High density lipoprotein and cardiovascular diseases

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Abstract

Several epidemiological studies have clearly shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, it is unclear if there is a causal association between HDL-C concentration and CVD. A recent study published in the Lancet, which performed two mendelian randomization analyses, showed that increased HDL-C levels were not associated with a decreased risk of myocardial infarction. These findings, together with the termination of the niacin-based AIM-HIGH trial and the discontinuation of cholesteryl ester transfer protein inhibitor dalcetrapib, challenge the concept that raising of plasma HDL-C will uniformly translate into reductions in CVD risk. HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity. Furthermore, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of the structure of HDL particle with its functionality and metabolism.

Key words: High density lipoprotein; Functionality; Structure; Cardiovascular risk; Niacin; Cholesteryl ester transfer protein inhibitors

Core tip: Epidemiological studies have shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, recent studies challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. Certain patients with atherosclerosis may have "dysfunctional" HDL despite normal HDL-C levels. Furthermore, HDL-C levels are influenced by dietary patterns, drugs or concomitant diseases. The association of the structure of HDL particle with its functionality and metabolism has not been fully clarified. More research is needed to assess the association of HDL functionality with CVD risk.

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sisting of 14 common SNPs that exclusively associate with HDL-C (12482 cases of myocardial infarction and 41331 controls)\(^{[13]}\). Carriers of the LIPG 396Ser allele (2.6% frequency) had significantly higher HDL-C levels (0.14 mmol/L higher, \(P < 0.001\)) but similar levels of other lipid and non-lipid CVD risk factors compared with non-carriers. This difference in HDL-C is expected to decrease the risk of myocardial infarction by 13% (OR = 0.87, 95%CI: 0.84-0.91). However, the LIPG 396Ser allele was not associated with a reduced risk of myocardial infarction (OR = 0.99, 95%CI: 0.88-1.11, \(P = 0.85\)). Furthermore, whereas it is expected from observational epidemiology that an increase of 1 SD in HDL-C will be associated with a 38% reduced risk of myocardial infarction (OR = 0.62, 95%CI: 0.58-0.66), an 1 SD increase in HDL-C due to genetic score was not associated with a reduced risk of myocardial infarction (OR = 0.93, 95%CI: 0.68-1.26, \(P = 0.63\))\(^{[13]}\). These results became more intriguing when a genetic score of 13 common SNPs exclusively associated with low density lipoprotein cholesterol (LDL-C), used as a positive control, was associated with myocardial infarction risk in concordance with observational epidemiology\(^{[13]}\). Additionally, the termination of the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib was recently announced. Dalcetrapib, in contrast with torcetrapib, was not associated with non-lipid adverse effects\(^{[14]}\). In the dal-VESEL trial, dalcetrapib reduced CETP activity and increased HDL-C levels without affecting nitric oxide-dependent endothelial function, blood pressure, or markers of inflammation and oxidative stress\(^{[15]}\). Furthermore, co-administration of dalcetrapib with pravastatin resulted in decreased CETP activity, increased HDL-C, apolipoprotein (apo) A-1 and A-II levels and increased CETP mass. A relative increase in large HDL and LDL subfractions, combined with adenosine triphosphate (ATP)-binding cassette A1- and scavenger receptor type BI-mediated cholesterol efflux increase were also observed\(^{[16]}\). These effects seemed promising, but recently Roche announced that, following the results of the second interim analysis of the dalcetrapib dal-OUTCOMES Phase III trial (aimed to evaluate the efficacy and safety profile of dalcetrapib when added to existing standard of care in patients with stable coronary heart disease following an acute coronary syndrome), the independent Data and Safety Monitoring Board recommended stopping the trial due to a lack of clinically meaningful efficacy\(^{[17]}\).

Moreover, the results of two large studies of niacin were recently added to these disappointing results. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36 mo follow-up period, despite significant improvements in HDL-C and triglyceride levels\(^{[16]}\). More specifically, 3314 patients with atherosclerotic CVD and LDL-C levels < 70 mg/dL (1.81 mmol/L), were randomly assigned to extended-release niacin (1500-2000 mg/d) or placebo. All patients received simvastatin (40-80 mg/d) plus ezetimibe (10 mg/d), if needed, to maintain an LDL-C level of 40-80 mg/dL (1.03-2.07 mmol/L). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL-C level from 35 mg/dL (0.91 mmol/L) to 42 mg/dL (1.08 mmol/L) and decreased triglyceride level from 164 mg/dL (1.85 mmol/L) to 122 mg/dL (1.38 mmol/L) and LDL-C concentration from 74 mg/dL (1.91 mmol/L) to 62 mg/dL (1.60 mmol/L). However, the primary end point did not differ significantly between niacin (282 patients, 16.4%) and placebo (274 patients, 16.2%) groups (HR = 1.02; 95%CI: 0.87-1.21; \(P = 0.79\))\(^{[18]}\). In the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) study, the combination of niacin and laropiprant in addition to statin therapy did not significantly reduce the risk of major vascular events in patients with well-controlled LDL-C levels\(^{[19,20]}\). More specifically, the primary end point (the combination of coronary death, nonfatal myocardial infarction, stroke, or coronary revascularization) occurred in 13.7% of patients in the control arm and 13.2% of patients in the niacin/laropiprant arm (RR = 0.96, 95%CI: 0.90-1.03, \(P = 0.29\))\(^{[20]}\).

These data challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. HDL-C may simply be a marker of CVD risk, or, alternatively, may represent a biomarker of adverse metabolic processes, as for example of insulin resistance and inflammation.

Some investigators proposed that the failure of dalcetrapib and niacin is related to the only moderate elevation of HDL-C and we have to wait until more potent HDL-increasing drugs to be tested. This thought is based on findings from previous trials. A meta-analysis of 23 trials showed that the sum of percent reduction in LDL-C plus the percent increase in HDL-C predicts CVD benefits much more effectively than either lipoprotein component\(^{[20]}\). Hence, in populations that have already low LDL-C we need potent HDL-elevating drugs to produce significant increases in HDL-C in order to show clinical benefit.

Moreover, differences between levels of LDL-C and HDL-C and their corresponding particle number measures were observed in many trials. This may be of clinical importance since recent studies have shown that CVD risk in patients with discordance between cholesterol and particle measures of LDL and HDL may be associated more with particle measures\(^{[22]}\). For example, the significant CVD event reduction in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) could not be fully explained by the 6% increase in HDL-C with gemfibrozil\(^{[23]}\). When HDL subpopulations (characterized by 2-dimensional gel electrophoresis) were determined in subjects who were treated with gemfibrozil (\(n = 754\)) or placebo (\(n = 741\)), it was shown that gemfibrozil-mediated improvement in CVD risk might not be reflected
by changes in blood lipids and HDL subpopulations. In contrast, when nuclear magnetic resonance (NMR) spectroscopy was used to quantify levels of LDL and HDL particle subclasses and mean particle sizes during treatment with gemfibrozil (364 men) or placebo (697 age-matched controls), it was shown that gemfibrozil increased LDL size and lowered numbers of LDL particles (5%), whereas it increased the numbers of HDL particles (+10%) and small HDL subclass particles (+21%). In fact, the concentrations of these LDL and HDL particles achieved with gemfibrozil were independent predictors of new CHD events [total LDL particles: OR = 1.28 (95% CI: 1.12-1.47), total HDL particles: OR = 0.71 (95% CI: 0.61-0.81)], whereas mean LDL and HDL particle sizes were not associated with CHD events. Additionally, a nested case-control study within the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk cohort showed that both HDL size and HDL particle concentration were independently associated with coronary artery disease (CAD), but only HDL particle concentration was independently associated with CAD risk after adjustment for apoB and triglyceride levels [adjusted OR = 0.50 (95% CI: 0.37-0.66)]. These findings suggest that increasing HDL-C without increasing HDL particle number may influence the clinical outcome. The results of AIM-HIGH could be partly explained by these observations. Niacin, similarly to CETP inhibitors, alters the composition of HDL, making the particle larger. However, whereas it significantly decreases the mean number of small HDL particles and increases the mean number of large HDL particles, niacin does not significantly alter the total number of NMR-determined HDL particles. If these effects played a significant role in the negative clinical outcomes of AIM-HIGH remains to be established.

HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity. In this setting it is important that certain patients with atherosclerosis may have “dysfunctional” HDL despite normal HDL-C levels. Furthermore, HDL-C levels are influenced by many factors, such as dietary patterns, drugs or concomitant diseases. The heterogeneity in functionality should be taken into account when assessing the association of HDL with CVD risk. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. However, we do not know which of the HDL functions are more strongly associated with CVD in order to use it in clinical trials. Furthermore, there are several methods assessing different aspects of HDL functionality and many of them are complex and not part of routine bioassays. More research is needed to assess the association of HDL functionality with CVD risk and to simplify its determination. Additionally, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism. These characteristics may play divergent roles and result in different clinical outcomes. Hence, the association of the structure of HDL particle with its functionality and metabolism should be clarified and accordingly used in the clinical setting.

The role of HDL in CVD may be clarified by the Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial which includes 30000 patients and is currently testing whether the CETP inhibitor anacetrapib (which markedly increases HDL-C along with a lowering of LDL-C) on top of statin therapy will reduce the incidence of major coronary events (coronary mortality, myocardial infarction, and coronary revascularization) in patients with a history of CVD. This phase III study is expected to be completed by 2017. It should be mentioned that niacin and other HDL-increasing drugs, such as anacetrapib, also exhibit beneficial effects on atherogenic lipoproteins, such as LDL or lipoprotein a, so the results of on-going trials will not definitely answer the HDL hypothesis. In this setting, the results of on-going trials with drugs increasing apolipoprotein A-I may help to clarify the role of HDL in CVD.

Overall, based on the current evidence, it is unclear if there is a causal association between HDL-C concentration and CVD. HDL particles are very heterogeneous in terms of size, structure, composition and metabolism and exhibit several anti-atherosclerotic properties. The conflicting results of epidemiological and interventional studies may be attributed to the fact that HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of CVD risk with HDL functionality and metabolism.

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