HDL: The Misunderstood Lipoprotein

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California Heart Associates (retired)
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Orange Coast Memorial

15th Annual Orange County Symposium for Cardiovascular Disease Prevention
Disclosures

• No Disclosures...
Before the discovery of lipoproteins ..... What did we know ???
THEY'RE HAPPY
Because they eat LARD

issued by the Lard Information Council

www.StrangeCosmos.com
What did we know about HDL in the 1960’s?
CHD RISK ACCORDING TO HDL-C LEVELS
FRAMINGHAM STUDY

Kannel WB. Am J Cardiol 1983;52:9B–12B
1980

- HDL-cholesterol: the negative risk factor for coronary heart disease
- M H Tan
- PMID: 7018364
<table>
<thead>
<tr>
<th>Points</th>
<th>Age 20-39</th>
<th>Age 40-49</th>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
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<tbody>
<tr>
<td>Nonsmoker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoker</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL (mg/dL)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>-1</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
</tr>
<tr>
<td>&lt;40</td>
<td>2</td>
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</table>

<table>
<thead>
<tr>
<th>Systolic BP (mmHg)</th>
<th>If Untreated</th>
<th>If Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators*
Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients

The HPS2-THRIVE Collaborative Group*
ILLUMINATE: TORCETRAPIB INCREASES EVENTS

- N=15,067 patients
  - Mean age 61 years
  - 73% male, 93% white
  - CVD or DM
  - Planned F/U 4.5 years

- Treatment arms:
  - Atorva
  - Atorva + torcetrapib
    - HDL-C increased 72%
    - LDL-C decreased 25%

- Trial stopped after 18 m due to harm
  - Increased CV and non-CV deaths
  - ? Off-target effect on aldosterone secretion

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**A Death from Any Cause**

- Patients without Event (%)
- Atorvastatin only
- Torcetrapib plus atorvastatin
- N=99 deaths
- N=93 deaths

**B Major Cardiovascular Events**

- Patients without Event (%)
- Atorvastatin only
- Torcetrapib plus atorvastatin
- N=464 patients
- N=373 patients

No. at Risk

- Atorvastatin only
  - 7534 7530 7521 7509 7487 5833 4043 2078 956 109
  - 7533 7526 7511 7494 7464 5827 4049 2069 943 114

- Torcetrapib plus atorvastatin
  - 7534 7489 7406 7340 7255 5627 3872 1965 898 103
  - 7533 7434 7345 7267 7177 5567 3838 1933 888 107

NEJM 2007; 357:2109-22
DAL-OUTCOMES: NO BENEFIT WITH DALCETRAPIB

- **N = 15,871**
- Recent ACS
- Dalcetrapib 600 mg daily vs. placebo
- Background statin therapy
- **BL:** HDL-C 42, LDL-C 76
- **1o EP:** composite of CHD death, nonfatal MI, ischemic stroke, UA, or cardiac arrest with resuscitation

**Placebo:** HDL-C +4% to +11%
**Dalcetrapib:** HDL-C +31% to +40%

Increasing HDL-C:

- Clinical trials with pharmacological therapies that only increase the cholesterol content of the HDL particles have failed to establish this approach as an effective strategy for preventing CV events.
So, What Do You Think About HDL-C Now?
And if the wasn’t’t enough.....
20,000 participants with CAD enrolled in either the UK Biobank or the Emory Biobank with HDL-C levels > 80 mg/dl had a 96% higher risk of all cause mortality and 71% higher risk of cardiovascular mortality after adjustments for covariates.
Figure 1. Nonlinear Association Between High-Density Lipoprotein (HDL) Cholesterol Levels and Adverse Outcomes

UK Biobank (UKB) coronary artery disease cohort model of all-cause death (A) and cardiovascular death (C) adjusted for age, sex, race and ethnicity, body mass index, hypertension, diabetes, smoking, triglycerides, low-density lipoprotein (LDL) cholesterol, stroke history, heart attack history, estimated glomerular filtration rate (eGFR), and frequent alcohol use (defined as alcohol consumption ≥3 times per week). Emory Cardiovascular Biobank (EmCAB) model of all-cause death (B) and cardiovascular death (D) adjusted for age, sex, race and ethnicity, body mass index, hypertension, diabetes, current/former smoking, triglycerides, LDL cholesterol, heart failure history, myocardial infarction history, eGFR, frequent alcohol use (defined as ≥8 alcohol beverages per week), statin use, aspirin use, β-blocker use, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use. HR indicates hazard ratio.

Liu C. et al JAMA Cardiol. 2022;7
Possible causes of high mortality with low and high HDL cholesterol

- High triglycerides
- High remnant cholesterol
- Infectious disease
- Confounding

- Genetic variants
- Dysfunctional/harmful HDL
- Infectious disease
- Confounding

ALCOHOL !!

TAKE HOME POINTS

- HDL-C ≠ HDL
- Low HDL-C predicts poor outcomes, high HDL-C may not be protective for ASCVD
- No reduction in ASCVD events by raising HDL-C with
  - Niacin or fibrates on statin background
  - Estrogens
  - Most CETP inhibitors
- Need to focus on HDL function, not only on HDL-C concentration

Von Eckardstein, EHJ 2022;1-14
### NMR Subpopulation Nomenclature

<table>
<thead>
<tr>
<th>HDL5</th>
<th>HDL4</th>
<th>HDL3</th>
<th>HDL2</th>
<th>HDL1</th>
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<tbody>
<tr>
<td>10–13 nm</td>
<td>8.8–10 nm</td>
<td>8.2–8.8 nm</td>
<td>7.8–8.2 nm</td>
<td>7.3–7.7 nm</td>
</tr>
</tbody>
</table>

### Gel Electrophoresis Subpopulation Nomenclature

<table>
<thead>
<tr>
<th>HDL₂ᵇ</th>
<th>HDL₂ᵃ</th>
<th>HDL₃ᵃ</th>
<th>HDL₃ᵇ</th>
<th>HDL₃ᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.6 nm</td>
<td>9.2 nm</td>
<td>8.4 nm</td>
<td>8.0 nm</td>
<td>7.6 nm</td>
</tr>
</tbody>
</table>
Increasing the Cholesterol Content of the HDL-C Lipoprotein...

- HDLs are really exist as many subpopulations that differ in their:
  - A- composition
  - B- metabolism
  - C- cellular interactions
  - D- functional properties

- Expansion of the cholesterol content of the HDL particle may interfere with cholesterol efflux, and alter the HDL protein mix to render it less effective in its antioxidant and anti-inflammatory properties

Otvos et al. Circ. 2000;101  Mackey et al. JACC 2012;60
SO EVIDENCE IS SUGGESTING THAT HDL PARTICLE CONCENTRATION (HDL-P) IS A BETTER CARDIOVASCULAR RISK MARKER THAN THE MEASUREMENT OF HDL-C.”
HDL-P vs. HDL-C

P = Paraoxonase

Adapted from Davidson MH. et al. Therapeutic Lipidology. Humana Press 2007
HDL Metabolism and Reverse Cholesterol Transport

ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I;
CE = cholesteryl ester; FC = free cholesterol;
LCAT = lecithin:cholesterol acyltransferase;
SR-BI = scavenger receptor class BI
HDL Metabolism and Reverse Cholesterol Transport

ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I; CE = cholesteryl ester; FC = free cholesterol; LCAT = lecithin:cholesterol acyltransferase; SR-BI = scavenger receptor class BI
Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.92 (1.26–2.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.80 (1.31–2.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.30 (0.95–1.73)</td>
<td>0.10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.01 (0.86–1.18)</td>
<td>0.93</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.85 (0.70–1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>Efflux capacity</td>
<td>0.75 (0.63–0.90)</td>
<td>0.002</td>
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</table>

HDL: Structure-Function Relationship:
CHOLESTEROL EFFLUX IS ENRICHED IN THE SMALL HDL PARTICLES (HDL3)

- Cholesterol efflux
- anti-oxidative
- antithrombotic
- anti-inflammatory
- anti-apoptotic

Rosenson R. ATVB 2016 36 777-782
The Structure of HDL Determines the Function of HDL!

1- Phospholipids are a major component of HDL
2- Cholesterol efflux was increased in small dense HDL3 and correlated with the HDL phospholipid. (phosphosphingolipodome)
The Structure of HDL determines the Function of HDL

Hunter WG et al. JACC 2019;73(2)
CENTRAL ILLUSTRATION: Proposed Protective Activities of Small High-Density Lipoprotein Particles

- **Anti-Oxidant**
  - Potent low-density lipoprotein protection
  - Inactivate lipid hydroperoxides, oxidized phospholipids

- **Endothelial Protection**
  - Enhanced endothelial nitric oxide synthase activity

- **Anti-Inflammatory**
  - Inhibit endothelial adhesion molecule expression
  - Neutrophil modulation

- **Anti-Atherogenic**
  - Enhanced cholesterol efflux
  - Lecithin-cholesterol acyltransferase activation

Upregulated:
- Sphingosine-1 Phosphate
- Hydrolytic Enzymes

Downregulated:
- Sphingomyelin
- Phospholipids

Membrane proteins:
- Factor H
- ABCA1
- Apolipoprotein A1

**References:**
APO C III
HR per SD = 1.09
(95% CI: 1.01, 1.18)

P heterogeneity < 0.01

HR per SD = 0.76
(95% CI: 0.70, 0.83)

Quintiles of HDL with and without apoC-III
Who’s in the BUS?? Which passengers?

HDL-C
Who’s in the BUS??

1-Phospholipid  2- ApoA1  3-Paraoxonase
4- No ApoC3
Who’s in the bus determines if HDL will be atheroprotective or pro-inflammatory.

Reduced antioxidative activity and diminished cholesterol efflux capacity.
Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction

Maryse Guerin, PhD, Johanne Silvain, MD, PhD, Julie Gall, PhD, Maryam Darabi, PhD, Myriam Berthet, PhD, Eric Frisdal, PhD, Marie Hauguel-Moreau, MD, Michel Zeitouni, MD, Mathieu Kerneis, MD, Benoit Lattuca, MD, Delphine Brugier, Jean-Philippe Collet, MD, PhD, Philippe Lesnik, PhD, Gilles Montalescot, MD, PhD
CENTRAL ILLUSTRATION: Cholesterol Efflux and Mortality in Myocardial Infarction: Kaplan-Meier Cumulative Survival Curve

Significance?

1- Cholesterol efflux capacity, a component of reverse cholesterol transport is independently associated with long term survival in MI patients.

2- Identify patients at higher risk of mortality after an acute coronary event

3- Independent of HDL-C
Cholesterol Efflux Hypothesis

1. CSL112 increases cholesterol efflux\(^1,2\)
   - Preclinical research data
   - Clinical development program

2. Increased cholesterol efflux in post-AMI patients\(^4,5\)

3. Reduced risk of CV events\(^6\)

- Phase 2a\(^1\)
- Phase 2b/AEGIS-II\(^4\)
- Phase 3/AEGIS-II\(^6\)

4. Well characterized mechanism of action\(^1\)
apoA-I (human) formulated with phospholipids that improve LCAT function

5. Appropriate dose\(^7\)
   - Upper end of dose range

6. Patients at high risk of CV events during 90 days post AMI\(^6\)
   - ACS patients with high event rates, multivessel disease, and established CV risk factors

7. Timely intervention\(^6\)
   - Early post-ACS, when cholesterol efflux is impaired

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HDL Particle Size and Structure Examined:

• 1- small particle size had greater efflux capacity, more anti-inflammatory, anti-oxidant, endothelial protective capacity than larger HDL particles

• 2- **HDL subfractions modulate key pathways in heart failure as well !**
High-Density Lipoprotein Particle Subfractions in Heart Failure With Preserved or Reduced Ejection Fraction

Wynn G. Hunter, MD, MHS, a Robert W. McGarah III, MD, b,c Jacob P. Kelly, MD, MHS, d Michel G. Khouri, MD, b Damian M. Craig, MS, c Carol Haynes, AB, c G. Michael Felker, MD, MHS, b,e Adrian F. Hernandez, MD, MHS, b,e Eric J. Velazquez, MD, b,e William E. Kraus, MD, b,c Svati H. Shah, MD, MS, MHS b,c,e
Adjusted for age, race, sex, body mass index, number of diseased coronary vessels (>75% stenosis), estimated glomerular filtration rate, history of hypertension, diabetes mellitus, smoking, dyslipidemia, low-density lipoprotein particles, and batch effects. Statistical significance ($p < 0.05$) denoted as follows: $^*$Significant difference in all-cause mortality between the highest and lowest tertiles. $^+$Middle and lowest tertiles. HDL-P = high-density lipoprotein particle(s); HFrEF = heart failure with preserved ejection fraction; HFpEF = heart failure with reduced ejection fraction.
Cardiometabolic Diseases in Which HDL Metabolism is Perturbed, and in Which the Proteome and Functionality of HDL Particles May Be Altered:

1. CAD / ACS
2. Acute Systemic inflammation / Sepsis / Endotoxemia
3. Uremia
Figure 18: Modulation of Apo A-I activity

A. Anti-inflammatory

B. Pro-inflammatory

- Myeloperoxidase
- Nitrotyrosine
- Chlorotyrosine
- Paraoxonase, other factors
- Proinflammatory factors, other factors

Apo A-I
Fig. 5. Compositional alterations in high-density lipoprotein (HDL) during acute phase reactions. During an acute phase reaction, the expression of a large number of inflammatory mediators increases, including C-reactive protein, fibrinogen, serum amyloid A, and secretory phospholipase A2. The normal enzymatic and apoprotein constituents of HDL can dissociate and be replaced by apoJ, serum amyloid A, and phospholipase A2. This attenuates the ability of HDL to engage in reverse cholesterol transport and decrease oxidation and inflammation. A-I, apoprotein A-I; A-II, apoprotein A-II; J, apoprotein J; CETP, cholesteryl ester transfer protein; LCAT, lecithin:cholesterol acyltransferase; PLTP, phospholipid transfer protein; PON1, paraoxonase 1; SAA, serum amyloid A; sPLA2, secretory phospholipase A2. Reproduced with permission from Ansell et al. (82). (see Color Plate 4)
3) HDL Remodelling in Uremic Patients

End-stage renal disease

THE LDL-C STORY...

• The story we know the best..................
THE LDL-C STORY....
THE HDL STORY...
the story we know less!
Atheroprotective & Vasculoprotective Activities of HDL

- Regulation of Glucose Homeostasis
- Reverse Cholesterol Transport
- Cellular Cholesterol Efflux
- Anti-Inflammatory and Anti-Oxidative activity
- Endothelial Repair; Vasodilation
- Anti-Infectious Activity
- Anti-Thrombotic Activity
- Anti-Apoptotic Activity
- Anti-proteolytic activity
- Regulation of Hematopoiesis
- Innate immune system

Hey, Have a little respect for HDL will ya!!

THANK YOU FOR LISTENING!!