

HDL cholesterol concentration or HDL function: which matters?

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This editorial refers to ‘Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies’, by C.M. Madsen et al., doi: 10.1093/eurheartj/ehx163.

The HDLs circulating in human plasma are extremely complex, and their relationship with atherosclerotic cardiovascular disease (ASCVD) is complicated. Human HDLs comprise multiple discrete subpopulations of particles that differ in size, shape, charge, and in composition of both lipids and proteins.¹ The individual constituents of HDLs enter the plasma separately and are assembled into HDL particles within the plasma. HDLs are subject to continuous remodelling by multiple plasma factors, and the individual constituents are subsequently removed from plasma separately rather than as an uptake of the intact particle. HDLs have several functions that have the potential to protect against atherosclerosis,² although how the different functions relate to different HDL subpopulations is not known. It is also uncertain whether any of the known HDL functions directly or indirectly protect against development of ASCVD and associated clinical events.

Large human population studies have shown consistently that a low concentration of HDL cholesterol is an independent predictor of an increased risk of having an ASCVD event.³ Furthermore, increasing HDL cholesterol levels in animals, whether by intravenous infusions of HDLs⁴ or by increasing the synthesis of apoA-I (the major HDL apolipoprotein) by transgenic expression of the *ApoA1* gene,⁵ markedly decreases susceptibility to the development of atherosclerosis in both mice and rabbits. However, interventions that increase the concentration of HDL cholesterol in humans have, to date, failed to translate into a decrease in the risk of having an ASCVD event. In addition, there is robust evidence that some gene variants that increase the plasma concentration of HDL cholesterol are not accompanied by a reduced risk of having an ASCVD event.⁶ Now, as reported in a paper published in this issue, there is compelling evidence that people with extreme high levels of HDL cholesterol have an increased rather than a decreased risk of death from cardiovascular disease, cancer and, other causes.⁷

Analysis of data from the Copenhagen City Heart Study and the Copenhagen General Population Study has shown that the presence of an extremely high concentration of HDL cholesterol is predictive of an increase in all-cause mortality in both men and women.⁷ This analysis included 52 268 men and 64 240 women and provided 745 452 person-years of follow-up with 5619 deaths. The relationship between HDL cholesterol concentration and mortality was U-shaped, with an increased risk observed at both low levels and extreme high levels of HDL cholesterol. The lowest mortality was observed with HDL cholesterol levels of 1.9 mmol/L in men and 2.4 mmol/L in women. The observed increase in mortality in those with low levels of HDL cholesterol is consistent with findings from previous studies of the relationship of HDL cholesterol level with ASCVD.³ An increased mortality in those with extreme high levels of HDL cholesterol has also been reported previously.^{8,9} This observation of an increased mortality associated with extreme high HDL cholesterol has clinical implications, and risk algorithms that include HDL should be revised accordingly. The observation also indicates that ratios, such as the ratio of total cholesterol to HDL cholesterol, should no longer be included in algorithms designed to calculate ASCVD risk.

There is no obvious mechanism to explain an increased mortality associated with extreme high levels of HDL cholesterol. It is possible, however, that some factor or factors leading to an increase in mortality also increase the concentration of HDL cholesterol, in which case the extreme high HDL cholesterol level may be a (non-causal) biomarker of an increased risk of death.

The results of human population studies showing that a low level of HDL cholesterol is an independent predictor of the risk of having an ASCVD event have led to a view that HDL cholesterol may be protective. It is highly unlikely, however, that the cholesterol contained in HDL plays any protective role. Rather, if HDLs do protect, it is most likely to be the consequence of their protective functions rather than a simple increase in the amount of cholesterol transported in this lipoprotein fraction.

Several well-documented functions of HDLs have the potential to protect against ASCVD² (Figure 1). The most extensively studied of

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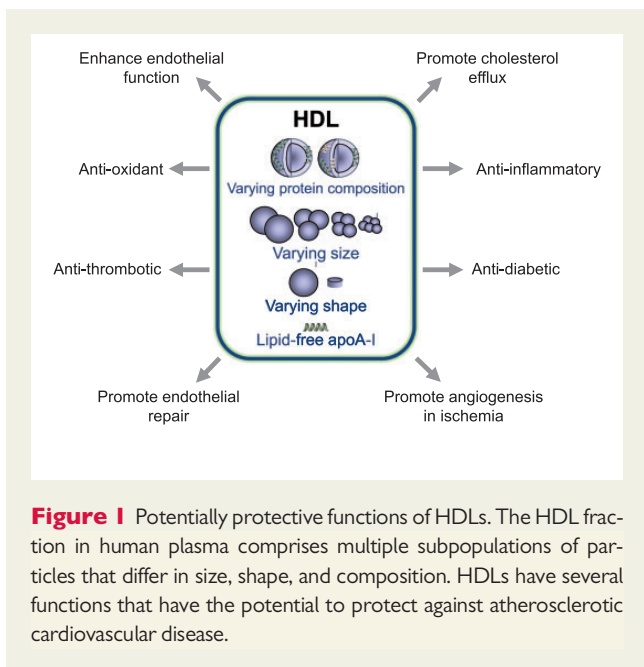


Figure 1 Potentially protective functions of HDLs. The HDL fraction in human plasma comprises multiple subpopulations of particles that differ in size, shape, and composition. HDLs have several functions that have the potential to protect against atherosclerotic cardiovascular disease.

these functions relates to the ability of HDLs to promote efflux of cholesterol from macrophages in the artery wall. There is evidence that the cholesterol efflux capacity of HDLs (as measured *ex vivo*) is an inverse predictor of the risk of having a clinical ASCVD event, independent of the plasma concentrations of HDL cholesterol and apoA-I.¹⁰ HDLs also have other potentially protective functions,² including an ability to inhibit vascular inflammation. HDLs also have anti-oxidant and anti-thrombotic properties. They enhance endothelial function, promote endothelial repair, increase angiogenesis in ischaemia, and have recently been reported to have anti-diabetic properties.¹¹ It is currently not known which HDL component(s) and which HDL subpopulations are responsible for these potentially cardio-protective functions.

The observation in human population studies that the HDL cholesterol concentration is an inverse predictor of ASCVD events may indicate that, in most people, the protective functions of HDLs correlate closely with the concentration of HDL cholesterol. If this is the case, the study reported by Madsen *et al.*⁷ may indicate that in people with extreme high levels of HDL cholesterol, the functionality of HDLs may be compromised, with the concentration of HDL cholesterol no longer reflecting HDL function. Such dysfunctional HDLs may even cause harm.

Impaired HDL functionality has been reported in people who have had a recent acute coronary syndrome (ACS) event.¹² This may explain why there was no relationship between HDL cholesterol concentration and ASCVD events in the placebo group in the dal-OUTCOMES trial that was conducted in people soon after an ACS event.¹³ A disconnect between HDL cholesterol concentration and HDL function may also explain the observation that gene variants resulting in an elevated level of HDL cholesterol are not invariably accompanied by a reduced ASCVD risk.

Clinical outcome trials of HDL cholesterol-raising agents have, to date, failed to show a reduction in ASCVD events. Increasing HDL cholesterol levels by inhibiting cholesteryl ester transfer protein

(CETP) has failed to translate into a reduction in ASCVD events in three large clinical outcome trials. This is despite observations that inhibiting CETP enhances HDL function.¹⁴ It should be noted, however, that results of the outcome trials with CETP inhibitors are difficult to interpret. Serious adverse effects of torcetrapib (unrelated to CETP inhibition) in the ILLUMINATE trial¹⁵ may have been responsible for the harm caused by the drug, making it impossible to determine the effects of CETP inhibition. The dal-OUTCOMES trial with dalcetrapib was conducted in people soon after an ACS event when HDLs are known to be dysfunctional.¹² The ACCELERATE trial using evacetrapib was also terminated for futility after a follow-up of ~2 years, a duration that may have been insufficient to see an effect on cardiovascular events. The results of the fourth clinical outcome trial investigating the effects of CETP inhibition, the REVEAL trial with anacetrapib, are not yet known. REVEAL included >30 000 participants with a follow-up of >4 years. A failure to observe a reduction in ASCVD events in this trial will establish beyond reasonable doubt that increasing HDL cholesterol levels by inhibiting CETP in statin-treated patients does not reduce ASCVD risk. The explanation is not known but may be because inhibition of CETP somehow impairs reverse cholesterol transport and may thus have the potential to increase rather than decrease ASCVD risk in statin-treated patients.

The many inconsistencies related to relationships between HDL cholesterol concentration, HDL function, and atherosclerosis, and now the observation of increased mortality associated with extreme high levels of HDL cholesterol highlight the fact that there remains a high degree of ignorance regarding the role of HDLs as either protectors or causes of disease. Without such knowledge, it is not possible to decide whether the HDL fraction should be considered as a therapeutic target and, if so, what interventions should be used to enhance HDL function in ways that may translate into a reduction in mortality and morbidity.

In conclusion, HDLs have several functions with the potential to inhibit development of ASCVD. However, while increasing HDL cholesterol levels by increasing apoA-I synthesis in animals reduces susceptibility to atherosclerosis, gene variants that increase the concentration of HDL cholesterol in humans are not accompanied by a reduced risk of having an ASCVD event. Furthermore, HDL cholesterol-raising therapies in humans have not, to date, translated into a reduction in ASCVD events. In addition, it is now apparent that an extremely high level of HDL cholesterol is an independent predictor of increased mortality. Whatever the explanation for this latter observation, it is clear that there is much that we still do not understand about HDLs. In our view, the inconsistencies and confusion about HDLs highlight the need for further research to establish definitively whether or not this lipoprotein fraction has the ability to protect against disease.

Conflict of interest: none declared.

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