The HDL Conundrum: Is There a Role in CVD Risk Reduction?

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Clinical Professor, Director of the Lipid Clinic*
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The University of Chicago*
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Pritzker School of Medicine*
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Chicago, IL*
## Presenter Disclosure Information

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
<th>Level</th>
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<tr>
<td>Research Support</td>
<td>None for the past 24 months</td>
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<tr>
<td>Consulting Fees</td>
<td>Amgen, Lipidemix, Merck, Regeneron, Sanofi-aventis,</td>
<td>Modest Level</td>
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<td>DSMB</td>
<td>Aegerion, Merck,</td>
<td>Modest Level</td>
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<td>Grants</td>
<td>None for the past 24 months</td>
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</tr>
<tr>
<td>Equity</td>
<td>Founder of Omthera now owned by Astra-Zeneca</td>
<td>Significant</td>
</tr>
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</table>
Relationship Between Low HDL-C and CHD Persists After Intensive Statin Treatment

Post hoc analysis of TNT trial

JUPITER: CVD Event Rates by Quartiles of HDL-C and Apo A-I

Median LDL-C with rosuvastatin: 55 mg/dL

Torcetrapib in Patients at High Risk for Coronary Events

*Death from CHD, nonfatal MI, stroke, and hospitalization for UA

Dalcetrapib Did Not Reduce Risk of Recurrent CVD Events

**Primary Efficacy***

- Placebo (N = 7933)
  - HR (95% CI): 1.04 (0.93-1.16)
  - P = .52

- Dalcetrapib (N = 7938)
  - HR (95% CI): 0.99 (0.82-1.19)
  - P = .90

**Death From Any Cause**

- Placebo
  - 8

- Dalcetrapib
  - 8.3

*Death from CHD, major nonfatal coronary events (acute MI, hospitalization for UA with objective evidence of acute myocardial ischemia, or cardiac arrest with resuscitation), or stroke of presumed atherothrombotic cause.

Cumulative Incidence of CVD Events for Dalcetrapib and Placebo Separately and Stratified by Three Genotypes

ACCELERATE Evacetrapib Clinical Program

High-Risk Vascular Disease (HRVD) – defined by the following groups:

- History of ACS ≥ 30 days through 365 days after discharge from ACS
- Cerebrovascular atherosclerosis disease
- Peripheral arterial disease
- Diabetes mellitus w/ documented coronary artery disease

Randomization n 1:1

Evacetrapib 130 mg

Placebo

Follow up every 3 months with an initial 1-month visit
Safety follow up 1 month after end of treatment

Study continues until all the following occur:

1) 1136 patients with 1º endpoint: CVD/MI/stroke/hospitalization for UA/coronary revascularization
2) 500 patients with CVD/MI/stroke
3) 1.5 years after last patient entered treatment
Mean difference in LDL-C in ACCERLATE

Mean LDL-C = 84 mg/dL

Mean difference 37%

Mean LDL-C = 55 mg/dL
Mean Difference in HDL-C in ACCELERATE

Mean HDL-C = 104 mg/dL
Mean difference = 130%
Mean HDL-C = 46 mg/dL

Percent Change in HDL-C (%)

Evacetrapib
Placebo
Primary Endpoint ACCELERATE

- Evacetrapib, 774 events (12.8%)
- Placebo, 768 events (12.7%)

HR = 1.01
95% CI, 0.91-1.12
P=0.85
DEFINE Trial: Effect of Anacetrapib on Plasma HDL-C and LDL-C

Decrease LDL-C = 40%
Increase HDL-C = 138%

## Clinical Events in the Anacetrapib DEFINE Clinical Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Anacetrapib (N=808)</th>
<th>Placebo (N=804)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prespecified, adjudicated cardiovascular safety end point</td>
<td>16 (2.0)</td>
<td>21 (2.6)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>4 (0.5)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>6 (0.7)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>1 (0.1)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>5 (0.6)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>11 (1.4)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (0.4)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>8 (1.0)</td>
<td>28 (3.5)</td>
</tr>
<tr>
<td>PCI</td>
<td>6 (0.7)</td>
<td>25 (3.1)</td>
</tr>
<tr>
<td>CABG</td>
<td>2 (0.2)</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>

Anacetrapib Pharmacokinetics

- Anacetrapib levels assessed in 30 patients previously treated for 1-77 weeks
- Patients were off study drug for 2.4-4 years
- During this period
  - Residual anacetrapib levels were still present, and
  - At levels expected to have low pharmacologic activity

REVEAL: Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification

- 30,000 patients with occlusive arterial disease in North America, Europe, and Asia
- Background LDL lowering with atorvastatin
- Randomized to anacetrapib 100 mg vs. placebo
- Scheduled follow-up: 4 years
- Primary outcome: coronary death, myocardial infarction, or coronary revascularization

Clinical Trials.gov NCT01252953
AIM-HIGH: HDL-C Results

**Combination Therapy**

- Baseline: 25 mg/dL
- Year 1: 35 mg/dL (↑25.0% vs. baseline)
- Year 2: 40 mg/dL (↑9.8% vs. baseline)
- Year 3: 45 mg/dL

**Monotherapy**

- Baseline: 30 mg/dL
- Year 1: 33 mg/dL
- Year 2: 34 mg/dL
- Year 3: 35 mg/dL

*P < 0.001

AIM-HIGH: Primary Endpoint

Cumulative Percentage of Patients With Primary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</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

Effect of ERN/LRPT on Major Vascular Events

Risk ratio 0.96 (95% CI 0.90 – 1.03)
Logrank P=0.29

Adapted from Prof. Jane Armitage. ACC Congress 2013, 15th March 2013.
Among 15 Variants That Alter HDL-C, 6 Also Affect MI Risk

<table>
<thead>
<tr>
<th>Gene(s) of interest within or near associated interval</th>
<th>Major allele, minor allele (minor allele frequency)*</th>
<th>Modeled allele</th>
<th>Effect of modeled allele on plasma HDL cholesterol (mmol/L)*</th>
<th>Effect of modeled allele on plasma triglycerides (mmol/L)*</th>
<th>Effect of modeled allele on plasma LDL cholesterol (mmol/L)*</th>
<th>Sample size (MI cases/MI-free controls)</th>
<th>For modeled allele, observed change in MI risk (%; 95% CI)</th>
<th>For modeled allele, p value for association with MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL†</td>
<td>G, T (0.10)</td>
<td>T</td>
<td>0.08</td>
<td>-0.24</td>
<td>...</td>
<td>19 139/50 812</td>
<td>-12% (-16 to -7)</td>
<td>4×10⁻⁷†</td>
</tr>
<tr>
<td>TRIB1†</td>
<td>A, G (0.45)</td>
<td>G</td>
<td>0.02</td>
<td>-0.11</td>
<td>-0.05</td>
<td>19 139/50 812</td>
<td>-7% (-9 to -4)</td>
<td>2×10⁻⁸†</td>
</tr>
<tr>
<td>APOA1-APOC3-APOA4-APOA5†</td>
<td>A, G (0.07)</td>
<td>A</td>
<td>0.05</td>
<td>-0.27</td>
<td>-0.09</td>
<td>18 310/49 897</td>
<td>-10% (-15 to -5)</td>
<td>8×10⁻⁷†</td>
</tr>
<tr>
<td>GALNT2†</td>
<td>A, G (0.40)</td>
<td>A</td>
<td>0.02</td>
<td>-0.03</td>
<td>...</td>
<td>19 139/50 812</td>
<td>-3% (-6 to -1)</td>
<td>0.02†</td>
</tr>
<tr>
<td>ANGPTL4†</td>
<td>C, T (0.16)</td>
<td>C</td>
<td>0.05</td>
<td>-0.07</td>
<td>...</td>
<td>13 595/16 423</td>
<td>-5% (-10 to -1)</td>
<td>0.03†</td>
</tr>
<tr>
<td>CETP†</td>
<td>C, A (0.32)</td>
<td>A</td>
<td>0.10</td>
<td>...</td>
<td>-0.03</td>
<td>16 503/46 576</td>
<td>-4% (-7 to 0)</td>
<td>0.04†</td>
</tr>
<tr>
<td>LIPG</td>
<td>A, G (0.015)</td>
<td>G</td>
<td>0.14‡</td>
<td>...</td>
<td>...</td>
<td>17 165/49 077</td>
<td>-6% (-18 to 9)</td>
<td>0.41</td>
</tr>
<tr>
<td>MLXIPL</td>
<td>C, T (0.11)</td>
<td>T</td>
<td>0.03</td>
<td>-0.15</td>
<td>...</td>
<td>19 139/50 812</td>
<td>-1% (-4 to 3)</td>
<td>0.61</td>
</tr>
<tr>
<td>ABCA1</td>
<td>G, A (0.14)</td>
<td>G</td>
<td>0.03</td>
<td>...</td>
<td>0.05</td>
<td>19 139/50 812</td>
<td>-1% (-5 to 4)</td>
<td>0.76</td>
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<tr>
<td>MMAB, MVK</td>
<td>G, C (0.46)</td>
<td>G</td>
<td>0.03</td>
<td>...</td>
<td>...</td>
<td>19 139/50 812</td>
<td>0% (-3 to 3)</td>
<td>0.85</td>
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<tr>
<td>TTC39B</td>
<td>T, C (0.12)</td>
<td>T</td>
<td>0.03</td>
<td>...</td>
<td>...</td>
<td>15 693/47 098</td>
<td>0% (-5 to 5)</td>
<td>0.97</td>
</tr>
<tr>
<td>LCAT</td>
<td>G, A (0.11)</td>
<td>A</td>
<td>0.03</td>
<td>...</td>
<td>...</td>
<td>19 139/50 812</td>
<td>4% (-1 to 8)</td>
<td>0.10</td>
</tr>
<tr>
<td>FADS1-FADS2-FADS3</td>
<td>T, C (0.33)</td>
<td>T</td>
<td>0.03</td>
<td>-0.06</td>
<td>...</td>
<td>19 139/50 812</td>
<td>3% (-1 to 6)</td>
<td>0.11</td>
</tr>
<tr>
<td>LIPC</td>
<td>C, T (0.22)</td>
<td>T</td>
<td>0.05</td>
<td>0.07</td>
<td>...</td>
<td>17 917/49 514</td>
<td>4% (0 to 7)</td>
<td>0.04</td>
</tr>
<tr>
<td>HNF4A</td>
<td>C, T (0.01)</td>
<td>T</td>
<td>0.01</td>
<td>...</td>
<td>...</td>
<td>17 041/20 137</td>
<td>31% (12 to 54)</td>
<td>9×10⁻⁴</td>
</tr>
</tbody>
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<td>-0.24</td>
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<td>-0.05</td>
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<td>-0.27</td>
<td>-0.09</td>
<td>18,310/49,897</td>
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<td>A</td>
<td>0.10</td>
<td>--</td>
<td>-0.03</td>
<td>16,503/46,576</td>
<td>-4% (-7 to 0)</td>
<td>0.04†</td>
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</tbody>
</table>

All 6 are ‘HDL-C Plus’ (alter HDL-C & at least one other lipid fraction)
HDL Metabolism with SRBI Blocked

Copyright © 2003 American Heart Association, Inc.
62 yo male with preclinical atherosclerosis

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Notes</th>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Optimal</th>
<th>High Risk Range</th>
<th>Intermediate Risk Range</th>
<th>Optimal Range</th>
<th>Previous Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td>146</td>
<td>≥ 240</td>
<td>200 - 239</td>
<td>&lt; 200</td>
<td></td>
</tr>
<tr>
<td>LDL-C Direct (mg/dL)</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td>≥ 130 CHD &amp; CHD risk eq. &gt; 100</td>
<td>100 - 129 CHD &amp; CHD risk eq. 70 - 100</td>
<td>&lt; 100 CHD &amp; CHD risk eq. &lt; 70</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 40</td>
<td></td>
<td>≥ 40</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 199</td>
<td>150 - 199</td>
<td>&lt; 150</td>
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<tr>
<td>Non-HDL-C (mg/dL) (calculated)</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
<td>≥ 160</td>
<td>130 - 159</td>
<td>&lt; 130</td>
<td></td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td>≥ 80</td>
<td>60 - 79</td>
<td>&lt; 60</td>
<td></td>
</tr>
<tr>
<td>LDL-P (nmol/L)</td>
<td>605</td>
<td></td>
<td></td>
<td></td>
<td>≥ 1300</td>
<td>1000 - 1299</td>
<td>&lt; 1000</td>
<td></td>
</tr>
<tr>
<td>sdLDL-C (mg/dL)'</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 30</td>
<td>21 - 30</td>
<td>&lt; 21</td>
<td></td>
</tr>
<tr>
<td>% sdLDL-C (calculated)</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 30</td>
<td>26 - 30</td>
<td>&lt; 26</td>
<td></td>
</tr>
<tr>
<td>Apo A-I (mg/dL)</td>
<td>137</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 114</td>
<td>114 - 131</td>
<td>&gt; 131</td>
<td></td>
</tr>
<tr>
<td>HDL-P (µmol/L)</td>
<td>24.8</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 28.0</td>
<td>28.0 - 34.0</td>
<td>≥ 35.0</td>
<td></td>
</tr>
<tr>
<td>HDL2-C (mg/dL)</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td>≤ 8</td>
<td>9 - 11</td>
<td>≥ 12</td>
<td></td>
</tr>
<tr>
<td>Apo B:Apo A-I Ratio (calculated)</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
<td>≥ 0.81</td>
<td>0.61 - 0.81</td>
<td>≤ 0.6</td>
<td></td>
</tr>
<tr>
<td>Lp(a) Mass (mg/dL)</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td>≥ 30</td>
<td></td>
<td>&lt; 30</td>
<td></td>
</tr>
<tr>
<td>Lp(a)-P (nmol/L)'</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 125</td>
<td>75 - 125</td>
<td>&lt; 75</td>
<td></td>
</tr>
</tbody>
</table>
Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

Cholesterol Efflux Capacity and ASCVD Events: Dallas Heart Study

ASCVD Events:
- MI
- Stroke
- PCI/CABG
- CV death
n=132

Log rank p=0.002

The Addition of Niacin to Statin Therapy Improves HDL-C Levels but not Metrics of Functionality

Khera et al. JACC. accepted: 13 July 2013
Non-HDL Cholesterol

Triglyceride Rich Lipoproteins

HDL

LDL

IDL

VLDL

Chylomicron remnant

Apo AI

Apo B

Apo B

Apo B

Apo B48

Non-HDL Cholesterol

Triglyceride Rich Lipoproteins (TRL)

TRL-C = Non-HDL-C – LDL-C
The Greater the Level of Triglycerides the More VLDL-C and Less LDL-C Within Non-HDL-C Associated with Increasing CV Risk

Meta-regression Demonstrates that VLDL-C Lowering Is Highly Correlated with a Reduction in the Hazard Ratio for a Major CV Event

Each 8.9 mg/dL reduction in VLDL-C (equivalent to 0.5 mmol/L for TG) in the fibrate outcome trials is associated with a reduction of 26% in the hazard for a CV event

![Graph showing the correlation between VLDL-C reduction and hazard ratio for CV events.](image)

### Fibrates, EPA, Niacin – CV Outcome Trials

#### Larger Risk Reductions in Hypertriglycerideridemia

<table>
<thead>
<tr>
<th>Trial (drug)</th>
<th>Entire cohort HR (95% CI)</th>
<th>Subgroup</th>
<th>Subgroup HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS</td>
<td>0.66 (0.47, 0.92)</td>
<td>TG ≥184 mg/dL BMI &gt;27.5 kg/m²</td>
<td>0.30 (0.15, 0.58)</td>
</tr>
<tr>
<td>BIP (bezafibrate)</td>
<td>0.91 (NR)</td>
<td>TG ≥200 mg/dL</td>
<td>0.60 (NR)</td>
</tr>
<tr>
<td>VA-HIT (gemfibrozil)</td>
<td>0.78 (0.65, 0.93)</td>
<td>TG ≥151 mg/dL</td>
<td>0.73 (0.58, 0.93)</td>
</tr>
<tr>
<td>FIELD (fenofibrate)</td>
<td>0.89 (0.75, 1.05)</td>
<td>TG ≥204 mg/dL HDL-C &lt;42 mg/dL</td>
<td>0.73 (0.58, 0.91)</td>
</tr>
<tr>
<td>ACCORD (fenofibrate)</td>
<td>0.92 (0.79, 1.08)</td>
<td>TG ≥204 mg/dL HDL-C ≤34 mg/dL</td>
<td>0.69 (NR)</td>
</tr>
<tr>
<td>JELIS (ethyl-EPA)</td>
<td>0.81 (0.69, 0.95)</td>
<td>TG &gt;150 mg/dL HDL-C &lt;40 mg/dL</td>
<td>0.47 (0.23, 0.98)</td>
</tr>
<tr>
<td>AIM-HIGH (niacin)</td>
<td>1.02 (0.87, 1.21)</td>
<td>TG &gt;198 mg/dL HDL-C &lt;33 mg/dL</td>
<td>0.74 (0.50, 1.09)</td>
</tr>
</tbody>
</table>

Meta-regression Demonstrates that VLDL-C Lowering is Highly Correlated with a Reduction in the Hazard Ratio for a Major CV Event

Each 8.9 mg/dL reduction in VLDL-C (equivalent to 0.5 mmol/L for TG) in the fibrate outcome trials is associated with a reduction of 26% in the hazard for a CV event.

\[ Y = -0.02955 \times X + 1.113; \quad r = -0.93, \quad P = 0.006 \]

# Summary: Evidence for Role in CVD

<table>
<thead>
<tr>
<th></th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
<th>TG+HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>epidemiologic</strong></td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>mechanistic: <em>in vitro</em></strong></td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>mechanistic: <em>in vivo</em></strong></td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>genetic - common</strong></td>
<td>++++</td>
<td>+/-</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>genetic - rare</strong></td>
<td>++++</td>
<td>+/-</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>clinical trials</strong></td>
<td>++++</td>
<td>+/-</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
## STRENGTH (Epanova) vs. REDUCE-IT (Vascepa) Outcomes Trials

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>STRENGTH</th>
<th>REDUCE-IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>~13,000</td>
<td>~8000</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>TG ≥200 mg/dL, &lt;500 mg/dL, HDL-C &lt;40 mg/dL (men)</td>
<td>TG ≥200 mg/dL, &lt;500 mg/dL, started with TG ≥150 mg/dL (women)</td>
</tr>
<tr>
<td></td>
<td>≥4 weeks on statin</td>
<td>≥4 weeks on statin</td>
</tr>
<tr>
<td></td>
<td>Established CVD or at high risk for development of CVD</td>
<td>Established CVD or at high risk for development of CVD</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>MACE</td>
<td>MACE</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>4 g/d</td>
<td>4 g/d</td>
</tr>
<tr>
<td>Placebo</td>
<td>Corn oil</td>
<td>Mineral oil</td>
</tr>
</tbody>
</table>
Old vs new paradigm for CV risk assessment

- T-Chol = HDL-c (good) + VLDL-c (uncertain) + LDL-c (bad)
- T-Chol = HDL-c (uncertain) + TRL-c (bad) + LDL-c (bad)
HDL Can Be Subdivided into Various Subpopulations

Particle shape
- Discoidal
- Spherical

Apolipoprotein composition
- A-I HDL
- A-I/A-II HDL
- E HDL
- Lipid-poor ApoA-I

Particle size
- HDL$_{2b}$
- HDL$_{2a}$
- HDL$_{3a}$
- HDL$_{3b}$
- HDL$_{3c}$

HDL Structure and Composition

Pre-beta Discoidal Shaped HDL

Initial Cholesterol Acceptor

Delivers Cholesterol to Liver

Alpha Spherical Shaped HDL
The HDL Proteome

Targeting the apoA-I and Nascent HDL
Transgenic Mice That Express Human apoA-I Decrease Atherosclerotic Lesions

ApoA-I is the major protein component and the rate-limiting precursor of HDL. Pre-β or lipid-poor HDL has highest potency in cholesterol efflux activity.
Effects of apoA-I vs LDL Interventions on Coronary Atherosclerosis by IVUS

Intensive Statin Treatment
Up to 53% reduction LDL-C for 2 years

apoA-I Milano or r-HDL for 4-5 weeks

Median Change in % Atheroma Volume

 apoA-I Milano
or r-HDL
for 4-5 weeks

 vs 

Intensive Statin Treatment
Up to 53% reduction LDL-C for 2 years

REVERSAL pravastatin 40 mg 540 days
Progression

REVERSAL atorvastatin 80 mg 540 days

ASTEROID rosuvastatin 40 mg 720 days

ERASE apoA-I Milano JAMA 2007

Delipidated HDL

apoA-I Milano JAMA 2003


Courtesy of Dr. Jan Johansson
HDL/RCT - Reason to Believe

Failures cast doubts on the HDL/RCT concept

Human population studies show that plasma levels of high-density lipoprotein (HDL) cholesterol correlate with cardiovascular risk.

- LXR agonists
  - Safety issues
- BET-BDi
  - RVX-208 positive data
- CETPi
  - Torcetrapib failed
  - Dalcetrapib failed
  - Anacetrapi failed?
  - Evacetrapib failed

↑ HDL Biogenesis
↑ ApoA1
↑ ABCG5/G8

↑ Cholesterol excretion into bile

*Anacetrapi failed in development.

Small HDL

RCT

Large HDL

CETP

LDL

Plaque Macrophages

↑ ABCA1/G1

Niacin
- AIM-high failed
- HPS-Thrive failed

Human population studies show that plasma levels of high-density lipoprotein (HDL) cholesterol correlate inversely with cardiovascular risk.