HDL: State of the Lipoprotein

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“It's what we think we know that keeps us from learning.”

-Claude Bernard (1811-1873)
French Physiologist
Low HDL-C Is a Well-Established, Independent CHD Risk Factor: ARIC

HDL-C Quintiles

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol/L</td>
<td>0.80</td>
<td>0.97</td>
<td>1.11</td>
<td>1.27</td>
<td>1.60</td>
</tr>
<tr>
<td>mg/dL (median)</td>
<td>31</td>
<td>38</td>
<td>43</td>
<td>49</td>
<td>62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol/L</td>
<td>1.01</td>
<td>1.25</td>
<td>1.44</td>
<td>1.69</td>
<td>2.09</td>
</tr>
<tr>
<td>mg/dL (median)</td>
<td>39</td>
<td>48</td>
<td>56</td>
<td>65</td>
<td>81</td>
</tr>
</tbody>
</table>

Adjusted for age and race, 12-year follow-up; N=12,339

HDL-C Levels and CV Events: TNT

Patients With LDL-C <70 mg/dL on Statin<sup>a,b</sup>

<table>
<thead>
<tr>
<th>HDL-C Quintiles&lt;sup&gt;a&lt;/sup&gt;, mg/dL</th>
<th>Hazard Ratio vs Q1&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 &lt;37</td>
<td>0.85</td>
</tr>
<tr>
<td>Q2 37 to &lt;42</td>
<td>0.57</td>
</tr>
<tr>
<td>Q3 42 to &lt;47</td>
<td>0.55</td>
</tr>
<tr>
<td>Q4 47 to &lt;55</td>
<td>0.61</td>
</tr>
<tr>
<td>Q5 ≥55</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> On-treatment level (3 months statin therapy); n = 2661

<sup>b</sup> Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL

*P=0.03 for differences among quintiles of HDL-C

HDL: State of the Lipoprotein

- Understanding HDL structure and function
- HDL functionality may be more relevant than current HDL testing
- Can HDL and/or its substituents be used to define CHD risk better than current practice?
- Can HDL and/or its substituents be targeted to reduce CHD risk better than current practice?
HDL – Proteomic Domains

HDL: Some Potential Atheroprotective Functions

- Reverse cholesterol transport (RCT)
- Improvement in endothelial function
- Limitation of hemostasis
- Protection of LDLs from oxidation
- Decrease vessel wall inflammation
  - ↓ expression of cytokine-induced cellular adhesion molecules
  - ↓ monocyte chemotactic protein-1 (MCP-1)
  - ↓ oxidized phospholipids
- Improved glycemia

# HDL: Assessing/Defining Functionality

## Assays of HDL function in humans

<table>
<thead>
<tr>
<th>Assay class</th>
<th>Assay</th>
<th>Advantages/limitations</th>
<th>Human studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL subpopulations and size</td>
<td>2D PAGE (27)</td>
<td>Identifies particles that may relate to HDL function and outcomes; low throughput, semiquantitative, surrogate of true function</td>
<td>Yes, small- to intermediate-sized studies</td>
</tr>
<tr>
<td></td>
<td>NMR (28)</td>
<td>Identifies HDL particle size and number; high throughput, but limited evidence for CVD risk prediction beyond HDL-C</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>Macrophage cholesterol efflux (12)</td>
<td>Analyzes ex vivo capacity of isolated HDL to efflux cholesterol from macrophages; low throughput</td>
<td>Yes, epidemiological and clinical trials</td>
</tr>
<tr>
<td></td>
<td>Fecal sterol excretion (29)</td>
<td>Estimates total body excretion of cholesterol; may lack sensitivity for macrophage RCT and be confounded by bowel cholesterol metabolism</td>
<td>Yes, small scale; relationship to atherosclerosis is lacking</td>
</tr>
<tr>
<td></td>
<td>HDL tracer kinetic studies (30)</td>
<td>Trace HDL lipid fluxes and excretion from body; do not assay macrophage RCT; hepatic and bowel activity confounds tracer kinetics</td>
<td>Yes, proof of concept; needs validation</td>
</tr>
<tr>
<td></td>
<td>Activity and mass assays of CEPT, LCAT, lipases etc.</td>
<td>Estimate mass or activity of HDL proteins involved in RCT; activity assays require standardization</td>
<td>Yes; greater evidence of relationship to RCT and atherosclerosis is required</td>
</tr>
<tr>
<td>HDL antiinflammatory</td>
<td>Monocyte chemotactic assay (7, 31); cell-free assay (7, 31)</td>
<td>Analyzes ex vivo capacity of HDL to suppress LDL-induced chemotaxis; low throughput, lacks standardization</td>
<td>Yes, proof-of concept studies</td>
</tr>
<tr>
<td></td>
<td>Vascular adhesion molecular expression or levels</td>
<td>Requires vascular tissue or plasma; plasma assays are not specific to HDL function</td>
<td>Yes, plasma assays</td>
</tr>
<tr>
<td>HDL antioxidant</td>
<td>HDL-associated paraoxonase or Lp-PLA₂ mass or activity</td>
<td>Assays HDL antioxidant enzymes; single dimension of HDL function, lacks standardization</td>
<td>Yes, limited proof of concept</td>
</tr>
</tbody>
</table>

RCT, reverse cholesterol transport.
Assessing HDL Anti-Inflammatory Function: Methods

– Ability of HDL to alter LDL-induced monocyte chemotactic activity (MCA) in a human artery wall coculture.

– Ability of HDL to alter oxidized phospholipid-induced fluorescence in a cell-free assay (CFA).

Inflammatory/Anti-inflammatory Properties: HDL Inflammatory Index

- **HII**

- **LDL**

- **LDL + HDL**

- **Anti-inflammatory**

- **Proinflammatory**

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CHD Despite High HDL Study: Monocyte Chemotaxis Assay (MCA)

Subjects:
• 20 adults with stable CHD, HDL-C ≥84 mg/dL
• Mean LDL-C 108 mg/dL
• No lipid medication, smoking, or diabetes

P<0.001

Correlation Between MCA and Cholesterol Efflux

Corr. = 0.760 ($P<0.001$).

HDL Function in High-Risk Patients: Controlled Interventional Studies

• CHD/risk equivalents (vs. placebo)
  – Simvastatin—partially improved LDL-induced MCA, CFA
  – Niacin—partially restored impaired HDL-induced eNO production in DM Patients
  – D4F—partially improved LDL-induced MCA, CFA in CHD (limited to those with adequate oral absorption)
  – Fat type—SFA-rich meal increased/PUFA-rich decreased HDL-induced endothelial ICAM-1/VCAM-1

• Metabolic syndrome
  – Multifaceted TLC—improved MCA in MetSyn patients

• Rheumatoid arthritis
  – Atorvastatin—significant decrease in CFA vs. placebo in active RA

Anti-Inflammatory HDL

Systemic inflammation, e.g. coronary disease, diabetes, metabolic syndrome, surgery, infection, rheumatologic diseases

Apo A-1

Antioxidant Enzymes
- e.g. PON-1, PAF-AH, LCAT

Phospholipid monolayer

Systemic inflammation, e.g. coronary disease, diabetes, metabolic syndrome, surgery, infection, rheumatologic diseases

Apo A-1

Antioxidant Enzymes

Phospholipid monolayer

↓Apo A-1

↓Antioxidant Enzymes

Anti-Inflammatory HDL

Systemic inflammation, e.g. coronary disease, diabetes, metabolic syndrome, surgery, infection, rheumatologic diseases

Apo A-1

Antioxidant Enzymes
  e.g. PON-1, PAF-AH, LCAT

Phospholipid monolayer

Systemic inflammation, e.g. coronary disease, diabetes, metabolic syndrome, surgery, infection, rheumatologic diseases

Anti-Inflammatory HDL

- Apo A-1
- Antioxidant Enzymes (e.g. PON-1, PAF-AH, LCAT)
- Phospholipid monolayer

Pro-Inflammatory HDL

- Oxidized Phospholipids
- Myeloperoxidase
- Acute Phase Proteins
- Enhanced Thrombosis, ECM Degradation
- Increased LDL Oxidation
- Impaired Cholesterol Efflux
- Chemically modified Apo A-1

- Antioxidant Enzymes

## Select Lifestyle Interventions and HDL-C

<table>
<thead>
<tr>
<th>Therapeutic Intervention</th>
<th>Increase in HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercise</td>
<td>5-10%</td>
</tr>
<tr>
<td>Tobacco cessation</td>
<td>5-10%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.35 mg/dL per kg weight lost</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>5-15%</td>
</tr>
<tr>
<td>Dietary factors (n-3, n-6 PUFA, MUFA)</td>
<td>0-5%</td>
</tr>
</tbody>
</table>

PUFA = polyunsaturated fatty acids  
MUFA = monounsaturated fatty acids

Insights From GWAS With Levels of LDL-C, HDL-C, TG

1. Many new loci identified that are associated with lipid levels
2. Loci associated with LDL-C levels usually are associated with CHD
3. Loci associated with HDL-C and TG levels are not as consistently associated with CHD
4. Implication: not all pathways that alter HDL-C levels have the same impact on the pathogenesis of atherothrombotic CHD; therefore, the same may be true of interventions that modify HDL metabolism

Drugs That Raised HDL-C But Did Not Reduce CVD Events

1. **Estrogen/progestin: WHI**
   - HDL-C increased by 7.3% (vs. placebo)
   - CHD risk increased by 29%
   - Stroke risk increased by 41%

2. **Torcetrapib: ILLUMINATE**
   - HDL-C increased by 70.3% (vs. placebo)
   - CHD risk increased by 21%
   - Stroke risk increased by 8%
   - Almost half excess death was noncardiovascular

AIM-HIGH: Primary Endpoint

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo plus statin</td>
<td>1696</td>
<td>1581</td>
<td>1381</td>
<td>910</td>
<td>436</td>
</tr>
<tr>
<td>Niacin plus statin</td>
<td>1718</td>
<td>1606</td>
<td>1366</td>
<td>903</td>
<td>428</td>
</tr>
</tbody>
</table>

P = 0.79 by log-rank test

AIM-HIGH: HDL-C Results

- **Combination Therapy**
  - ↑25.0% vs. baseline
  - P<0.001
- **Monotherapy**
  - ↑9.8% vs. baseline

AIM-HIGH: LDL-C Results

- Combination Therapy
- Monotherapy

Baseline: ↓5.5% vs. baseline
Year 1: ↓12% vs. baseline
Year 2: ↓12% vs. baseline
Year 3: ↓12% vs. baseline

P<0.001

AIM-HIGH: TG Results

Combination therapy: ↓28.6% vs. baseline
Monotherapy: ↓8.1% vs. baseline

AIM-HIGH vs Previous Niacin Trials

• Previous niacin trials were largely placebo-controlled and/or combination regimens, and did/could not rule out the impact of LDL-lowering and other therapies.
• Previous niacin trials almost exclusively used immediate-release niacin.
• Previous trials evaluated primarily angiographic endpoints, with conclusions drawn from small numbers of clinical events.
Coronary Drug Project - Clinical Outcomes (Total Follow-up, Adjusted for Baseline)

![Bar chart showing event rates for different outcomes: Nonfatal MI/CHD death, Nonfatal MI, Stroke/TIA, CV Surgery.]

- Nonfatal MI/CHD death: -14%* for Placebo, -27%* for Niacin
- Nonfatal MI: -26%* for Niacin
- Stroke/TIA: -26%* for Niacin
- CV Surgery: -47%* for Niacin

* p<0.05
† 5-year rate

JAMA 1975;231:360-381.
HDL Atherosclerosis Treatment Study (HATS) Clinical Events

HATS: Numbers of Subjects With Events

<table>
<thead>
<tr>
<th></th>
<th>Placebos (N=38)</th>
<th>Simvastatin-Niacin (N=38)</th>
<th>Anti-oxidant Vitamins (N=42)</th>
<th>Simvastatin-Niacin + Antioxidants (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular causes</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nonfatal Infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cerebral</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Composite of death from CV causes or nonfatal infarction</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Revascularization Procedure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Coronary angioplasty or stenting</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral endarterectomy or grafting</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Composite of death from cardiovascular causes, nonfatal infarction, or revascularization procedure†</td>
<td>9</td>
<td>1‡</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td><strong>Hospitalization for confirmed ischemia without revascularization</strong></td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Composite of death from cardiovascular causes, nonfatal infarction, revascularization procedure, or hospitalization for confirmed ischemia</td>
<td>12</td>
<td>1§</td>
<td>11</td>
<td>6</td>
</tr>
</tbody>
</table>

- Only 30/160 subjects with clinical events
- Only 25 total subjects with a primary endpoint
- Revascularization in 22/30 (73%) of patients

HPS2-THRIVE (Heart Protection Study 2 – Treating HDL to Reduce Vascular Events)

Does ER niacin/laropiprant 2 g/40mg daily prevent vascular events in high-risk patients who are receiving intensive LDL-C lowering treatment?

**Patient Population**
- **Subjects**
  - Age 50-80
  - History of MI or cerebrovascular atherosclerotic disease or PAD or diabetes mellitus with any of the above or with other evidence of symptomatic CHD

**Subjects**
- 20,000
  - UK (n=7500), Scandinavia (n=5000), China (n=7500)

**Primary Endpoint**
- Major vascular events during the scheduled treatment period (nonfatal MI or coronary death, nonfatal or fatal stroke, or revascularisation)

- Study start: January 2007. Study ended in December 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 (%)

Years of follow-up

Helsinki Heart Study

- 4,081 men aged 40-55 years with non-HDL-C ≥200 mg/dL, initially free of coronary disease
- LDL-C –11%, HDL-C +11%
- 34% reduction in CHD endpoints
- Greatest benefits when triglyceride high or HDL-C low
- LDL-C/HDL-C >5.0 and triglycerides >200 mg/dL: risk was reduced by 71%

VA-HIT: Changes in Plasma Lipids During Treatment as Predictors of Coronary Events

Subjects: 2,531 men with known CHD, baseline lipids:
- HDL-C (≤40), mean 32
- LDL-C (≤ 140), mean 111

Intervention: RCT, gemfibrozil 1200 mg/d vs placebo
Outcome: 22% ↓CHD events/nonfatal MI vs placebo (P = 0.006)

<table>
<thead>
<tr>
<th>Variable (Change)</th>
<th>Risk Factor (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (5.0 mg/dL)</td>
<td>0.89 (0.81–0.98)</td>
<td>.02</td>
</tr>
<tr>
<td>Triglycerides (50 mg/dL)</td>
<td>1.03 (0.95–1.11)</td>
<td>.48</td>
</tr>
<tr>
<td>LDL-C (25 mg/dL)</td>
<td>1.09 (0.98–1.21)</td>
<td>.13</td>
</tr>
</tbody>
</table>

ACCORD Lipid Trial: Kaplan-Meier Estimates of Cumulative Incidence

## Comparison of ACCORD Subgroup Results With Those From Prior Fibrate Studies

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Primary Endpoint: Entire Cohort (P value)</th>
<th>Lipid Subgroup Criterion</th>
<th>Primary Endpoint: Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (Gemfibrozil)</td>
<td>-34% (0.02)</td>
<td>TG &gt; 200 mg/dl LDL-C/HDL-C &gt; 5.0</td>
<td>-71% (&lt;0.05)</td>
</tr>
<tr>
<td>BIP (Bezafibrate)</td>
<td>-7.3% (0.24)</td>
<td>TG ≥ 200 mg/dl</td>
<td>-39.5% (0.02)</td>
</tr>
<tr>
<td>FIELD (Fenofibrate)</td>
<td>-11% (0.16)</td>
<td>TG ≥ 204 mg/dl HDL-C &lt; 42 mg/dl</td>
<td>-27% (0.005)</td>
</tr>
<tr>
<td>ACCORD (Fenofibrate)</td>
<td>-8% (0.32)</td>
<td>TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl</td>
<td>-31% (&lt;0.05)</td>
</tr>
</tbody>
</table>

www.lipid.org
AFCAPS/TexCAPS: Results by Baseline HDL-C Tertile

Events per 1,000 pt./yrs

- **≤34**: n=2,115, 45% RRR
- **35-39**: n=2,347, 44% RRR
- **≥40**: n=2,143, 15% RRR

**Table of Events**

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Placebo</th>
<th>Lovastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤34</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>35-39</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>≥40</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Addition of Eicosapentaenoic Acid (EPA) to Statin Therapy in Japanese Patients: JELIS Results


Major CHD Events<a>

<table>
<thead>
<tr>
<th>Statin</th>
<th>Statin + EPA 1.8 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>

19% Reduction

*P = 0.011*

Lipid Effects

<table>
<thead>
<tr>
<th></th>
<th>Statin (n = 9319)</th>
<th>Statin + EPA 1.8 g (n = 9326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.001*

4.6-year mean follow-up

<a>Sudden cardiac death, fatal and nonfatal MI, unstable angina pectoris, angioplasty, stenting, or CABG

Patient Subgroup - TG >150mg/dL and HDL <40mg/dL: JELIS

Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Control</th>
<th>EPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>475</td>
<td>482</td>
</tr>
<tr>
<td>1</td>
<td>444</td>
<td>455</td>
</tr>
<tr>
<td>2</td>
<td>432</td>
<td>443</td>
</tr>
<tr>
<td>3</td>
<td>414</td>
<td>427</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>413</td>
</tr>
<tr>
<td>5</td>
<td>392</td>
<td>403</td>
</tr>
</tbody>
</table>

Hazard ratio and P value adjusted for age, gender, smoking, diabetes, and hypertension.

HR = hazard ratio; CI = confidence interval.


HR: 0.47
95% CI: 0.23-0.98
P=0.043
Reduction of Cardiovascular Events With EPA—Intervention Trial (REDUCE-IT)

OUTCOME MEASURES

PATIENTS
~8000 men and women aged ≥45 years with:
• CVD or high CVD risk
• Hypertriglyceridemia
• On statin therapy ≥4 wks

INTERVENTION
Highly purified ethyl ester of eicosapentaenoic acid (AMR101) or Placebo

PRIMARY
Incidence of CV events, such as coronary revascularization

SECONDARY
Incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as diabetic patients

Follow-up: 4-6 years

Estimated PRIMARY completion date: November 2016
(Final data collection date for primary outcome measure)

http://clinicaltrials.gov/ct2/show/NCT01492361
Emerging HDL Therapies

- Infusion of apoA-I and apoA-I/PL complexes
- Delipidated autologous HDL infusions
- ApoA-I mimetic peptides
- ATI-5261 synthetic peptide (animal studies)
- EL inhibitors
- LCAT inhibitors (ETC-642)
- ApoA1 Upregulators (RVX-208)
Emerging HDL/ApoA-1 Therapies

<table>
<thead>
<tr>
<th>Pharmacotherapeutic strategy</th>
<th>Drug</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant apoA-I</td>
<td>ETC-216</td>
<td>Directly augmenting apoA-I/HDL pool</td>
</tr>
<tr>
<td>Milano/phospholipids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified native apoA-I/phospholipids</td>
<td>CSL-111 and CSL 112</td>
<td>Directly augmenting apoA-I/HDL pool</td>
</tr>
<tr>
<td>Upregulators of endogenous apoA-I production</td>
<td>RVX-208</td>
<td>Directly augmenting apoA-I/HDL pool</td>
</tr>
<tr>
<td>ApoA-I mimetic peptides</td>
<td>D-4F</td>
<td>Mimicking apoA-I functionality</td>
</tr>
<tr>
<td></td>
<td>L-4F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATI-5261</td>
<td></td>
</tr>
<tr>
<td>Autologous delipidated HDL</td>
<td>Selective HDL delipidated</td>
<td>Directly augmenting apoA-I/HDL pool</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>miR-33</td>
<td>Modulating HDL levels and cholesterol efflux expression</td>
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<td>Liver X receptor agonists</td>
<td>LXRα/β agonists</td>
<td>Enhancing RCT &amp; Macrophage cholesterol efflux</td>
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<td>ARI-3037MO</td>
<td>Indirectly augmenting apoA-I and HDL-cholesterol</td>
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<td>Farnesoid X receptor</td>
<td>FxR-450</td>
<td>Modulate HDL levels</td>
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<td>Cholesteryl ester transfer inhibitors</td>
<td>Anacetrapib MK-0859</td>
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<td>Evacetrapib LY248595</td>
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<td>Endothelial lipase inhibition</td>
<td>Boronic acid inhibitors</td>
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<td>Selective sulfonylfluran urea</td>
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<td>LCAT activators</td>
<td>rLCAT</td>
<td>Enhancing RCT</td>
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DAL-Outcomes: Recent ACS Patients

A

HDL Cholesterol (mg/dL)

Months

No. at Risk
Placebo 7907 7685 7498 7272 6959 6436 3650
Dalcetrapib 7910 7663 7400 7196 6871 6333 3599

B

LDL Cholesterol (mg/dL)

No. at Risk
Placebo 7907 7679 7473 7265 6947 6427 3640
Dalcetrapib 7910 7657 7382 7191 6863 6324 3591

Dal-Outcomes: Primary Endpoint

Cumulative Incidence of Primary Outcome (% of patients)

P = 0.52 by log-rank test

No. at Risk

<table>
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<tr>
<th></th>
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<th>Dalcetrapib</th>
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</table>
Dal-Outcomes: HDL-C vs 1° Endpoint

A

Annualized Event Rate (%) vs HDL Cholesterol (mg/dl) at Baseline, According to Quintile

B

Annualized Event Rate (%) vs Change in HDL Cholesterol (mg/dl) from Baseline to Month 1, According to Quintile

Summary

• Low HDL-C/Apo A-I levels are clearly associated with increased risk for CHD

• Not all genetic variants and therapies that raise HDL-C have reduced CHD events
Summary

• Optimizing statin therapy and lifestyle practices should remain the primary focus
• Gemfibrozil and omega 3 FAs reduce CVD risk in subgroups of patients with low HDL-C/high TG
• Using ER-niacin in low-HDL-C CHD patients does not reduce CVD risk further in comparison to optimized LDL-based therapy
• Raising HDL-C may neither be necessary nor sufficient to improve HDL-mediated CVD risk
Some Remaining Questions

- Are the disparate results in niacin trials a reflection of different niacin preparations?
- Was there an adverse effect of laropiprant in HPS-2?
- Was AIM-HIGH stopped too soon?
- Does the heterogeneity of results in fibrate trials reflect pharmacologic differences between gemfibrozil and the rest of the class, or differing populations studied?
- What factors, beyond HDL-C, are viable treatment targets for HDL-based therapeutics?
- Can functionality be specifically measured and targeted?