Mini Review

# High-density lipoprotein cholesterol: How High

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## ABSTRACT

The high-density lipoprotein cholesterol (HDL-C) is considered anti-atherogenic good cholesterol. It is involved in reverse transport of lipids. Epidemiological studies have found inverse relationship of HDL-C and coronary heart disease (CHD) risk. When grouped according to HDL-C, subjects having HDL-C more than 60 mg/dL had lesser risk of CHD than those having HDL-C of 40-60 mg/dL, who in turn had lesser risk than those who had HDL-C less than 40 mg/dL. No upper limit for beneficial effect of HDL-C on CHD risk has been identified. The goals of treating patients with low HDL-C have not been firmly established. Though many drugs are known to improve HDL-C concentration, statins are proven to improve CHD risk and mortality. Cholesteryl ester transfer protein (CETP) is involved in metabolism of HDL-C and its inhibitors are actively being screened for clinical utility. However, final answer is still awaited on CETP-inhibitors.

**Key words:** High-density lipoprotein cholesterol, cardiovascular risk, cholesteryl ester transfer protein inhibitors

## Introduction

The high-density lipoprotein cholesterol (HDL-C) is a group of heterogeneous lipoproteins that are involved in the transport of sterols and lipids. HDL-C is considered as anti-atherogenic good cholesterol. Guidelines for management of patients with dyslipidemia primarily focus on achievement of target low-density lipoprotein cholesterol (LDL-C) levels for coronary heart disease (CHD) risk reduction (NCEP-ATP III).[1] However, there is increasing interest in high-density lipoprotein cholesterol (HDL-C) as a second line target of therapy. It is well-established that low concentration of HDL-C is associated with a higher risk of CHD and rising concentrations are associated with a fall in risk of CHD.[2,3] However, how high serum concentration of HDL-C is good enough, is not very clear.

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### Data from observational studies

HDL-C is popularly known as "good cholesterol" and high levels are associated with low cardiovascular risk, but the role of HDL in vascular disease is complex. Anti-atherosclerotic effects of HDL-C include increment in reverse cholesterol transport and macrophage cholesterol efflux, anti-inflammatory activity, inhibition of low-density lipoprotein (LDL) cholesterol oxidation, endothelial cell apoptosis. It also interferes with the thrombotic component of atherosclerosis by inhibiting platelet aggregation and reducing expression of cellular adhesion molecules.

The protective effect of HDL on atherosclerosis is suggested by the observation in humans that plasma HDL-C concentrations above 75 mg/dL are associated with prolonged life (the longevity syndrome) and relative freedom from coronary heart disease.[4]

Studies in animals have shown that overexpression of the apolipoprotein A-I gene (the major apolipoprotein in HDL cholesterol) prevents the development or progression of atherosclerosis.[5]

In an analysis of 4 prospective studies, it was shown that the risk of CHD with low HDL-C is independent of the risk attributed to elevated levels of LDL-C.[6] An increase

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of 1 mg/dl of HDL-C resulted in decrease of CHD by 2% in men and 3% in women. Low serum HDL-C can occur alone or be combined with insulin resistance, hypertriglyceridemia, and small dense LDL-C.[7] The inverse association between HDL-C and CHD risk is a continuous variable; No threshold relationship has been identified.[8] NCEP-ATP II specified low HDL-C (< 35 mg/dL) as one of several major coronary risk factors used to modify the therapeutic goal for LDL cholesterol. But, in ATP III, a level of less than 40 mg/dL was set as a low HDL-C both in men and women and a level of greater than 60 mg/dl as high HDL-C. In the Framingham Heart Study, the risk for myocardial infarction increased by about 25% for every 5 mg/dL decrement in serum HDL-C.[8] When using HDL-C of 35-59 mg/dL as a reference stratum, CHD was increased in those with HDL-C < 35 mg/dL while it was less in those with HDL-C > 60 mg/dL {multivariate adjusted relative risk 1.47 (men) and 2.02 (women) vs. 0.56 (men) and 0.58 (women), respectively}.)

Serum HDL-C inversely predicts the time to a first major cardiovascular event as well as the risk of coronary events in patients with known CHD across a broad range of LDL-cholesterol levels.[9] Low HDL-C is also a stronger predictor of CHD events in patients with an LDL-C < 125 mg/dl.[10]

When divided into quintiles, the highest quintile of HDL-C (mean ± SD 61.5 ± 10.1 mg/dL) had 40% lower rates of CHD than the lowest quintile (35.7 ± 4.5 mg/dL).[9]

In a meta-analysis of studies in the Asia-Pacific region, there was a negative correlation between HDL-C and CHD events (hazard ratio 1.57; 95% CI 1.31-1.87), again underscoring the role of low HDL-C.[11]

Patients with diabetes mellitus have a higher risk of CHD and in general, have been assigned a lower target value for serum LDL-C. However, in Chinese patients with type 2 diabetes mellitus, HDL-C was again found to have no definite threshold for CHD risk. With every 1 mmol/L (mmol/L= mg/dL X 0.02586) increase in HDL-C, the risk of CHD decreased (HR 0.61, 95% CI 0.45-0.84).[12] Use of statins reduced the risk of CHD by 51% in those with low HDL (<1 mmol/L in males and <1.3 mmol/L in females).

However, certain conditions with low HDL-C do not have increased risk for CHD, such as Tangier disease, and stand out as exceptions to the HDL-C and CHD association.

It has also been reported that it may not be the HDL-C concentrations but the HDL-C particle number that is protective for markers of atherosclerosis.[13]

### Data from intervention studies

The drugs in clinical use that alter the serum HDL-C concentration favorably are niacin and gemfibrozil. However, many other drugs like statins, cholestyramine, and colestipol have been known to have some effect. A new class of drugs, cholesteryl ester transfer protein (CETP) inhibitors, is currently under trial for the same purpose.

On intervention with pravastatin for each 10 mg/dL increase in HDL-C, the event rate decreased by 29% in those with LDL-C < 125 mg/dL compared to 10% in those with an LDL-C ≥ 125 mg/dL.[10] With atorvastatin, 1 mg/dL increment in HDL at 3 months has been reported to decrease the risk of CHD by 1.1% irrespective of sex.[9] However, no threshold of HDL-C for the beneficial effect was observed in either of the trial.

Similarly, use of gemfibrozil has also been found to be effective in elevating HDL-C and reducing vascular events in patients with CHD having LDL-C ≤ 140 mg/dL, an HDL-C ≤ 40 mg/dL, and triglycerides ≤ 300 mg/dL.[14] In a trial of combined use of simvastatin and niacin for 3 years in patients with CHD who also had HDL-C < 35 mg/dL and LDL-C < 145 mg/dL, HDL-C improved by 26%.[15] It also resulted in reduction in vascular events much more than that expected with statins alone, possibly due to improvement in HDL-C. Trials of niacin in patients with CHD or CHD risk equivalent, having low HDL-C have, shown elevation of HDL-C with niacin with reduction in carotid intima medial thickness.[16]

CETP AND CARDIOVASCULAR RISK—CETP is involved in metabolism of HDL-C and its role has also been studied. Polymorphisms affecting the activity of CETP reduce the activity of CETP and increase HDL-C. CETP inhibitors have been tried to modify HDL-C, and they are still under trial. Torcetrapib, anacetrapib, evacetrapib, and dalcetrapib inhibit CETP and raise HDL-C. However, torcetrapib was reported to increase risk of CHD and interest in it has waned.

## Conclusions

The National Cholesterol Education Program (Adult Treatment Program [ATP] III) guidelines, published in 2001, identified HDL-C more than 60 mg/dL as reasonably good level while less than 40 mg/dL was considered low. The goals of treating patients with low HDL-cholesterol have not been firmly established. Relationship of HDL-C and CHD risk is linear, and no upper limit of HDL-C has been identified. Among all the drugs tried to improve serum HDL-C concentrations, statins only have shown reduction in CHD risk and mortality. As far as CHD risk

is concerned, it appears that higher the HDL cholesterol is, better it is.

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