence of CVD who had an HDL-C less than 35 mg/dL and LDL-C less than 145 mg/dL were included [21]. Compared with placebo, patients receiving simvastatin plus niacin were developed significantly less frequent cardiovascular events and demonstrated angiographic regression.

Causes of low plasma HDL- cholesterol

The causes of low HDL-C include rare genetic disorders [22], familial hypoalphalipoproteinemia [23,24], familial HDL-C deficiency, Tangier disease, familial combined hyperlipidemias [25], elevated CETP activity, lipoprotein lipase deficiency [26,27], elevated hepatic triglyceride lipase activity [28], LCAT deficiency [29-30], secondary factors such as smoking, type 2 diabetes, Insulin resistance [31] metabolic syndrome and abdominal obesity acute infections or other inflammatory conditions, and drugs (beta blockers, benzodiazepines, and anabolic steroids) [32,33,34].

Current and Future Approaches to Increase Plasma HDL-C Levels

The current international guideline for the management of dyslipidemia in individuals with low HDL is recommendations of lifestyle changes. It includes exercise, elimination of cigarette smoking, and caloric restriction if not at ideal body weight. If these lifestyle changes do not adequately increase the HDL levels, selected patients may require pharmacotherapy. Most effective currently available drugs that increase plasma HDL levels are nicotinic acid, statins, and fibrates, which increase HDL by approximately 25, 5–8, and 15%, respectively[35].

Cholesteryl ester transfer protein (CETP) inhibitors

It has been shown that torcetrapib, anacetrapib, and dalcetrapib inhibit CETP and increase the HDL-cholesterol levels [35-37]. However, trial with torcetrapib has stopped due to unexpected pharmacological effects that led to an increased risk of cardiovascular events and deaths. Anacetrapib and dalcetrapib, which differ in their mechanism of action from torcetrapib, are under investigation [38,40]. The ultimate effect of CETP inhibition on cardiovascular disease outcomes remains to be determined

Therapies that under investigations

The intravenous administration of *apo A-I Milano* reduced intimal thickening and macrophage content in cholesterol-fed rabbits [41]. Similarly, patients treated with recombinant apoA-1 Milano phospholipid complexes ETC-216 had a significant decrease in the mean percentage atheroma volume in coronary artery (from 38.96 to 37.91 percent), while there was no significant change for the placebo group (from 34.80 to 34.94 percent). However, Infusions of *reconstituted human HDL* was failed decrease coronary atheroma volume in ERASE trial [42].

It is well established that reducing LDL-C levels using statins can significantly reduce CV risks [43]. However, even in patients who fully attain their recommended LDL-C target, residual CV risks remains high (~65%). Because, low level of HDL-C also an independent risk factor for CVD and the low HDL-C is often present in high-risk CVD patients [44].

Future strategies to reduce residual CV risk should therefore include increasing HDL-C levels in addition to lowering levels of atherogenic lipoproteins. In these regards promising agents like apo-AI analogs and new CETP inhibitors have opened new expectations for the treatment. However, to clarify, what is the best method to increase HDL-C, and will it reduce clinical cardiovascular events? Further studies are needed.

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