

High Density Lipoproteins - Do We Have Clue? -

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Wisdom & Open-mindedness

Samurai Hagakure, Yamamoto Tsunetomo, September 10, 1716

*“It is **not good** to settle into a set of opinions. At first putting forth great effort to be sure that you have grasped the basics, then practicing so that they may come to fruition is something that will never stop for your whole lifetime.”*

“Do not rely on following the degree of understanding that you have discovered, but simply think. . .This is not enough.”

Tsunetomo, Y. *Hagakure*. Wilson WS, trans. Tokyo, Japan: Kodansha America Inc; 1716.

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Risk of Low HDL-C

Evidence statement

A low HDL cholesterol level is **strongly and inversely** associated with risk for CHD

High Density Cholesterol: The Editor's Roundtable

Scott Grundy

- 50% of HDL-C levels is genetically determined
- African-Americans have higher HDL-C than Caucasians
- It is difficult to know the exact contribution of population HDL-C variances to CV risk

Vincent Friedewald, H Bryan Brewer, Scott Grundy,
Daniel Rader and William Roberts. Amer J Cardiol 2007;99:1698-1705

High Density Lipoprotein Cholesterol: The Editor's Roundtable

Dan Rader

- Plasma HDL-C is the least accurate of standard lipid measurements
- Performed correctly, which is true with large labs, HDL-C accuracy is $\pm 10\%$
- You do not make a treatment recommendation based on a single measurement of HDL-C. A low HDL-C or one that falls unexpectedly should be confirmed with at least one repeat measurement
- **Dr William Roberts:**
 - An accuracy or $\pm 10\%$ could give errors of up to 4 mg/dL

Vincent Friedewald, H Bryan Brewer, Scott Grundy,
Daniel Rader and William Roberts. Amer J Cardiol 2007;99:1698-1705

High Density Cholesterol: The Editor's Roundtable

Scott Grundy

- An important problem is that we **do not ascertain the kinetics of HDL** by simply measuring the blood level. The flux of cholesterol through the HDL system is **not measured** by the plasma HDL-C alone.
 - A single HDL-C level is a poor indicator of HDL functionality especially with respect to reverse cholesterol transport

High Density Lipoprotein Cholesterol: The Editor's Roundtable

Dan Rader

- It is not necessarily true that if the HDL-C is high enough, its functionality is likely to be good. One cannot assume a high HDL-C level guarantees protection from CAD, because there are many anecdotal situations in which people with very high HDL-C develop CAD
- Physicians should not prescribe alcohol for raising HDL-C to reduce CV risk
- Exercise as a way to raise HDL-C is overrated except as part of an overall program to loose weight. It is moderate exercise, which when accompanied by weight loss, raises HDL-C

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Associations of Low HDL-C

- F The direct role of HDL in atherogenesis **probably cannot fully account** for the strong predictive power of HDL in epidemiological studies.
- F Because of the **association of low HDL with other atherogenic factors (some of which are not included among standard risk factors)**, a low HDL cholesterol is **not as strongly independent** in its prediction of CHD as suggested by usual multivariate analysis
- F Its independence is partially confounded by some risk factors that are not routinely measured

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Risk of Low HDL-C

- F This confounding raises the possibility that **therapeutic raising** of HDL-cholesterol levels **will not reduce CHD risk** as much as might be predicted from prospective epidemiological studies

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Treatment of Low HDL-C

F **Low HDL-C: is defined as <40 mg/dL**
No specific goal defined for raising HDL-C

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Adult Treatment Panel III NCEP-ATP III Addendum

Low HDL-Cholesterol

Although the potential benefit of HDL-raising therapy has evoked considerable interest, current documentation of risk reduction through controlled clinical trials **is not sufficient** to warrant setting a specific goal value for raising HDL-C.

Recent lipid-lowering drug trials provide **no new evidence** in this regard.

High Density Lipoproteins

REVIEW

CLINICIAN'S CORNER

JAMA, August 15, 2007—Vol 298, No. 7

High-Density Lipoprotein as a Therapeutic Target A Systematic Review

 CME available online at
www.jama.com

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Context High-density lipoprotein cholesterol (HDL-C) is a cardiovascular risk factor
lipoproteins (HDLs)

High Density Lipoproteins

Despite the preponderance of evidence linking low HDL-C levels to cardiovascular morbidity and mortality, **there is no definitive evidence proving that increasing HDL-C levels reduces the incidence of major cardiovascular events.**

Indeed, major clinical guidelines have avoided providing an HDL-C target, despite some consensus statements that increasing HDL-C levels has merit.

Macrophage Reverse Cholesterol Transport

Although efflux of cholesterol from macrophages
represents only a tiny fraction of overall
cellular cholesterol efflux,

it is the most important part of RCT
with regard to atherosclerosis.

High Density Lipoproteins

- F The functionality of different HDL subfractions appears to vary substantially. Of the known forms of HDL-C (pre- β HDL, HDL2, HDL3) **pre- β HDL appears to be the most antiatherogenic form.**
- F Therefore, therapies that increase the most atheroprotective subfraction(s) of functioning HDL may be most promising.
- F Additionally, functional testing of HDL may provide insight as to the therapeutic promise of investigational compounds.

HDL Particles & Cardioprotection

Collectively, the data leads to the conclusion that **both large and small HDL subclasses are cardioprotective.**

Determining whether one subclass is more cardioprotective than the other and whether therapies that primarily affect levels of one or the other subclass are more or less beneficial are questions that await further investigation.

High Density Lipoproteins

The failure of recently developed agents that substantially increase HDL-C levels suggests that **functionality of HDL may be a more appropriate target than HDL-C levels themselves.**

In addition, the relationship between systemic inflammation and HDL function may be particularly relevant

While LDL-C lowering strategies have consistently reduced CHD risk, **HDL based approaches are much more complex and sometimes disappointing.**

High Density Lipoproteins

The simple goal of increasing levels of “good” cholesterol can no longer be applied to all forms of HDL without consideration of therapeutic effect on HDL function and ultimately cardiovascular risk.

A New Age of Discovery for Plasma Lipoproteins

Somehow, the unstoppable progression of the **LDL concept** dragged along the notion that its perceived counterpart and nemesis, HDL, would carry equally large opportunities for therapeutic maneuvers in atherosclerosis.

Indeed, armed solely with the power of epidemiological observations, **the idea that raising one's plasma HDL cholesterol levels will reduce the risk of a heart attack has become so entrenched in clinical thinking that many doctors switch to target an unproven HDL goal before 'finishing off' the LDL villain.**

Therefore, a current was created for an expectation that any rise in plasma HDL cholesterol would always indicate improved reverse cholesterol transport and enhanced vascular protection. Here, too, we got our share of shocking surprises in the last few months.

A New Age of Discovery for Plasma Lipoproteins

The most devastating blow, however, was taken by all of us lipidologists, who are now forced to rethink reverse cholesterol transport as a therapeutic target and cannot expect any longer for HDL to follow LDL's easy street.

This means that any target leading to HDL increases must be tested for cardiovascular benefits, and, most importantly, **that there may be interventions on HDL that may be beneficial without raising HDL cholesterol or even by decreasing it.**

HDL Therapies

Plasma steady state **HDL-C levels are not an assay of the rate of RCT**, which is a dynamic process that can only be assessed through kinetic measures of cholesterol flux.

HDL & Cholesterol Transport

*“Simply enhancing the **cholesterol content of HDL** without understanding the effect on cholesterol flux between critical tissues or other functions of HDL may prove to be a hazardous undertaking”*

High Density Lipoproteins

The failure of recently developed agents that substantially increase HDL-C levels suggests that **functionality of HDL may be a more appropriate target than HDL-C levels themselves**. In addition, the relationship between systemic inflammation and HDL function may be particularly relevant

While LDL-C-lowering strategies have consistently reduced CHD risk, **HDL based approaches are much more complex and sometimes disappointing.**

Association Between Change in HDL-C and CVD Mortality: Meta-regression Analysis

- ▶ Meta-regression analysis of 108 randomized trials involving 299,310 patients at risk for CVD.
- ▶ All analyses adjusted for LDL-C showed no association between treatment-induced change in HDL-C and risk ratios for CHD deaths, CHD events, or total deaths.
- ▶ With all trials included, change in HDL-C explained almost no variability (< 1%) in any of the outcomes

Association Between Change in HDL-C and CVD Mortality: Meta-regression Analysis

- ▶ Our findings contribute to the accumulating evidence that simply increasing the amount of circulating HDL-C does not necessarily confer cardiovascular benefits.
- ▶ Lipid modifying agents and diets may affect the functionality of HDL particles, converting HDLs from a pro-inflammatory to an anti-inflammatory state.
- ▶ Further development is necessary to satisfy the urgent need for a reliable and easily applicable assay of HDL functionality

Association Between Change in HDL-C and CVD Mortality: Meta-regression Analysis

Available data suggest that **simply increasing the amount of circulating HDL-C does not reduce the risk of CHD events, CHD deaths, or total deaths.**

The results support reduction in LDL-C as the primary goal for lipid modifying interventions

Association Between Change in HDL-C and CVD Mortality: Meta-regression Analysis

Raising HDL-C without considering effects on HDL function seem to have little promise for the prevention of CVD events

Future research should prospectively consider the results of assays to measure HDL function and then provide definitive evidence of pharmacological effects of patient important outcomes in long term randomized trials

Association Between Change in HDL-C and CVD Mortality: Meta-regression Analysis

Skepticism about interventions to lower CHD by increasing the amount of circulating HDL-C without considering effects on its function is reinforced

Association Between Change in HDL-C and CVD Mortality: Meta-regression Analysis

NCEP ATP-III confirmed low HDL-C (<40 mg/dL) as a major CVD risk factor.

Although the guidelines recommend that clinicians consider combining a LDL-C lowering drug with a fibrate or niacin in patients with low HDL-C, they refrained from making recommendations about specific targets for raising HDL-C concentrations

HDL Therapies

An important concept is that **simply raising HDL-C levels may not necessarily be the optimal target** for the development of new therapies targeted toward HDL.

Raising plasma HDL-C levels **is neither adequate nor necessary** for a successful HDL-targeted therapy

Duffy D & Rader D. Circulation 2006;113:1140-1150
Rader D. J Clin Invest 2006;116:3090-3100

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

High HDL-C

- F In prospective studies, including the Framingham Heart Study, a high HDL-C is associated with reduced risk for heart disease
- F In ATP-II, this level (≥ 60 mg/dL) was also called a negative risk factor, and its presence evoked removal of one risk factor from the risk factor count used for setting treatment goals for LDL-C
- F ATP-III affirms the validity of this statement

Risk Factors for CAD in Patients With Elevated HDL Cholesterol

- From a population of 41,982, a cohort of 1,610 patients with CAD was characterized, including 98 patients (6.1%) with **high HDL-C levels (>70 in men and 80 in women)**
- Prevalence of traditional CAD risk factors was measured by comparing these 98 patients with patients with CAD and normal HDL levels (n = 1,512): 44% women 56% Men
- Patients with **high HDL and CAD** had a similar or lower prevalence of traditional CAD risk factors compared with patients with normal HDL levels and CAD

This population-level result raises the possibility that these patients have HDL particles with lesser antiatherogenic properties.

The Copenhagen City Heart Study

Elevated HDL-C and Increased Risk of Ischemic Heart Disease

- ▶ Increased HDL levels may in certain situations be not protective, **but rather associated with increased IHD risk**, and that our assessments of HDL levels **do not directly measure reverse cholesterol transport**.
- ▶ Thus, although the average person with high HDL levels is protected against IHD, a subgroup of such individuals where the opposite is true may also exist.
- ▶ Therefore, some patients **with high HDL levels**, particularly those with manifest IHD, need both **aggressive lipid lowering** medication and other preventive measures against atherosclerosis and IHD.

Estrogen and HDL

All that Glitters Is not Gold

“Just because a biomarker is associated with coronary heart disease (CHD) events in epidemiologic studies is not a guarantee that pharmacologically altering the biomarker will result in changes in CHD risk in the anticipated direction.

To successfully forecast clinical consequences requires an extremely detailed understanding of the physiology of the biomarker and its regulation.

David M. Herrington, and John S. Parks
Arterioscler Thromb Vasc Biol. 2004;24:1741-1742.

Shedding Light on High-Density Lipoprotein Cholesterol

Future new classes of HDL-C therapies **should focus on the quality** (especially that which stimulates RCT), **not just the quantity of HDL-C**, and will require absolute proof of benefit and safety from large-scale randomized, controlled trials assessing CHD events, noncardiovascular morbidity and mortality, and all-cause mortality.

Reverse Cholesterol Transport Pathways

In mitigating against atherosclerosis, it is critical that HDL or lipid-poor apoA-I be present to promote regression of foam cells.

The existence of pathways for macrophage cholesterol transport implies that **effective intervention** against atherosclerosis may require LDL-C lowering with statins **in combination with specific agonists to increase the function of ABCA1 and ABCG1 as well as SR-B1**

Additional Thoughts on HDL

Bryan Brewer: Am J Cardiol: 2003 Vol 91 Supplement 7A 1E-2E. "Unlike the benefits seen from reduction in LDL cholesterol or triglycerides, the benefits from raising HDL cholesterol are less clear and vary among patients and therapies. There is increasing evidence that the functionality of HDL particles, rather than the gross amount, is the more important factor."

Phil Barter: Atherosclerosis 2003;168 :195 - 211 We need to understand the precise mechanisms by which drugs increase HDL levels and what are the associated effects on HDL function and anti-atherosclerotic potential. We need to know which, if any, of the factors that influence intra-plasma HDL metabolism should be targeted for anti-atherosclerotic therapy. We need to know **whether it matters how the level** of HDL-C is raised.

Dan Rader: Circ Res. 2005;96:1221-1232. 1) RCT does not necessarily imply a unidirectional flux of cholesterol from extrahepatic tissues to liver. HDL also promote substantial cholesterol egress from the liver, which may be a significant source of lipidation for newly secreted nascent HDL particles.

2) We need to understand the critical role that intravascular remodeling of HDL by lipid transfer factors, lipases, cell-surface receptors, and non-HDL lipoproteins play in determining the ultimate metabolic fate of HDL.

Sergio Fazio & MacRae Linton: J Clin Endo & Metab. 2006;91:3271-73. We need to continue to apply extreme care in approaching the reverse cholesterol transport pathway as a target for therapeutic interventions and that the notorious inverse correlation between HDL-C levels and CVD rates should not reassure us that **higher is always better.**

Controversy: Is lowering low-density lipoprotein an effective strategy to reduce cardiac risk?

Whether raising HDL by pharmacological intervention that directly targets HDL will reduce cardiovascular risk **remains to be proven.**

It is possible that a low HDL is primarily a marker of risk caused by other factors (eg, metabolic syndrome) and that **direct HDL raising will not substantially modify risk.**

Controversy: Is lowering low-density lipoprotein an effective strategy to reduce cardiac risk?

To resolve this question, two things are needed: development of a drug that will effectively raise HDL (without a confounding lowering of apolipoprotein B-containing lipoproteins) and demonstration of the efficacy of such a drug in a morbidity/mortality outcome trial.

Until these have been accomplished, the benefit of raising HDL per se remains in the arena of speculation.

The Yin and Yang of High Density Lipoprotein Cholesterol

When the clinical laboratory gives a report, it refers to the mass of cholesterol within the specific particle (i.e., the HDL-C level). Relatively little used is the measurement of serum apoA-I levels, the major protein moiety of HDL particles, which may reflect the number of circulating HDL particles.

Given the extraordinary biological diversity of HDL particles, these measurements, HDL-C and apoA-I levels, do not provide much functional information.

The Yin and Yang of High Density Lipoprotein Cholesterol

HDL has a well-characterized role in reverse cholesterol transport. It is this latter mechanism (i.e., removal of macrophage cholesterol from the plaque) that is considered to be **the most potent anti-atherosclerotic** mechanism of HDL

This epidemiologic association (of low HDL-C and CVD risk) was thought to work in reverse: raising HDL should prevent coronary artery disease. This simple paradigm remains unproven to date.

The Yin and Yang of High Density Lipoprotein Cholesterol

The apparently counterintuitive finding in EPIC Norfolk & IDEAL that **elevated levels of HDL-C are no longer cardioprotective and may confer additional risk** may have important clinical implications:

First, naturally occurring high levels of HDL-C may not protect against heart disease, and

Second, and herein lies the most important and provocative finding, HDL-C as a therapeutic goal may be fraught with potential dangers.

The Yin and Yang of High Density Lipoprotein Cholesterol

The finding that apoA-I, even when corrected for HDL-C and apoB, remains cardioprotective suggests

that the means by which HDL particles are increased may be far more important than the cholesterol mass in HDL particles.

The Yin and Yang of High Density Lipoprotein Cholesterol

Commonly used drugs (statins and fibrates) have a modest (5% to 10%) effect on HDL-C, and this **effect is of uncertain clinical significance.**

Niacin increases HDL-C by 25% to 35% but has been used in combination therapy with other lipid-lowering drugs in most trials, and **evidence of unequivocal reduction in hard cardiovascular end points remains elusive.**

Presently, there are no data showing unequivocally that raising HDL-C pharmacologically reduces cardiovascular risk.

The Yin and Yang of High Density Lipoprotein Cholesterol

Given the multiple potentially beneficial effects of HDL on cardiovascular biology, **there is scientific support for the concept that raising small HDL particles (often referred to as “nascent” HDL particles) may be more important than generating large, cholesterol-rich HDL particles.**

Drugs that modulate HDL-C levels can be conceptually seen as those that decrease catabolism (CETP inhibitors, possibly niacin) and those that increase the production rate (fibrates and possibly small molecules that increase apoA-I production, and agonists of the liver specific receptor LXR to increase ABCA1-mediated cholesterol efflux from cells).

The Yin and Yang of High Density Lipoprotein Cholesterol

Proper life-style that includes no smoking, physical activity, and normal body weight are all **associated with higher HDL-C** levels and stand on their own merits with respect to cardiovascular health.

High-density lipoprotein: A fall from grace?

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Annals of Medicine 40:8,584-593

Abstract

Based on a plethora of *in-vitro* and *in-vivo* research data, high-density lipoprotein cholesterol (HDL) has been regarded as universally atheroprotective. Consequently, pharmacologically mediated HDL increase has emerged as a potential means to improve prevention and treatment of patients with atherosclerotic vascular disease. In particular, inhibition of cholesteryl ester transfer protein (CETP) was considered a promising strategy. Recently, the unanticipated and disappointing results of four large clinical trials with the CETP inhibitor torcetrapib have necessitated refinement of the HDL hypothesis. In addition, the progressive insight that HDL may actually be predominantly a carrier molecule of a wide array of proteins rather than merely a cholesterol-transporter has resulted in the interest to look beyond HDL levels alone. Here we will discuss the impact of recent developments on the HDL hypothesis as well as the advent of even more recent therapeutic developments in the HDL field.

In addition, the progressive insight that HDL may actually be predominantly **a carrier molecule of a wide array of proteins** rather than merely a cholesterol-transporter has resulted in the interest to look beyond HDL levels alone.

High Density Lipoprotein A Fall From Grace

“It has become apparent that HDL may no longer be considered a static plasma parameter of atheroprotection but rather a carrier lipoprotein with a dynamic and multidimensional functionality pattern.

Consequently, ways of looking at HDL are diversifying but essays evaluating the various biological functions of HDL remain, as of yet, sorely lacking.”