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HDL: Is it protective?

- ***Note: HDL cholesterol is not a surrogate for HDL function***

High-density lipoprotein (HDL) cholesterol is a contentious subject. While experimental studies support a number of potentially atheroprotective effects for HDL,[1] other findings have been less promising. Recent outcomes trials of agents targeting HDL cholesterol have failed to show any clinical benefit.[2-5] In addition, genetic analyses failed to show a causal association between genetically raised plasma HDL cholesterol levels and risk for heart attack.[6] Is this the demise of the 'HDL hypothesis'?

However, it is important to consider what is so far understood about the nature of the HDL particle population, and the relevance of plasma HDL cholesterol levels to the potential atheroprotective functions of HDL.

There is indisputable epidemiological evidence that a low plasma concentration of HDL cholesterol is a cardiovascular risk factor, supporting its inclusion in SCORE risk assessment. In the largest analysis to date, the Emerging Risk Factors Collaboration with data from more than 300,000 individuals without cardiovascular disease at baseline, showed that a low plasma HDL cholesterol concentration was an independent cardiovascular risk factor, with each 0.38 mmol/L (15 mg/dL) increase in levels associated with a 22% reduction in coronary risk. However, the relationship between the level of HDL cholesterol and coronary risk appeared to plateau at about 1.3 mmol/L or 50 mg/dL, beyond which there was no further benefit associated with raising HDL cholesterol levels.[7] This relationship also persists among patients with very well-controlled low-density lipoprotein (LDL) cholesterol levels on statin therapy.[8]

There is also compelling evidence in animal studies,[9] that treatments that raise HDL can reduce progression or even promote regression of atherosclerosis.

How to reconcile these findings?

'*We need to dispel the confusion around HDL. First, it is a misnomer to consider plasma HDL cholesterol concentration as a surrogate for HDL function.'* – Professor Arnold von Eckardstein, University of Zurich and Institute of Clinical Chemistry, University Hospital of Zurich, Switzerland.

Unlike LDL, the HDL particle population is much more complex. HDL particles are highly heterogeneous in terms of size, molecular composition, structure and function. HDL particles contain about 100 proteins and hundreds of lipids; these lipid and protein constituents are continuously undergoing remodelling. Historically, as incorporation of cholesterol (as cholesteryl esters) was

shown to be critical for the formation of large mature HDL particles that transport cholesterol to the liver for eventual elimination from the body, it was thought that HDL cholesterol concentration was a biomarker of this critical aspect of HDL function.[10] However, as understanding of HDL biology increases, it is clear that HDL cholesterol plasma concentration is not a surrogate for HDL function. Indeed, HDL plasma concentration is a static measurement which does not take into account the dynamic remodelling of the plasma pool of HDL particles.

If HDL cholesterol is not the best measure, which is?

'So far, this remains largely unknown. Overall, there is no evidence that apolipoprotein A-I, the main protein in HDL, performs better than HDL cholesterol as a surrogate of HDL function. While some studies indicate statistically significant differences, these are probably of no clinical relevance. Certainly apolipoprotein A-I does not perform better than HDL cholesterol in risk assessment.' – Professor Arnold von Eckardstein

The hunt for new biomarkers for HDL has recently focused on bioassays assessing the functionality of HDL. Most evidence to date relates to assessment of macrophage cholesterol efflux capacity, with a recent study showing that this was inversely associated with increased risk of coronary artery disease.[11] However, here again there is controversy, as other groups have failed to show any association.[12] At the moment, measuring HDL function remains a research tool that requires much more refinement before becoming feasible for use in clinical laboratories, or as a surrogate marker in large clinical trials. Finally, how do we translate changes in HDL function, such as cholesterol efflux capacity, to cardiovascular risk?

'While HDL cholesterol is very good in risk assessment, changes in HDL cholesterol cannot be translated to risk prediction. This may be one of the reasons why recent trials of agents targeting HDL cholesterol have failed.' – Prof. Arnold von Eckardstein

Clearly, we need better biomarkers of HDL that are relevant to its biological functions in protecting against atherosclerosis. Ongoing attention is focusing on modification of protein/lipid within the HDL particle, as this may offer important insights into what is happening within the arterial wall.

A final point about recent trials

The design of the trial, including the nature of the patient population, also warrants a note. So far, trials have failed to specifically select those patients with low HDL cholesterol. For example, in the recent HPS2-THRIVE trial, mean HDL cholesterol after the pre-randomisation 8-week run-in period (on niacin/laropiprant) was 1.14 mmol/L (44 mg/dL).[4] Considering the epidemiological evidence discussed above, it was therefore unlikely that any increase in HDL cholesterol concentration from this baseline value would translate to improved clinical benefit.

It is also important to consider the potential for confounding due to the extent of concomitant preventive therapy. In the dal-OUTCOMES study[3] in patients with acute coronary syndrome, there was extensive co-treatment including aspirin, statins, thienopyridines, betablockers, and agents

acting on the angiotensin renin system. It is therefore unlikely that it would be feasible to show any benefit from HDL-raising against the confounding due to this high level of co-treatment.

The search for agents that target HDL continues; however, it is important to be more circumspect in selecting the most appropriate patient population.

'While recent trials testing HDL raising agents have been flawed in design, this does not exclude the likelihood that correctly defined trials would have shown an effect. However, to date nobody has defined a trial to test specific agents in the correct patient population. With the focus on personalised medicine this would be the ideal way forward.' – Prof. Arnold von Eckardstein

Details of Congress Sessions:

***Accredited Educational Symposium: Mixed hyperlipidemia and triglycerides in cardiovascular prevention, Sunday June 1st, 13:00-14:30**

***Workshop: Novel protective effects of HDL: Monday June 2nd, 15:00-16:30**

*** Clinical and Latebreaking Session II: Monday June 2nd, 15:45-16:30**

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