Jekyll and Hyde of HDL: a lipoprotein with a split personality

Prediman K. Shah*

Division of Cardiology and Oppenheimer Atherosclerosis Research Center, Cedars Sinai Heart Institute and Department of Medicine at Cedars Sinai Medical Center and UCLA, CA, USA

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This editorial refers to ‘Lack of protective role of HDL-C cholesterol in patients with coronary artery disease undergoing elective coronary artery bypass grafting’, by E. Angeloni et al., on page 3557 and ‘High-density lipoprotein cholesterol, angiographic coronary artery disease, and cardiovascular mortality’, by G. Silbernagel et al., on page 3563

Strange Case of Dr Jekyll and Mr Hyde

Robert Louis Stevenson 1886

Epidemiological data that showed the inverse relationship between HDL- cholesterol (HDL-C) levels and coronary heart disease (CHD) events led to the labelling of HDL-C as the ‘Good Cholesterol’. Recent analyses have provided conflicting results regarding whether the inverse relationship between HDL-C and CHD risk is retained in statin-treated patients with low LDL-C levels; some studies showing persistence of this relationship whereas others failed to show such a relationship. Although epidemiological associations do not necessarily imply causality, the known biological functions of HDL and its constituents in vitro and in vivo (Figure 1), as well as the vascular benefits of direct administration or overexpression of HDL-related proteins, specifically Apo A-I, have supported such a causality. Despite these seemingly concordant data, the notion that higher HDL-C is better has been turned upside down by the results from several clinical trials, seriously challenging the conventional dogma or the so-called HDL hypothesis. These trials have failed to show CHD or mortality benefits from raising HDL-C levels by inhibiting cholesteryl ester transfer protein (CETP), using two different compounds (torcetrapib and dalcetrapib) or by using extended release niacin (ER-niacin) with or without a flushing inhibitor [niaspan and niaspan–laropiprant combination (tredaptive)]. In fact, increased cardiovascular and non-cardiovascular death rates observed with torcetrapib suggested actual harm which was attributed, in part, to activation of the aldosterone pathway and increase in blood pressure. The possibility that the limitations of trial design in the AIM-High trial of niacin (inclusion of low-dose niacin in the placebo group and underpowering of the study) and inclusion of laropiprant in the HPS-Thrive study may have contributed to the failure of niacin in these trials cannot be totally excluded.

Recent genetic Mendelian randomization studies have also questioned the causality of inverse relationship between HDL-C and CHD risk while reaffirming the relationship of LDL-C levels and CHD risk. So what is up with HDL and CHD? How can it be protective and non-protective at the same time: a sort of Jekyll and Hyde split personality? Two observational studies, published in this journal, further add to this conundrum. In the study by Angeloni et al., the association of HDL-C levels (dichotomized as below or above 40 mg/dL in men and below or above 50 mg/dL in women) with cardiovascular events and death was examined in a cohort of patients with known coronary artery disease (CAD) undergoing elective isolated coronary artery bypass graft surgery (CABG). There was no significant relationship between low vs. high HDL-C levels and clinical outcomes; if anything, higher levels of HDL-C were paradoxically associated with a trend towards higher morbidity. This study is limited by its retrospective nature even though the authors used propensity-adjusted analysis as well as analysis of the entire cohort with appropriate multivariate adjustments. In the second study, Silbernagel et al. provide further challenge to the HDL-C hypothesis. In a carefully characterized cohort of 3141 subjects with and without angiographic evidence of CAD, the authors noted a robust inverse relationship between HDL strata and 8 year CHD risk in subjects without angiographic CAD but not in the subgroup with established CAD at baseline. Similar results were noted in the analysis of AtheroGene (n = 3413) and ESTHER (n = 5738) study cohorts, as well as in the meta-analysis of all three cohorts (n = 12 292). Once again these data conflict with the long-standing view that HDL-C and CHD risk are inversely related.
and, in fact, indirectly support the concept that HDL in CAD patients may be relatively impotent in as far as its vascular protective effects are concerned. These two observational studies further demonstrate the complex relationship between HDL and CHD risk that does not fit in a simple neat package but appears to be much more nuanced: HDL-C does not equal HDL function.

Why is HDL so difficult?

How can we reconcile the variable epidemiology and the failure of several HDL-C-raising therapies with the compelling body of data that shows vascular protective effects of HDL-related proteins in pre-clinical and clinical models of atherosclerosis? One possible explanation for these disparate results is that the vascular protective function of HDL may vary under different conditions and that HDL-C levels may not be a reliable indicator of vascular protective function of HDL under different conditions.

HDL-C vs. HDL composition and function

Despite compelling epidemiology, why has raising HDL-C not proven to be effective against CHD? The precise answer is not known, but several potential reasons could explain the conundrum. HDL is a highly heterogeneous family of particles that vary by size, charge, shape, density, and composition (cargo of proteins) with probably different functionality based on one or more of these attributes. Simply measuring HDL-C levels (cholesterol content of HDL particles) does not appear to be a reliable predictor of HDL function. There is experimental and some clinical data to suggest that HDL particle composition may change with different diseases and different therapeutic interventions that may not be reflected simply by changes in HDL-C levels. Acute and chronic inflammatory states may render HDL depleted of atheroprotective molecules such as Apo A-1, paraoxonase (PON), clusterin (Apo J), and sphingosine 1 phosphate (S1P), and enriched in proinflammatory proatherogenic molecules such as serum amyloid A (SAA), haemoglobin–haemopexin complex, caeruloplasmin, symmetrical dimethylarginine (SMDA), and, importantly, Apo CIII, making the HDL particles more pro-oxidant and proinflammatory (so-called dysfunctional HDL). The presence of so-called dysfunctional HDL has been demonstrated in patients with established CAD, diabetes, and other chronic inflammatory conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Crohn’s disease, antiphospholipid syndrome, psoriasis, chronic renal failure, and exposure to particulate matter and environmental pollution. The failure of the CETP inhibitor torcetrapib, while often attributed to activation of the aldosterone pathway, may also have resulted from production of dysfunctional HDL; a concept supported by the failure of another CETP inhibitor dalce-trapib which did not activate the aldosterone pathway. Rodent studies have also shown that genetic deletion of SRB1 increases atherosclerosis despite elevations in HDL-C levels, and gain of function of SRB1 reduces atherosclerosis despite HDL-C lowering. The human carriers of genetic variants of SRB1 have shown discordance between HDL-C levels and HDL function. Similarly, not all low HDL-C states in humans are associated with increased CHD risk: carriers of Apo A-I Milano mutation have very low HDL-C levels and yet appear to be relatively protected from vascular disease.

Could the HDL conundrum be solved if we could measure HDL function in a reliable, simple, and reproducible way? The answer to this question remains largely unknown at this time, although some clinical data seem to suggest that HDL-mediated cholesterol efflux capacity measurement may be a better correlate of inverse cardiovascular risk and CAD incidence than HDL-C levels; this paradigm, however, needs more extensive validation.
Could raising HDL-C when LDL-C is already well controlled be less beneficial?

Interventional trials to raise HDL-C with niacin and dalcetrapib, conducted against a background of statin therapy with well controlled LDL-C levels (~70 mg/dL) have been negative, suggesting the possibility that once LDL-C is well controlled, HDL-C may be less relevant for risk assessment and risk mitigation. These findings are in keeping with the analysis of the Jupiter and DalOucomes trials where the actively treated group failed to show an inverse relationship between HDL-C and CHD risk, but contradict findings from the TNT trial. Favourable vascular and clinical effects of niacin in trials where the comparator is placebo (therefore involving subjects with higher LDL-C levels) rather than a statin are consistent with this possibility.

HDL particle number and particle size

Some have argued that low HDL-C may simply serve as a marker of risk rather than a mediator of risk. While this may be true for HDL-C levels, it is clear that HDL-C is not the same as HDL, as discussed above. Measuring HDL particle numbers and small pre-beta HDL (lipid-poor particles considered to be the major acceptors of free cholesterol from macrophages) has been suggested to be a better descriptor of HDL’s relationship to CHD risk, but whether particle number or HDL particle size will predict HDL function and the effects of HDL-C-raising therapies remain unknown, and will require further investigation.

What is likely to be the future of HDL-based therapies?

It is clear that therapies that utilize HDL-based interventions can no longer rely simply on HDL-C levels as a surrogate for benefit or lack of benefit; therefore, one would need to rely on measures of atherosclerotic plaque burden and/or plaque composition as an intermediate step for proof of concept and/or only rely on event-based large-scale clinical trials. The imperative to develop bioassays that measure HDL function in a reliable and reproducible manner is obvious. Inhibition of CETP to raise HDL-C is still being pursued, even though the role of CETP in atherosclerosis is controversial. Two new CETP inhibitors, evacetrapib and anacetrapib, that produce large increases in HDL-C (>100%) and reductions (~20%) in LDL-C and do not appear to have off-target effects of activating the aldosterone pathway, are currently being tested in phase III trials, and it will be interesting to see if they can resurrect the HDL hypothesis or bury it once again. Other HDL-based strategies in development include various Apo A-I-mimetic peptides, an oral inducer of Apo A-I

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**Figure 2** This schematic depicts how changes in the composition of HDL in various conditions could result in non-functional or dysfunctional HDL which loses vascular protective effects or create a superfunctional HDL containing a mutant of Apo A-I. CAD, coronary artery disease; Hgb, haemoglobin; MPO, myeloperoxidase; RA, rheumatoid arthritis; SAA, serum amyloid A; SLE, systemic lupus erythematosus; SMDA, symmetric dimethylarginine; S1P, sphingosine 1 phosphate.
gene transcription (RVX-208), nuclear hormone receptor agonists, HDL delipidation, whole HDL particle infusion with CER-001, MDCO-216, or CSL-112, and gene therapy using HDL-related proteins such as Apo A-I. Further clinical evaluation of direct infusion of mutant (Apo A-1 Milano) or wild-type Apo A-1, linked with a phospholipid carrier, appears warranted since their vascular benefits have been repeatedly demonstrated in animal models and small clinical studies. Despite well-established cardiovascular benefits of statins in CAD, there remains a substantial residual CHD risk which may be mitigated by the right HDL-based intervention and, therefore, we should not give up on HDL despite its split personality.

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References