HDL-C, HDL-P, & HDL Function: Relation to Risk Prediction & Treatment

Rachel H. Mackey, PhD, MPH, FAHA
Assistant Professor of Epidemiology
Graduate School of Public Health
University of Pittsburgh

NLA Spring Clinical Lipid Update
March 1, 2015
Presenter Disclosure Information

• Rachel H. Mackey, PhD, MPH

FINANCIAL DISCLOSURE/ UNLABELED/UNAPPROVED USES DISCLOSURE:

• Previously PI of investigator-initiated grant, LipoScience, Inc., to University of Pittsburgh
Recent History:
“The HDL hypothesis is on the ropes”

- Genetically ↑ HDL-C without ↓ CHD
- ↑HDL-C via CETP inhibition or modulation
  - Torcetrapib: ILLUMINATE stopped
  - Dalcetrapib: DAL-OUTCOMES stopped
- ↑HDL-C via Niacin:
  - AIM-HIGH stopped
  - HPS2-THRIVE stopped
- “Dysfunctional” HDL
Potential Explanations

• Possible problems with clinical trials:
  – Off-target effects of drugs?
  – Follow-up too short, wrong sample?
  – Inability to show benefit on top of statin therapy?

• HDL is not causally related to CVD?

• HDL-C, the cholesterol cargo of HDL, is an inadequate index of HDL quantity and quality, i.e., function
New Focus: HDL Function, Dysfunction

Functional Assays for HDL: Current Barriers to Clinical Use

• Reproducibility, Validation, Standardization
• Need high-throughput & cost-effective
• Relating range of HDL functions (quality) to HDL quantity, subclasses, proteome, lipidome…
• Recommendation: “… determination of HDL-P and individual concentrations of HDL subclasses should be considered in any clinical study that investigates HDL functionality.”

HDL Particle (HDL-P) Measurement

- NMR Spectroscopy
  - High-throughput, fully automated FDA approved NMR analyzer platform (LipoScience/LabCorp.)
  - Many published studies over >20 years
- Ion Mobility Analysis (IMA)
  - Commercially available via Quest
- Calibrated Ion Mobility Analysis (cIMA)
  - improved version of IMA

Davidson WS. Clin Chem 2014.60(11)e3-e1.
## HDL Subclasses- Nomenclature

<table>
<thead>
<tr>
<th>HDL:</th>
<th>Very Large (VL-HDL)</th>
<th>Large HDL (HDL-L)</th>
<th>Med. HDL (HDL-M)</th>
<th>Small HDL (HDL-S)</th>
<th>Very Small HDL (HDL-VS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GGE</strong></td>
<td>HDL2b 12.9-9.7</td>
<td>HDL2a 9.7-8.8</td>
<td>HDL3a 8.8-8.2</td>
<td>HDL3b 8.2-7.8</td>
<td>HDL3c 7.8-7.2</td>
</tr>
<tr>
<td><strong>NMR (LP3)</strong></td>
<td>Large HDL-P 14-9.4</td>
<td>Medium HDL-P 9.4-8.2</td>
<td></td>
<td>Small HDL-P 8.2-7.3</td>
<td></td>
</tr>
<tr>
<td><strong>Ion Mobility</strong></td>
<td>14.5-10.5 10.5</td>
<td></td>
<td></td>
<td>7.65</td>
<td>---</td>
</tr>
<tr>
<td><strong>CIM</strong></td>
<td>Large 11.8-9.7</td>
<td>Medium 9.7-8.2</td>
<td></td>
<td>Small 8.2-7.2</td>
<td></td>
</tr>
</tbody>
</table>

Cholesterol* Per Particle Much Greater for Large vs. Small HDL Particles

Kontush A et al. J. Lipid Res. 2013. 54: 2950–2963

*FC= Free Cholesterol
*CE= Cholesteryl Ester
HDL-C and HDL-P Weight HDL Particles Differently

- Large HDL-P
- Medium HDL-P
- Small HDL-P

Particle Diameters (nm)

14 → 9.4 → 8.2 → 7.3

- 2-5 ApoA1 per particle, decreases with particle size
- HDL-C Gives Greater Weight to Larger Subclasses
- HDL-P Gives Equal Weight to All Subclasses
# Cholesterol Content Misrepresents Particle Concentrations

<table>
<thead>
<tr>
<th>MESA n=5314</th>
<th>Incident Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>118.0</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>52.4</td>
</tr>
<tr>
<td>LDL-P, nmol/l</td>
<td>1236</td>
</tr>
<tr>
<td>HDL-P, nmol/l</td>
<td>34000</td>
</tr>
<tr>
<td>Large HDL-P, nmol/l</td>
<td>6300</td>
</tr>
<tr>
<td>Medium HDL-P, nmol/l</td>
<td>13900</td>
</tr>
<tr>
<td>Small HDL-P, nmol/l</td>
<td>14200</td>
</tr>
</tbody>
</table>

Adapted from Mackey RH et al. *Diabetes Care*. 2015: online before print.
## Smaller HDL = More Functional?

<table>
<thead>
<tr>
<th>Functions</th>
<th>Smaller HDL</th>
<th>Larger HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol Efflux</td>
<td>ABCA1*</td>
<td>ABCG1</td>
</tr>
<tr>
<td>Anti-oxidative</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Cytoprotective</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Endothelial/ Vasodilatory</td>
<td>S1P?</td>
<td>x</td>
</tr>
<tr>
<td>Anti-thrombotic</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Anti-infectious</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>


HDL Proteome Relates to Function

<table>
<thead>
<tr>
<th>Lipid Metabolism and Transport</th>
<th>Hemostasis</th>
<th>Immune Response</th>
<th>Metal Binding</th>
<th>Vitamin Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoH, α-2 macroglobulin</td>
<td>Fibrinogen γ</td>
<td>Haptoglobin rel. prot.</td>
<td>Hemopexin</td>
<td>Hemopexin</td>
</tr>
<tr>
<td></td>
<td>ApoH</td>
<td>Ac-muramoyl amidease</td>
<td>Serotransferrin</td>
<td>Serotransferrin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Igα-1 chain C</td>
<td>His-rich glycoprot.</td>
<td>AMBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Igγ-1 chain C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Igκ-1 chain C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Igλ-1 chain C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMBP, AZGP1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelet factor 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ApoL-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoA-IV, α-1-acid glycoprot. 1, α-1-acid glycoprot. 2, SAA1/2</td>
<td>Prothrombin, Kininogen</td>
<td>ApoA-IV</td>
<td>α-1 anti-trypsin</td>
<td>Acute Phase Response/Inflammation</td>
</tr>
<tr>
<td></td>
<td>Kallistatin</td>
<td>LPS-binding protein</td>
<td>Serum amyloid P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-2 antiplasmin</td>
<td>ITIH4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α-1 anti-chymo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fibronectin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α-2 HS glycoprot.</td>
<td></td>
</tr>
<tr>
<td>Anti-thrombin III, Plasminogen, Serpin G1, Serpin D1, Kalikrein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoJ</td>
<td>Comp. C9</td>
<td>Complement</td>
<td>Prenyl-Cys-oxid.</td>
<td>Proteolysis/Inhibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α-1 anti-trypsin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hep. cofactor 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ITIH4, ITIH1, ITIH2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α-1 anti-chymo.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serpin F1, AMBP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Functional Proteins on Small HDL

Lipidome: Preferential distribution to small HDL particles, correlated with functions

Small, Dense High-Density Lipoprotein-3 Particles Are Enriched in Negatively Charged Phospholipids
Relevance to Cellular Cholesterol Efflux, Antioxidative, Antithrombotic, Anti-Inflammatory, and Anti-apoptotic Functionalities

Laurent Camont, Marie Lhomme, Fabiana Rached, Wilfried Le Goff, Anne Nègre-Salvayre, Robert Salvayre, Catherine Calzada, Michel Lagarde, M. John Chapman, Anatol Kontush

Time For a Paradigm Shift?

HDL-C vs HDL-P: How Changing One Letter Could Make a Difference in Understanding the Role of High-Density Lipoprotein in Disease

W. Sean Davidson

Clin Chem 2014.60(11)e3-e1.
HDL-P vs. HDL-C in MESA

- Multi-Ethnic Study of Atherosclerosis: NHLBI observational cohort study of 6,814 men & women ages 45-84, without baseline CHD
- In current study n=5,598 after excluding subjects taking lipid medications and with TG>400
- Outcomes:
  - Carotid IMT, mean (max internal and max common)
  - 227 CHD events (MI, angina, revascularization) with mean 6.0 year follow-up

HDL particles (HDL-P) vs. HDL cholesterol (HDL-C)

Spearman correlation
\[ \rho = 0.69; \ p < 0.0001. \]

**Differences in HDL-C vs. HDL-P**

<table>
<thead>
<tr>
<th></th>
<th>HDL-C</th>
<th>HDL-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-P</td>
<td>0.69</td>
<td>-</td>
</tr>
<tr>
<td>Mean HDL size</td>
<td>0.68</td>
<td>0.34</td>
</tr>
<tr>
<td>Large HDL-P</td>
<td>0.87</td>
<td>0.53</td>
</tr>
<tr>
<td>Medium HDL-P</td>
<td>0.45</td>
<td>0.58</td>
</tr>
<tr>
<td>Small HDL-P</td>
<td>-0.28</td>
<td>0.07</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.48</td>
<td>-0.09</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.08</td>
<td>-0.13</td>
</tr>
<tr>
<td>LDL-P</td>
<td>-0.38</td>
<td>-0.25</td>
</tr>
<tr>
<td>Small LDL-P</td>
<td>-0.69</td>
<td>-0.38</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.38</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

*spearman correlations adjusted for age, sex, race-ethnicity. N=5598 p<0.0001 for all.

Mean cIMT* by HDL-C or HDL-P Quartiles

Mean Difference* in Carotid IMT (µm) per SD increase in HDL-C or HDL-P

Covariates: Base* LDL-P HDL-P LDL-P HDL-C LDL-P HDL-C HDL-C

HDL-C HDL-P

*Adjusted age, sex, race-ethnicity, hypertension & smoking.

CHD Risk per SD HDL-C or HDL-P: Effects of adjusting for lipoproteins

*All models adjusted for age, sex, race-ethnicity, hypertension & smoking.

Mean cIMT* by HDL-C & HDL-P Tertiles

HDL-P:
<30.6, 30.6-36.1, ≥36.2 umol/l

HDL-C:
<42, 43-54, >54, ≥55 mg/dl

*p trend = n.s. for all HDL-C tertiles
p trend <0.05
p trend <0.05

*Adjusted for age, sex, race-ethnicity, hypertension & smoking.

Mean cIMT* by HDLC/ HDLP tertiles, LDL-P ≥ 1236 nmol/l (median)

*Adjusted age, sex, race-ethnicity, hypertension & smoking. Median= 1236 nmol/l

Mean cIMT* by HDLC/HDLP tertiles, LDL-P < 1236 nmol/l (median)

*Adjusted age, sex, race-ethnicity, hypertension & smoking.

Additional Analyses

- Interaction terms for sex, race-ethnicity, diabetes and CRP were not significant; results similar for sex-stratified models, or adjusted for diabetes or hormone therapy (HT), or when HT users were excluded.
- Similar results for “hard” CHD, all CVD, or “hard CVD”
- Adjusted for LDLP, HDL-P and log-TG, CHD HR (95%CI)
  - for very high HDL-C (≥80) vs. low (<40 mg/dl)
  - = 2.59 (1.11, 6.02)
  - for very high HDL-P (≥45.7) vs. low HDL-P (<29 umol/l)
  - = 0.50 (0.19, 1.35)

EPIC-Norfolk Study

- Nested case-control (822 major CVD events/ 1401 controls)
- HDL-C and HDL size are positively associated with risk adjusted for apoB and apoA1.
- HDL size (NMR or GGE) inverse association is abolished (HR Q4 vs. Q1=1.0) if adjusted for ApoB, TG, and HDL-P or apoA1.
- ApoA1: inverse association attenuated at high apoA1 levels adjusted for apoB and HDL-C or HDL size
- HDL-P: inverse association with CVD persists adjusted for ApoB, TG, and HDL particle size or large HDL-P

Van Der Steeg et al. JACC 2008; 51:634-42.
Heart Protection Study (HPS)

- HPS: RCT (simvastatin vs. placebo), >20,000 adults ages 40-80 with TC ≥ 135 mg/dl, existing CVD, T2DM, etc., 5000 events over 5.3 years, non-fasting samples
- HDL-P, HDL-C, ApoA-1 had similar associations with MCE*, with larger X² for HDL-P
- Adjusting for LDL-P attenuated associations with major occlusive coronary events for HDL-C, apoA-1 and HDL size more than for HDL-P
- Given HDL-P and LDL-P, HDL size was positively associated with MCE

*Major coronary event
IDEAL

IDEAL: n=8564 RCT of high vs. low statin

• HDL-C:
  • Weak inverse associations with MCE is attenuated if adjusted for apoA1
  • adjusted for apoA1 & apoB becomes positive with HR $\geq 2$ for HDL-C $\geq 70$ mg/dl

• ApoA-1:
  – Inverse associations with MCE are strengthened when adjusted for apoB and HDL-C, but very high ApoA1 ($>1.95$) not associated with lower risk.

*Major CVD events

Van Der Steeg et al., JACC 2008; 51:634-42.
Higher Risk with Higher HDL-C Per Particle

- Among Korean men and women:
- Higher HDL-C, adjusted for apoA1, is positively associated with Coronary artery calcification (CAC)
- Higher HDL-C/apoA1 ratio (or higher HDL-C, adjusted for apoA1,) is associated with higher risk of CVD and total mortality.

Sung KC et al. *Heart*. 2015; online before print.
“Cholesterol-Overloaded Particles”
HDLC/HDLP Ratio: New Risk Factor?

Residual Risk: HDL-C, HDL-P, ApoA1

In JUPITER, adjusted for age, sex, race, smoking, SBP, BMI, glucose, LDL-C, TG and family hx of premature CHD:

• Endpoint: Incident CVD:
  • On-treatment levels of HDL-P (HR(95%CI)= 0.73 (0.57-0.93)
  • On-treatment levels of HDL-C, apoA1 were not significantly related to CVD events.
  • On-treatment HDL size unrelated to CVD events in placebo or treated group

• Endpoint of CVD plus mortality:
  • Joint model HDL-P: 0.64 (0.53, 0.78), p<0.0001
  • HDL size: 1.25 (1.04, 1.52). P=0.02

Is HDL-P better than HDL-C for African Americans?

- Dallas Heart Study: 1,977 men & women w/out CHD (51% women, 46% black):
  - African-American (AA) participants: HDL-P, but not HDL-C, significant inverse association with CHD events
  - White participants: both HDL-P and HDL-C were significantly inversely associated with CHD, but HDL-C associations were attenuated adjusted for HDL-P
  - For AA and white participants: HDL-P inversely associated with CAC, but HDL-C positively associated with CAC, adjusted for HDL-P

Chandra et al. *Am J Cardiol.* 2015; online before print.
Using HDL-P to Reinterpret Recent History
Paradoxical Genetic Studies:

“HDL” Mendelian Randomization Study:
Endothelial lipase gene (LIPG) mutation
  • Higher levels of HDL-C but not lower CHD risk
  • Higher mean HDL particle size, but not higher HDL-P


Phospholipid transfer protein (PLTP) gene score
  • Lower lifetime HDL-C levels and lower CVD risk
  • Less large HDL-P and smaller mean HDL size
  • Higher levels of total and small HDL-P

Failed HDL-Raising Clinical Trials:

↑↑↑ HDL-C much more than ↑HDL-P

- Niacin\(^1\)
- Niacin (+ Statin)\(^2\)
- Torcetrapib\(^3\)
- Dalcetrapib (+ Statin)\(^4\)

Citations
3. Rashedi N, Brennan, Kastelein, Nissen, Nicholls; 2011 EAS
Different Intervention Effects
HDL-P vs. HDL-C

<table>
<thead>
<tr>
<th>HDL-P more than HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>statins</td>
</tr>
<tr>
<td>ezetimibe</td>
</tr>
<tr>
<td>fibrates</td>
</tr>
<tr>
<td>metformin</td>
</tr>
<tr>
<td>metformin+colsevelam</td>
</tr>
</tbody>
</table>

Smaller subclasses increased proportionately, or more than larger ones

<table>
<thead>
<tr>
<th>HDL-P less than HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>niacin</td>
</tr>
<tr>
<td>glitazones</td>
</tr>
<tr>
<td>omega 3 FAs</td>
</tr>
<tr>
<td>CETP inhibitors</td>
</tr>
<tr>
<td>exercise</td>
</tr>
</tbody>
</table>

Larger subclasses increased more or at expense of smaller ones
HDL-P and HDL-C: VA-HIT

• **VA-HIT**: RCT of gemfibrozil vs. placebo among men with CHD, low HDL-C and low LDL-C
  – Nested case-control study (364 incident CHD cases) 697 controls, 5.1 year median follow-up

• HDL-P increased more than HDL-C

• HDL-P: Both baseline and on-treatment levels inversely associated with CHD events

• HDL-C: Neither baseline nor on-treatment levels associated with fatal CHD

Otvos JD et al. *Circulation* 2006;113:1556-63
Lifestyle Changes: Smoking

• Smoking associated with lower HDL-P as well as lower HDL-C

• Smoking cessation similarly increases HDL-C and HDL-P, with a larger increase in large HDL-P

• Larger weight gain in smokers positively associated with increase in HDL-C, HDL-P and large HDL-P

Alcohol: ↑ HDL-P and ↑ HDL-C

Mean difference in HDL indices among CHS participants by usual alcohol intake (ref= long-term abstainers)

<table>
<thead>
<tr>
<th></th>
<th>Former (n = 144)</th>
<th>&lt;1 (n = 359)</th>
<th>1–6 (n = 315)</th>
<th>7–3 (n = 109)</th>
<th>14+ (n = 147)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HDL-C (mg/dl)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>+0.4 ± 1</td>
<td>+2 ± 1</td>
<td>+5 ± 1</td>
<td>+9 ± 2</td>
<td>+11 ± 2</td>
<td>&lt;0.001/0.80</td>
</tr>
<tr>
<td>Men</td>
<td>+2 ± 2</td>
<td>+0.1 ± 1</td>
<td>+6 ± 2</td>
<td>+10 ± 3</td>
<td>+12 ± 2</td>
<td>&lt;0.001/0.66</td>
</tr>
<tr>
<td>Women</td>
<td>−2 ± 2</td>
<td>+3 ± 1</td>
<td>+5 ± 2</td>
<td>+8 ± 3</td>
<td>+10 ± 3</td>
<td>&lt;0.001/0.86</td>
</tr>
<tr>
<td><strong>Total HDL-P (μmol/lite)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>−1.2 ± 0.7</td>
<td>+0.7 ± 0.4</td>
<td>+1.0 ± 0.5</td>
<td>+1.6 ± 0.8</td>
<td>+4.0 ± 0.7</td>
<td>&lt;0.001/0.08</td>
</tr>
<tr>
<td>Men</td>
<td>−1.8 ± 1.0</td>
<td>−0.4 ± 0.7</td>
<td>+2.0 ± 0.8</td>
<td>+2.1 ± 1.0</td>
<td>+5.1 ± 1.0</td>
<td>&lt;0.001/0.14</td>
</tr>
<tr>
<td>Women</td>
<td>−0.1 ± 0.8</td>
<td>+1.1 ± 0.6</td>
<td>+0.1 ± 0.6</td>
<td>+0.9 ± 1.3</td>
<td>+2.9 ± 1.0</td>
<td>0.02/0.45</td>
</tr>
<tr>
<td><strong>Large HDL-P (μmol/lite)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>+0.2 ± 0.4</td>
<td>+0.6 ± 0.3</td>
<td>+1.6 ± 0.4</td>
<td>+2.2 ± 0.5</td>
<td>+2.5 ± 0.4</td>
<td>&lt;0.001/0.51</td>
</tr>
<tr>
<td>Men</td>
<td>+0.7 ± 0.4</td>
<td>+0.01 ± 0.4</td>
<td>+1.4 ± 0.5</td>
<td>+2.8 ± 0.6</td>
<td>+2.4 ± 0.6</td>
<td>&lt;0.001/0.90</td>
</tr>
<tr>
<td>Women</td>
<td>−0.6 ± 0.6</td>
<td>+0.8 ± 0.4</td>
<td>+1.8 ± 0.5</td>
<td>+1.5 ± 0.8</td>
<td>+2.6 ± 0.6</td>
<td>&lt;0.001/0.38</td>
</tr>
<tr>
<td><strong>Medium HDL-P (μmol/lite)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>−0.3 ± 0.5</td>
<td>−0.04 ± 0.3</td>
<td>+0.2 ± 0.4</td>
<td>+0.9 ± 0.6</td>
<td>+2.6 ± 0.6</td>
<td>&lt;0.001/0.004</td>
</tr>
<tr>
<td>Men</td>
<td>−1.0 ± 0.3</td>
<td>−0.1 ± 0.4</td>
<td>+0.4 ± 0.4</td>
<td>+1.1 ± 0.6</td>
<td>+3.8 ± 0.8</td>
<td>&lt;0.001/0.001</td>
</tr>
<tr>
<td>Women</td>
<td>+0.4 ± 0.9</td>
<td>−0.3 ± 0.4</td>
<td>+0.01 ± 0.7</td>
<td>+0.6 ± 1.1</td>
<td>+1.0 ± 0.8</td>
<td>0.26/0.29</td>
</tr>
<tr>
<td><strong>Small HDL-P (μmol/lite)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>−1.0 ± 0.7</td>
<td>+0.2 ± 0.5</td>
<td>−0.7 ± 0.6</td>
<td>−1.5 ± 0.8</td>
<td>−1.1 ± 0.8</td>
<td>0.02/0.90</td>
</tr>
<tr>
<td>Men</td>
<td>−1.4 ± 0.9</td>
<td>−0.2 ± 0.8</td>
<td>+0.2 ± 0.8</td>
<td>−1.8 ± 1.1</td>
<td>−1.1 ± 1.2</td>
<td>0.11/0.58</td>
</tr>
<tr>
<td>Women</td>
<td>−0.001 ± 0.9</td>
<td>+0.6 ± 0.6</td>
<td>−1.7 ± 0.8</td>
<td>−1.1 ± 1.3</td>
<td>−0.7 ± 1.1</td>
<td>0.10/0.70</td>
</tr>
</tbody>
</table>

Mukamal KJ, Mackey RH et al. JCEM 2007. 92(7):2559-2566
Implications for Risk Assessment & Treatment Strategies

Risk assessment:
• Low HDL-C largely reflects risk due to lower HDL-P and higher LDL-P or apoB
• Low HDL-P is associated with increased CHD risk independent of LDL-P or apoB and HDL-C.

Treatment strategies:
• Statins reduce risk due to elevated LDL-P, apoB, that may not be apparent from low LDL-C levels
• Statins will also increase HDL-P
• Lifestyle interventions, particularly smoking cessation, will increase HDL-P as well as HDL-C
**Implications for Assessing Residual Risk in Statin Users**

- Associations of HDL-C, mean HDL size and larger HDL-C (but not HDL-P) with CHD are confounded by LDL-P (or ApoB).
- Therefore for those with very low treated levels of LDL-P or apoB, HDL-P, but not HDL-C, will be inversely related to risk.
- Note: For women with very low untreated levels of LDL-P or apoB, CHD risk is very low, so HDL-P & HDL subclasses are unlikely to add to risk prediction as shown in WHS*

Implications for Assessing Effects of Medications that raise “HDL”

- the potential role of decreases in LDL-P or apoB should be evaluated (multivariable models), and changes in HDL-P when evaluating HDL-C


- Clinical benefit of raising HDL-C without raising HDL-P is uncertain.

- Additional data relating HDL-P and subclasses (quantity) to HDL quality and outcomes is needed.
Questions?
HDL Subclasses: HPS

- In multivariable-adjusted models, HR(95%CI) were
  - Small HDL-P: 1.03 (0.98-1.09)
  - Medium HDL-P: 0.88 (0.83-0.93)
  - Large HDL-P: 0.79 (0.71-0.88)
  - The joint prediction of HDL subclasses added to HDL-P

- Additionally adjusted for LDL-P and each other, HR(95%CIs) were
  - Small HDL-P: 0.90 (0.85-0.96)
  - Medium HDL-P: 0.87 (0.81-0.93)
  - Large HDL-P: 0.92 (0.81-1.03)
  - The joint prediction of HDL subclasses did not add to HDL-P

*Major coronary event

HDL-P Subclasses: WHS

Women’s Health Study (WHS): 26,332 healthy women over median 17 year follow-up- 5 subclasses defined

• Total HDL-P with lower CHD risk, adj LDL-P etc.
• Minimal adjusted models
  – Very large (VL), large and medium HDL subclasses ↓ CHD risk
  – Small HDL-P not associated with CHD risk
  – Very Small (VS) HDL-P associated ↑ CHD risk
• Adjusted for LDL-P and each other,
  – large, medium and small HDL-P associated ↓ CHD risk.
  – VL and VS HDL-P not associated with CHD risk

HDL-P by Calibrated Ion Mobility Analysis (IMA)

- IMA or Measures particle size using all components
- Requires HDL isolation by ultracentrifugation, may alter results (loss of certain apolipoproteins)
- Extrapolation of CIM values back to circulating HDL-P concentrations requires careful accounting of volumes, dilutions and sample loss
- Intra-assay CV: 6.2%, inter-assay CV 11.4%
- Low throughput, labor intensive

Davidson WS. Clin Chem 2014.60(11)e3-e1.
Residual Risk: HDL-C & ApoA1

- JUPITER: HDL-C and apoA1 not associated with residual risk among potent statin-treated adults with low LDL-C
  

- Meta-analysis of statin trials (38,153/5387 events) found inverse association of HDL-C and apoA1 with events even at low LDL-C;

- HR(95%CI) per SD HDL-C was 0.92 (0.88,0.96) for men and 0.96(0.88,1.04) for smokers.

- Risk not associated with change in HDL-C but 0.93(0.90-0.97) for apoA1 change, driven by highest quartile.