NLA HDL CONSENSUS STATEMENT

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Incidence of CHD by HDL-C and LDL-C
Framingham Heart Study

Risk of CHD after 4 years*

*Risk of coronary heart disease over 4 years of follow-up for men ages 50 to 70.

Castelli WP. Can J Cardiol 1988;4 Suppl A:5A-10A.
Correlation of HDL-C with CHD incidence

CHD events per 1000 per year

Plasma HDL-C (mg/dL)

< 40  40 to 49  > 50

FHS men
CPPT Placebo
FHS women
MRFIT

*LRCF men
*LRCF women

FHS = Framingham Heart Study
CPPT = Coronary Primary Prevention Trial (placebo)
MRFIT = Multiple Risk Factor Intervention Trial (usual care)
LRCF = Lipid Research Clinics Follow-up Study *mortality

Kaplan-Meier survival curves by HDL-C and TC Groups: 21-year CHD mortality

Israeli Ischemic Heart Disease Study

Consistency of Low HDL-C

Low HDL-C has been found repeatedly to be best predictor of CHD, especially in men older than 50 years.
Observational studies do show inverse relationship of HDL-C and CVD (CHD).

Extremely low HDL-C not consistently associated with premature CVD development and extremely high HDL-C not consistently associated with protection in a reliable manner.

Epidemiologic inconsistency has also arisen between levels of HDL-C and CVD events and monogenic abnormalities (Apo AI Milano and Paris, Tangier Disease) or high HDL-C (CETP LOFM) that result in extremely low or high HDL-C have not reliably demonstrated premature CVD or longevity, respectively.
Effect of APOA1 genotype and genotype combinations on HDL cholesterol levels and theoretically predicted and observed risks of IHD and MI

Haase, C. L. et al.  
*J Clin Endocrinol Metab* 2010;95:E500-E510
NHANES III: Prevalence of isolated low HDL-C*

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>3,047</td>
<td>2.5%</td>
<td>8.8%</td>
</tr>
<tr>
<td>35–44</td>
<td>1,721</td>
<td>2.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>45–54</td>
<td>1,076</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>55–64</td>
<td>1,133</td>
<td>1.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>65–74</td>
<td>1,143</td>
<td>1.7%</td>
<td>1.1%</td>
</tr>
<tr>
<td>75+</td>
<td>1,161</td>
<td>2.4%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

*Cut points: HDL-C <40 mg/dL in men and <50 mg/dL in women; triglycerides <150 mg/dL; and LDL-C <100 mg/dL

HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
NHANES = National Health and Nutrition Examination Survey
IS HDL-C A CAUSATIVE RISK FACTOR OR A BIOMARKER OF RISK?

HDL-C levels are inversely related to weight, waist circumference, triglycerides, insulin resistance and cigarette smoking.

HDL-C levels (OR THE CHANGE IN THEM) may not be the proper parameter to assess adequately the contribution of HDL to CVD risk.
On-treatment HDL-C and CHD rate in VA-HIT

CHD Event Rate (%) vs. HDL-C (mg/dL)

<29  HDL-C  >35
0  5  10  15  20  25  30  35

16%
1° Endpoint: CHD Death, nonfatal MI, ischemic stroke, high-risk ACS, hospitalization for coronary or cerebrovascular revascularization

HR 1.02, 95% CI 0.87, 1.21
Log-rank P value = 0.79

16.4%
16.2%

Cumulative % with Primary Outcome
Effect of High Risk Groups on Primary Outcome

<table>
<thead>
<tr>
<th># Pts. with Events (% of Category)</th>
<th>ERN Better</th>
<th>ERN Worse</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-val.** Int.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TG ≥ 198 and HDL &lt; 33</strong> *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 (17.0) 54 (22.4)</td>
<td></td>
<td></td>
<td>0.74 (0.50, 1.09)</td>
<td>0.073</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>234 (16.3) 220 (15.1)</td>
<td></td>
<td></td>
<td>1.09 (0.91, 1.31)</td>
<td></td>
</tr>
<tr>
<td><strong>TG ≥ 200 and HDL &lt; 32</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 (16.7) 50 (25.0)</td>
<td></td>
<td></td>
<td>0.63 (0.40, 0.98)</td>
<td>0.017</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>242 (16.2) 224 (15.0)</td>
<td></td>
<td></td>
<td>1.11 (0.93, 1.33)</td>
<td></td>
</tr>
</tbody>
</table>

*Highest tertile of TG and lowest tertile of HDL-C  **Heterogeneity by treatment
The numbers of patients and % of category confused me. These appear to be for ERN vs placebo, but which group is which should be clarified. Same color coding should be used as in prior slide.

Fleg, Jerome L (NIH/NHLBI), 10/29/2012
Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Risk ratio 0.96 (95% CI 0.90 – 1.03)

Logrank P=0.29

Patients suffering events (%) vs Years of follow-up
**Torcetrapib: Increased Cardiovascular and Non-cardiovascular Morbidity and Mortality**

Is the toxicity of torcetrapib related to the mechanism or the molecule?

dal-OUTCOMES Results: \( \text{No} \downarrow \text{CVD} \)


<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Dalcetrapib</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>7933</td>
<td>7938</td>
</tr>
<tr>
<td>1</td>
<td>7386</td>
<td>7372</td>
</tr>
<tr>
<td>2</td>
<td>6551</td>
<td>6495</td>
</tr>
<tr>
<td>3</td>
<td>1743</td>
<td>1736</td>
</tr>
</tbody>
</table>

Cumulative Incidence of Primary Outcome (% of patients)

\( P = 0.52 \) by log-rank test
Robust evidence from animal studies using infusible apoA-I/HDL and viral hepatic transfection with apoA-I

Robust evidence that HDLs have several properties with the potential to protect against atherosclerosis.

But the hypothesis that HDL-C targeted therapies in humans will reduce clinical cardiovascular events has still not been substantiated. In fact, four recent human trials with HDL-C targeted agents did not show a reduction in CV events.

The results of ILLUMINATE, dal-OUTCOMES, AIM-HIGH and HPS2-THRIVE should not be interpreted as evidence that the HDL hypothesis is now dead.
The inverse relationship between the concentration of HDL-C and CV risk observed in population studies may represent an epiphenomenon rather than reflecting an ability of HDL to protect. This proposition is not supported by the animal studies in which increasing HDL is demonstrably anti-atherogenic.

Effects (regression, stabilization) on the development of atherosclerosis in animals (or humans with CSL 111, apoA-I_Milano) do not necessarily translate into effects on clinical events in humans.
However, the fact that there are plausible reasons for why these trials failed suggests that the HDL hypothesis has still not been tested.

For this reason, it is far too premature to abandon the HDL hypothesis.

On the contrary, we need much more research in order to understand the reason for the unexpected results in these failed trials.

It is premature to abandon research efforts to better elucidate how the modulation of HDL metabolism and functionality impacts risk for CHD.
Interventions that increase the concentration of HDL-C may not be accompanied by an increase in the protective properties of HDL particles.

Increasing the level of HDL-C may be of little value when the concentration of LDL-C is very low as was the case in each of the failed trials.

Some of the agents used had adverse off-target effects that may have off-set the potential benefits of the HDL raising.

A reduction in clinical CV events may require a much greater increase in HDL-C/HDL particles than has been achieved in the trials with niacin and CETP inhibitors.
EMERGING THERAPIES

1) HDL infusions (including HDL delipidation)

2) HDL mimetics

1) CETP inhibitors

2) LXR and FXR agonists

3) RVX-208

4) Novel PPAR-alpha, gamma, delta agonists
MAJOR ISSUES FOR HDL PARTICLES

There is a need to move beyond HDL-C as a surrogate for HDL particles, particle concentrations, and subfractions. Must define HDL particles and subfractions in terms of size, density, charge, composition. Correlate such measures with prospective risk for CVD, whether protective or detrimental.

HDL-C refers only to the cholesterol content and carrying capacity of HDL particles. Targeting the cholesterol content of an HDL particle for elevation with drugs does not make much sense unless it reliably reflects RCT capacity, which is unlikely.

The cholesterol content of HDL does not represent many important HDL functions that are related to cardiovascular risk. Specific examples include the portion of macrophage cholesterol efflux that is mediated by ABCA1, as well as anti-oxidant, anti-inflammatory, anti-apoptotic, and anti-infective properties.
MAJOR ISSUES FOR HDL PARTICLES

Need to establish the most informative clinical measures of HDL particles/subfractions so as to: (A) improve cardiovascular risk assessment; (B) develop therapies that could influence the content of specific components of HDL that have atheroprotective properties; (C) more clearly establish impact of specific therapies on HDL raising and/or functionality; (D) correlate effect of specific types of functional HDL particles or subfractions with risk reduction.

Standardize methods that measure specific features of HDL functionality. Validation will require prospective, randomized trials.

Improve capacity to identify certain HDL subclasses with specific properties using other analytical methods such as proteomics, lipidomics and functional measures such as capacity for RCT.
HDL-C is a biomarker of cardiovascular risk and not a target of therapy. Measures of HDL particles/subfractions may be more useful than HDL-C in: (1) assessing the effectiveness of cardiovascular risk management; and (2) may be a more appropriate target of therapy.

Levels of various HDL particles and subfractions are strongly correlated with serum triglycerides and concentrations of subclasses of atherogenic lipoproteins (chylomicron remnants, VLDL, IDL, LDL). Thus, the risk relationships between HDL-C and cardiovascular risk must consider concentrations of the full spectrum of circulating lipoproteins.
MAJOR ISSUES FOR HDL PARTICLES

Future studies for management of dyslipidemia are needed to determine the predictive utility of HDL subclass concentrations, and the functional properties of individual HDL particle sizes and subfractions.

Prospective, randomized studies should be designed to more precisely and quantitatively ascertain the impact of specific interventions on HDL functionality and role in risk modulation.
Large HDL (11.0 nm) 
(α-1)

Medium Sized HDL (9.2 nm) 
(α-2)

Small HDL (8.05 nm) 
(α-3)

Very Small HDL (7.43 nm) 
(α-4)

Precursor HDL (5.58 nm) 
(Preβ-1)
HDL Proteome and Lipidome

1. The composition of HDL is much more complicated than previously appreciated.

2. Predicted functions from known protein constituents implies that HDL plays roles in lipid transport and exchange, inflammation, innate immunity, hemostasis, extracellular matrix remodeling, complement, metal ion transport, and modulation of endothelial function, among many others.

3. The HDL lipidome is potentially even more complicated and the presence of low abundance and potentially bioactive (i.e. signaling, anti/pro-oxidant, anti/pro-inflammatory) lipids may have important functional/pathological significance.
HDL Proteome and Lipidome

HDL also carries microRNA cargos that are distinct from typical microparticle cargos and these may be important mediators of HDL signaling and vascular cell function.

“HDL” is a phospholipid-based platform for the extracellular assembly of proteins and lipids to form particles that perform distinct and diverse functions. Many of these functions may be important for CAD, but also for other disease states as well.
MAJOR ISSUES FACING THE FIELD

How does the composition of individual HDL particles relate to specific functions and to protection from (or promotion of) atherosclerotic disease?

What are the quantitative differences in HDL’s proteome and lipidome in well characterized human populations (CAD, diabetes, other chronic inflammatory states) and how does this impact function and risk for CHD?
MAJOR ISSUES FACING THE FIELD

It is critical to identify and characterize specific HDL particles (both from a protein and lipid standpoint) that may be cardioprotective. This may involve methods such as physical isolation, tandem affinity purification (TAP), immuno co-precipitation, chemical cross-linking, co-separation and bioinformatic analyses.

Which proteins and lipids colocalize in discrete populations of HDLs and what are the forces driving this and can they be therapeutically manipulated?
Clinical Correlates

1. Must understand: HDL is not just a singular molecular entity. Its functions are not entirely reflected by HDL-C or apoA-I levels.

2. With more understanding, it may become possible to identify and pharmacologically raise subpopulations of HDL that have desirable atheroprotective effects. Such treatments may or may not raise HDL-C.

3. With more understanding, it may be possible to produce clinical assays that measure HDL or its components that better identify individuals who are at heightened risk for atherosclerotic vascular disease.
**Extant Questions**

- Why have recent clinical outcomes trials shown no benefit?
  - Baseline HDL-C levels not low enough
  - Use of concomitant therapies
  - Some agents not potent enough
  - Unanticipated off target toxicities
  - Choice of combination therapies (e.g. niacin+fibrates)

- How can we reconcile the positive outcomes with surrogate measures and the absence of benefit in clinical outcomes trials (e.g. niacin)?
  - Are surrogate endpoints (e.g. QCA, CIMT and IVUS) informative measures of atherosclerosis stabilization/regression?
  - Different patient populations studied

- What are the effects of HDL-raising therapies in patients with low HDL-C/high triglycerides?
  - Numerous post-hoc subgroup analyses have shown significant clinical outcomes benefit in patients with low HDL-C/high triglycerides
Extant Questions (2)

• To what extent does the fact that all CETP inhibitor trials to date have taken ‘all comers’, without specific HDL-C entry criteria, contribute to their lack of observed benefit?

• Need to address role of LDL-C, apoB, and Lp(a) reduction and other lipoprotein effects of CETP inhibitors and niacin

• Despite the use of aggressive secondary prevention interventions and guideline-directed medical therapy, residual CVD risk remains appreciable
Extant Questions (3)

Should HDL-P or specific measures of HDL function be used as inclusion criteria in future studies?

What is the most appropriate assay for HDL functionality? Rates of RCT, inhibition of oxidation/inflammation, etc?

What will the outcome of ongoing or planned clinical outcomes studies of novel HDL-targeted therapies be?

Should more extensive study of novel agents be performed using intermediate endpoints before launching large scale outcomes studies?
Extant Questions (4)

To what extent does the occurrence of a recent acute coronary syndrome alter the relationship between HDL/HDL-C levels/functionality and outcomes?
Clinical Recommendations (1)

There is currently insufficient evidence from clinical trials to recommend HDL-targeted therapy.

No new guideline for the management of dyslipidemia will be recommending pharmacologic intervention for low HDL-C given the absence of positive data from randomized, prospective studies.
Clinical Recommendations (2)

• In patients with established CHD who are able to achieve and maintain optimal levels of LDL-C and non-HDL-C on statins, current data do not support additional clinical benefit with additional lipid-altering agents.

• Patients who are unable to achieve their LDL-C and non-HDL-C goals on a statin should continue to be considered for combination therapy.
Clinical Recommendations (3)

For patients with metabolic syndrome/insulin resistance, the likely best approach to raising HDL-C is lifestyle modification, as set forth by NCEP ATP III.

The results of clinical trials should not be extended to patient populations not represented by the study population.
ANTICIPATED PUBLICATION OF FULL DOCUMENT IN JCL IS NOVEMBER/DECEMBER ISSUE