The Future of HDL Diagnostics
and Therapeutics

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Low Levels of HDL-C Strongly Associate
with Risk of Coronary Artery Disease

TNT Study: Low HDL-C predicts CVD Risk in High-risk Subjects with LDL-C at Goal

Patients with on treatment LDL-C ≤ 70 mg/dL

<table>
<thead>
<tr>
<th>HDL-C Quintiles mg/dL</th>
<th>5-Year Risk of Major CVD Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 &lt;37</td>
<td>4.2</td>
</tr>
<tr>
<td>Q2 37 to &lt;42</td>
<td>3.7</td>
</tr>
<tr>
<td>Q3 42 to &lt;47</td>
<td>3.0</td>
</tr>
<tr>
<td>Q4 47 to &lt;55</td>
<td>2.5</td>
</tr>
<tr>
<td>Q5 ≥55</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Hazard Ratio Versus Q1:
- Q2: 0.85
- Q3: 0.57
- Q4: 0.55
- Q5: 0.61


Macrophages and Inflammation in the Artery Wall

Moore & Tabas, Cell 2011
Recent Issues in HDL Biology

In Humans:
- Gene Association Studies
  - Mendelian Randomization
  - SNPs
- Mutations
  - ApoAI
  - ABCA1
  - Endothelial Lipase
  - SCARB1
- Changes in HDL-C not associated with altered CAD risk
  - IDEAL and EPIC (Norfolk) studies
    - High HDL-C not lowered CAD risk.
- HDL-C Elevating Therapies
  - Niacin (AIM-HIGH)
    - No clear clinical benefit
  - CETP inhibition
    - No clear clinical benefit
- Recombinant HDL infusion
  - No clear benefits on plaque size

Conclusion: Changes in HDL-C ≠ Change in CAD

In Rodents:
- SR-B1 overexpression
  - Low HDL-C, reduced Athero
- SR-B1−/−
  - High HDL-C, increased Athero
- LCAT−/−
  - Low HDL-C, reduced Athero
- ABCA1−/−
  - Low HDL-C, Athero not affected

- Lifestyle modification
- Statin
- Niacin
- Fibrate
- Combination therapy

Current Options for Management of Low HDL Cholesterol
AIM HIGH: No Measurable Effects of Niacin Added to Simvastatin

- 3414 Subjects with CAD
- Simvastatin alone or with ezetimibe ± ER niacin
- On niacin TG 120, HDL 44, LDL 65
- Controls TG 152, HDL 38, LDL 67
- 282 subjects on niacin had primary endpoint (16.4%)
- 274 controls had primary endpoint (16.2%)
- Niacin does not seem to be affecting residual risk

NEJM November 2011
Reduced Risk of CV Events in ACCORD Lipid

Novel Therapies to Raise HDL-C or Improve HDL Function

- CETP inhibitors
- LXR agonists
- ABCA1 activators
- ApoAI mimetics
- ApoAI injectables
- SR-BI Inhibitors
- LCAT activators

CETP Inhibitors and Modulators
**Lipid Effects of CETP Inhibitors/Modulators**

<table>
<thead>
<tr>
<th>CETP Agent</th>
<th>Dose (Mg/day)</th>
<th>HDL-C (%)</th>
<th>LDL-C (%)</th>
<th>TG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torcetrapib</td>
<td>60</td>
<td>61</td>
<td>-24</td>
<td>-9</td>
</tr>
<tr>
<td>Anacetrapib</td>
<td>100</td>
<td>138</td>
<td>-40</td>
<td>-7</td>
</tr>
<tr>
<td>Evacetrapib</td>
<td>500</td>
<td>129</td>
<td>-36</td>
<td>-11</td>
</tr>
<tr>
<td>Dalcetrapib</td>
<td>600</td>
<td>31</td>
<td>-2</td>
<td>-3</td>
</tr>
</tbody>
</table>


**ILLUMINATE**

**Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events**

15,067 patients
- Men and women
- Aged 45-75 years
- 250 sites in 7 countries
- CHD or risk equivalent, any HDL-C level, statin eligible

**Primary End Point**
Composite of fatal CHD, nonfatal MI, stroke (fatal and non-fatal and unstable angina requiring hospitalization)

**Torcetrapib: Increased Cardiovascular and Non-Cardiovascular Morbidity and Mortality**

Patient Survival Curve

Was the toxicity of torcetrapib related to off-target effects specific to this molecule?

**Dalceptrapib Phase IIb Trial**

**HDL-C Increase at Week 12**

![Graph showing change in HDL-C levels at Week 12](image)

*NOTE: Dalceptrapib 600 mg is the dose used in phase III*

- Placebo: n = 73
- Dalceptrapib 300 mg: n = 75
- Dalceptrapib 600 mg: n = 67
- Dalceptrapib 900 mg: n = 72

*P < 0.0001 vs placebo*

**Dal-OUTCOMES:**

- No toxicity but no ↓CVD

- Placebo: n = 73
- Dalceptrapib: n = 75


**Evacetrapib:**

**Effects on HDL-C and LDL-C**

![Graph showing effects on HDL-C and LDL-C](image)

*P<0.001 compared with placebo.*

**CETP Inhibition with Anacetrapib**

**LDL-C**
- Anacetrapib: 39.8% (P<0.001)
- Placebo

**HDL-C**
- Anacetrapib: +138.1% (P<0.001)
- Placebo

**REVEAL Trial**

Randomized Evaluation of the Effects of Anacetrapib through Lipid-Modification

- Anacetrapib 100 mg
- Placebo

Primary End Point
- Coronary death, myocardial infarction or coronary revascularization

Sites in North America, Europe and Asia

30,000 patients aged ≥ 55 with occlusive arterial disease

Planned completion in 2017

- 4 year follow-up

Does HDL become dysfunctional in CAD or does dysfunctional HDL cause CAD?

- Lack of association between function and HDLc levels suggests that atherosclerosis may modify HDL
- Dysfunctional HDL may be hiding in either the low or high HDLc range
- Dysfunctional HDL may be present in unique patient types

**CAD* Risk Reduction with LDL Lowering in ESRD Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D (atorva)</td>
<td>33 (1.91%)</td>
<td>35 (2.02%)</td>
</tr>
<tr>
<td>AURORA (rosuva)</td>
<td>91 (1.97%)</td>
<td>107 (2.33%)</td>
</tr>
<tr>
<td>SHARP (simva/eze)</td>
<td>134 (0.71%)</td>
<td>159 (0.85%)</td>
</tr>
</tbody>
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*Non-fatal myocardial infarction

**Uremia Inhibits Atherosclerosis Regression**

HDL of Patients on Renal Dialysis Have Impaired Cholesterol Efflux Capacity


New Generation of HDL Metrics

HDL Biogenesis

Genetics

Macrophage Sterol Exchange
**Macrophage Sterol Efflux**

Modified from Duffy and Rader, Nature Reviews, 2009

**Serum Cholesterol Efflux Capacity**

Cholesterol Efflux Capacity in Coronary Artery Disease Patients

- 442 CAD patients and 351 controls
- Serum efflux capacity independent predictor of coronary artery disease status
- Results only partially explained by HDLc levels
- Efflux improved by pioglitazone, not by statins


Sterol Efflux Capacity of Serum HDL Strongly Associates with Prevalent CAD Status

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>1.50 (1.26–1.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.80 (1.31–2.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.30 (0.95–1.73)</td>
<td>.10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.81 (0.80–3.59)</td>
<td>.19</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.80 (0.60–1.08)</td>
<td>.09</td>
</tr>
<tr>
<td>Efflux capacity</td>
<td>0.71 (0.51–0.98)</td>
<td>.03</td>
</tr>
</tbody>
</table>


HDL Prevents Polymerization of von Willebrand Factor

Conclusions and Take Home Messages

- HDL-C levels predict CVD risk, but HDL-C manipulation is not linked to clinical benefits.
- Functionality of HDL may relate to CVD risk reduction.
- Many HDL functions can be studied, but the one ahead is the ability to extract cholesterol from cells.
- There may be a correlation between HDL-C levels and HDL functionality, but this can easily be lost in conditions such as renal disease or systemic inflammation.
- No therapy is available to improve HDL function.