Is it Time for HDL to Change its Tune?

Running title: Nicholls et al.; HDL particles and risk

Stephen J. Nicholls MBBS, PhD1; Rishi Puri MBBS2

1South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia; 2Dept of Cardiovascular Medicine and C5Research, Cleveland Clinic, Cleveland, OH

Address for Correspondence:
Stephen Nicholls, MBBS, PhD
South Australian Health and Medical Research Institute
PO Box 11060
Adelaide, SA, 5001, Australia
Tel: +61-8-8116-4432
Fax: +61-8-8116-4432
E-mail: stephen.nicholls@sahmri.com

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Over the course of the last century, increasing evidence has accumulated to implicate a central role for atherogenic lipoproteins in the pathogenesis of atherosclerotic cardiovascular disease. This is supported by the importance of cholesterol measurement for risk prediction and use of lipid modifying therapies in primary and secondary prevention. Recent reports have suggested that particle based measurements of atherogenic lipoproteins may provide additional information in risk stratification.\(^1\) In particular, persistently elevated measures of low-density lipoprotein (LDL) particles, in patients whose LDL-cholesterol (C) appears optimally controlled, may identify individuals more likely to benefit from more intensive lipid lowering.

In parallel, there has been considerable interest in the potential protective properties of high-density lipoproteins (HDL) for the development of new risk prediction markers and cardiovascular therapeutics. This is based upon observations from large population cohorts of an inverse relationship between HDL-C levels and prospective risk of cardiovascular events\(^2\) and of favorable effects with HDL targeted interventions in animal models of atherosclerosis.\(^3\) While HDL-C is used in traditional risk stratification, and raising HDL-C may contribute to the clinical benefit of current therapies,\(^4\) it remains to be determined whether substantial HDL-C raising will be protective of incident cardiovascular events.

However, a number of recent developments have brought the potential protective role of HDL into question. Several clinical trials of agents that substantially raise HDL-C have been demonstrated to not reduce cardiovascular event rates.\(^5-8\) While some clinical trials demonstrated the association between on-treatment levels of HDL-C and cardiovascular events,\(^9\) others did not.\(^6,10\) Mendelian randomization studies demonstrated the association between polymorphisms and differences in levels of HDL-C. Unlike LDL-C, HDL-C appears not to associate with varying levels of cardiovascular risk, nor a causal role in the atherosclerotic disease process.\(^11\)
While there continues to be hope that potent cholesteryl ester transfer protein inhibitors, which substantially raise HDL-C, will be of clinical benefit, such benefit may ultimately be derived exclusively from their LDL-C lowering properties.

What has become apparent in the course of these sobering messages regarding HDL-C is that cholesterol based measures of HDL may only tell us part of the story. HDL is known to circulate in plasma as a heterogeneous cohort of particles, varying markedly in terms of their size, shape and composition of proteins and lipids. To what degree this influences the relative functional properties of these particles and their ability to protect the artery wall remains unknown. In recent years, a plethora of functional assays have been reported in relation to HDL, which in some cases have been reported to correlate with the likelihood of coronary disease. However, a lack of standardization of these assays and conflicting reports of their clinical correlation continue to limit their ability to be successfully integrated in risk prediction algorithms or early evaluation of novel lipid-modifying therapies undergoing clinical development.

Measurement of the circulating HDL particle load has received increasing attention. Given that it is the HDL particle, as opposed to its cholesterol content, that traffics lipid and conducts non-lipid transporting activities, this may provide particularly useful information. The potential clinical implications of a given HDL-C measure differ depending on whether it reflects the presence of a large number of HDL particles, each containing small amounts of cholesterol, as opposed to much fewer, cholesterol rich, particles. The challenge has been to develop high-throughput, well-standardized and reproducible approaches to the measurement of HDL particle concentration and size.

In the current issue of Circulation, Mora and colleagues present further data highlighting...
the potential clinical distinction between cholesterol and particle based measures of HDL. In an analysis of 10,886 patients from the JUPITER study, the authors report that the on-treatment concentration of HDL particles as measured by nuclear magnetic resonance spectroscopy, inversely associated with adverse cardiovascular events in both placebo and rosuvastatin-treated patients. This contrasts with a previous report by this group, in which HDL-C was found not to significantly associate with cardiovascular events in the statin-treated group. Overall, these findings add to an accumulating body of data that support the concept that HDL-C and its recent failures may only tell us a small part of the overall HDL picture. It has been a quarter century since the introduction of statins to clinical practice. During that time there has been an ongoing search to develop additional therapeutic strategies to achieve greater reductions in cardiovascular risk. However, to date HDL-C raising has proven to be disappointing. Despite this, HDL continues to attract major interest as a target of value. The current data from Mora and colleagues continue to suggest that we should not throw the baby out with the bath water. Perhaps it is time for us to change the way in which we look at HDL, and to perhaps move from a cholesterol-based to a particle-based world. This requires considerable ongoing validation and testing in the clinical trial setting. However, by doing this we may ultimately get one step closer to a setting in which functional HDL takes center stage.

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