Controversies in Lipid Therapy: Is there any value in adjusting HDL levels?

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Disclosures

Consulting Fees: Kowa, Merck, Genzyme, Roche, Amarin, Aegerion, Lupin

Contracted Research: ISIS, Merck, Pfizer, NIH
Many Ways to Get in Trouble

- Genetics
- Overweight/Obesity
- Age
- Insulin Resistance Syndrome
- Lipids
- BP
- Glucose
- Smoking, Physical Inactivity, Unhealthy Eating

Arterial Wall Plaque

Abnormal Lipid Metabolism
- LDL
- ApoB
- HDL
- Triglycerides

Hypertension

Inflammation, Hypercoagulation

Age, Race, Gender, Family History

Macrophages and Inflammation in the Artery Wall

Macrophages and Inflammation in the Artery Wall

CVD Prevention Is Based Only on Systemic Maneuvers

- Lifestyle changes
- Blood pressure control
- Diabetes treatment
- Inhibition of platelet aggregation
- Lipid Management
CVD Prevention Is Based Only on Systemic Maneuvers

- Lifestyle changes
- Blood pressure control
- Diabetes treatment
- Inhibition of platelet aggregation
- Lipid Management

Future Therapies Must Target The Plaque!

- Activation of cholesterol efflux
- Regulation of cell death, egress
- Control of oxidation and inflammation
LDL-C Reduction and Atheroma Burden

Nissen SE, et al. JAMA. 2006;295:1556-65

Median ΔPercent Atheroma Volume

Mean LDL-C (mg/dL)

IVUS trials

CAMELOT Placebo

REVERSAL Atorvastatin

A-Plus Placebo

ASTEROID Rosuvastatin

REVERSAL Pravastatin

r² = 0.97
P < 0.001
SATURN Trial: Maximum Dose
Atorvastatin or Rosuvastatin

• Subjects with CAD, on A-80 or R-40 for 104 weeks
• IVUS at baseline and end of study
• Treatment LDL 70 (A) and 62 (R), HDL 48 (A) and 50 (R), TG<130 in both
• PAV -0.99% (A) and -1.22% (R)
• Two thirds of subjects showed regression
• Authors conclude that this is “evidence that atherosclerotic plaques can regress”

Low HDL-C Predicts Risk At Any LDL-C Level

Adapted from Castelli WP. Can J Cardiol. 1998;4(suppl):5A-10A.
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

On-treatment level (3 months statin therapy); n = 2661
Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL

<table>
<thead>
<tr>
<th>HDL-C Quintiles</th>
<th>Q1 &lt;37</th>
<th>Q2 37 to &lt;42</th>
<th>Q3 42 to &lt;47</th>
<th>Q4 47 to &lt;55</th>
<th>Q5 ≥55</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year Risk of Major CVD Events, %</td>
<td>9.3</td>
<td>8.1</td>
<td>6.3</td>
<td>5.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Hazard Ratio Versus Q1</td>
<td>0.85</td>
<td>0.57</td>
<td>0.55</td>
<td>0.61 *</td>
<td></td>
</tr>
</tbody>
</table>

*P= .03

Current Options for Management of Low HDL Cholesterol

- Lifestyle modification
- Statin
- Niacin
- Fibrate
- TZD
- Combination therapies
HATS (HDL-C Atherosclerosis Treatment Study) Clinical End Points

**Quantitative Coronary Angiography**

- Placebo: n = 34, Change in Stenosis: 3.9%
- Niacin + Simvastatin: n = 33, Change in Stenosis: -0.4%
- Niacin + Simvastatin + AO: n = 40, Change in Stenosis: 0.7%

**CVD Events**

- Placebo: n = 38, CVD Event Rate: 24%
- Niacin + Simvastatin: n = 38, CVD Event Rate: 3%
- Niacin + Simvastatin + AO: n = 42, CVD Event Rate: 14%

**90% Reduction**

- P = .03

*P ≤ .005 versus placebo*

Mean dose of simvastatin was 13 mg/day
Mean dose of niacin was 2400 mg/day

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 mg/dL, HDL 44 mg/dL, LDL 65 mg/dL
- Controls TG 152 mg/dL, HDL 38 mg/dL, LDL 67 mg/dL
- 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 15, 2011. Epub ahead of print
AIM-HIGH—Results

Primary Outcome

1° Endpoint: CHD Death, nonfatal MI, ischemic stroke, high-risk ACS, hospitalization for coronary or cerebrovascular revascularization

HPS2-THRIVE: Active pre-randomization run-in

Screened (51,698)

High cardiovascular risk patients screened in 245 sites within 6 countries

LDL lowering phase (36,059)

Standardise background LDL-lowering therapy with simvastatin 40 mg (+/- ezetimibe) daily (to total cholesterol target of 135 mg/dL)

Active ER niacin plus laropiprant (38,369)

Test compliance with ER niacin 2 grams plus laropiprant 40 mg (ERN/LRPT) daily for 1 month

Randomization (25,673)

ER niacin 2g plus laropiprant 40 mg daily vs. matching placebo tablets
Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Risk ratio 0.96 (95% CI 0.90 – 1.03)
Logrank P=0.29
Effect of ERN/LRPT on SERIOUS adverse events (median follow-up 3.9 years)

<table>
<thead>
<tr>
<th>Condition</th>
<th>ERN/LRPT Excess</th>
<th>Placebo Percentage</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic complication</td>
<td>3.7%</td>
<td>0.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>1.8%</td>
<td>0.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infection</td>
<td>1.4%</td>
<td>0.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.0%</td>
<td>0.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0.7%</td>
<td>0.0%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.4%</td>
<td>0.0%</td>
<td>0.05</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.7%</td>
<td>0.0%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Skin</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.0026</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>ERN/LRPT</td>
<td>Placebo</td>
<td>Risk ratio (95% CI)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------</td>
<td>---------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Participants with diabetes at randomization (n= 8299)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor hyperglycaemic problem</td>
<td>8.7%</td>
<td>5.8%</td>
<td>1.55 (1.32-1.82)</td>
</tr>
<tr>
<td>Major hyperglycaemic problem</td>
<td>1.0%</td>
<td>0.3%</td>
<td>3.09 (1.81-5.27)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>1.1%</td>
<td>0.7%</td>
<td>1.50 (0.96-2.35)</td>
</tr>
<tr>
<td>Other diabetic complication</td>
<td>1.1%</td>
<td>1.2%</td>
<td>0.93 (0.62-1.40)</td>
</tr>
<tr>
<td><strong>Any diabetic complication</strong></td>
<td>460</td>
<td>311</td>
<td>1.55 (1.34-1.78)</td>
</tr>
<tr>
<td></td>
<td>(11.1%)</td>
<td>(7.5%)</td>
<td></td>
</tr>
</tbody>
</table>

| **Participants without diabetes at randomization (n= 17,374)** |          |         |                   |
| New-onset diabetes mellitus                  | 792      | 632     | 1.27 (1.14-1.41)  |
|                                            | (9.1%)   | (7.3%)  |                   |
## Effect of ERN/LRPT on infection and bleeding

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>ERN/LRPT (12,838)</th>
<th>Placebo (12,835)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>4.3%</td>
<td>3.7%</td>
<td>1.17 (1.03-1.32)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>0.9%</td>
<td>0.8%</td>
<td>1.07 (0.82-1.39)</td>
</tr>
<tr>
<td>Abdominal/gastrointestinal</td>
<td>0.6%</td>
<td>0.5%</td>
<td>1.26 (0.91-1.75)</td>
</tr>
<tr>
<td>Skin</td>
<td>0.5%</td>
<td>0.3%</td>
<td>1.66 (1.14-2.43)</td>
</tr>
<tr>
<td>Other</td>
<td>2.4%</td>
<td>1.7%</td>
<td>1.38 (1.16-1.63)</td>
</tr>
<tr>
<td><strong>Any infection SAE</strong></td>
<td>1031</td>
<td>853</td>
<td>1.22 (1.12-1.34)</td>
</tr>
<tr>
<td></td>
<td>(8.0%)</td>
<td>(6.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.8%</td>
<td>0.6%</td>
<td>1.53 (1.14-2.05)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>1.1%</td>
<td>0.9%</td>
<td>1.17 (0.92-1.50)</td>
</tr>
<tr>
<td>Other</td>
<td>0.6%</td>
<td>0.4%</td>
<td>1.66 (1.18-2.34)</td>
</tr>
<tr>
<td><strong>Any bleeding SAE</strong></td>
<td>326</td>
<td>238</td>
<td>1.38 (1.17-1.62)</td>
</tr>
<tr>
<td></td>
<td>(2.5%)</td>
<td>(1.9%)</td>
<td></td>
</tr>
</tbody>
</table>
HPS2-THRIVE: SUMMARY

- No significant benefit of ER niacin/laropiprant on the primary outcome of major vascular events when added to effective statin-based LDL-lowering therapy.

- Significant excesses of serious adverse events (SAEs) due to known and unrecognised side-effects of niacin. Over 4 years, ER niacin/laropiprant caused SAEs in ~30 patients per 1000.

- No clear evidence of differences in efficacy or safety in different types of patient (except for an excess of statin-related myopathy in Chinese patients).

- Findings are consistent with previous niacin trials. The role of ER niacin for the treatment and prevention of cardiovascular disease needs to be reconsidered.
Potential New Therapies to Raise or Improve HDL-C

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

Torcetrapib

Evacetrapib

Anacetrapib

Dalcetrapib

CETP


<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>

Adapted from Cannon C et al. JAMA. 2011;306:2153-2155.
Dalcetrapib and Torcetrapib Inhibit CETP Via Different Mechanisms

- Dalcetrapib binds irreversibly to CETP, inducing a conformational change to CETP that hinders association to HDL.\(^1\)
- Dalcetrapib binds to CETP only.\(^2\)
- Anacetrapib binding to CETP is a reversible high affinity complex of CETP inhibitor, HDL, and CETP.\(^2,3\)

NB: The clinical relevance of these differences is unknown; these compounds have not been studied in head-to-head clinical trials.

\(^3\)Clark RW et al. *J Lipid Res*. 2006;47:537-552.
**Dalcetrapib Phase IIb Trial**

**HDL-C Increase at Week 12**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change From Baseline (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>Dalcetrapib 300 mg</td>
<td>15*</td>
<td>75</td>
</tr>
<tr>
<td>Dalcetrapib 600 mg</td>
<td>30*</td>
<td>67</td>
</tr>
<tr>
<td>Dalcetrapib 900 mg</td>
<td>35*</td>
<td>72</td>
</tr>
</tbody>
</table>

*P <0.0001 vs placebo

NOTE: Dalcetrapib 600 mg is the dose used in phase III

Stein EA. *Am J Cardiol.* 2009;104:82-91.
The dal-OUTCOMES trial evaluated the efficacy and safety profile of dalcetrapib when added to existing standard of care in patients with stable coronary heart disease following an acute coronary syndrome.

Following the results of the second interim analysis of the dalcetrapib dal-OUTCOMES Phase III trial the Independent Data and Safety Monitoring Committee (DSMC) has recommended stopping the trial due to a lack of clinically meaningful efficacy. No safety signals relating to the dal-OUTCOMES trial were reported from the DSMC.

As a result, Roche has decided to terminate the dal-OUTCOMES trial, as well as all other on-going studies in the dal-HEART program, including dal-PLAQUE 2 and dal-OUTCOMES 2. Additional information will be provided in due course as data become available.

Excerpt from letter to dal-OUTCOMES Investigators from Roche.
Predictive Value of HDL: Mendelian Studies

The diagram shows a comparison between observational and genetic studies of HDL cholesterol. The x-axis represents LDL cholesterol and HDL cholesterol, while the y-axis represents the predictive value. The bars indicate that genetic studies have a higher predictive value compared to observational studies.
Dal-Outcomes Study

Graph showing the changes in HDL and LDL cholesterol levels over time.

**HDL cholesterol (mg/dl)**

- Placebo: Black line and markers
- Dalcetrapib: Red line and markers

**LDL cholesterol (mg/dl)**

- Placebo: Black line and markers
- Dalcetrapib: Red line and markers

Months: 0, 1, 3, 6, 12, 24, 36

NEJM, Nov 2012
Dal-Outcomes Study

Hazard ratio 1.04
(95% CI 0.93-1.16)

P = 0.52 by log rank test

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dalcetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7933</td>
<td>7938</td>
</tr>
<tr>
<td>1</td>
<td>7386</td>
<td>7372</td>
</tr>
<tr>
<td>2</td>
<td>6551</td>
<td>6495</td>
</tr>
<tr>
<td>3</td>
<td>1743</td>
<td>1736</td>
</tr>
</tbody>
</table>
## Dal-Outcomes Study

### Risk of primary and secondary outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Dalcetrapib (% at 3 years)</th>
<th>Placebo (% at 3 years)</th>
<th>Hazard Ratio (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>9.2</td>
<td>9.1</td>
<td>1.04 (0.93-1.16) 0.52</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.6</td>
<td>1.8</td>
<td>0.94 (0.73-1.21) 0.66</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>5.9</td>
<td>6.0</td>
<td>1.02 (0.89-1.17) 0.80</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.3</td>
<td>1.3</td>
<td>0.91 (0.68-1.22) 0.54</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>0.2</td>
<td>0.1</td>
<td>1.41 (0.63-3.18) 0.40</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>1.4</td>
<td>1.0</td>
<td>1.25 (0.92-1.70) 0.16</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>3.1</td>
<td>3.4</td>
<td>0.99 (0.82-1.19) 0.90</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>9.5</td>
<td>9.6</td>
<td>1.00 (0.87-1.11) 0.97</td>
</tr>
</tbody>
</table>
Dal-Outcomes Study

Annualized Event Rate (%) for Placebo and Dalcetrapib by HDL Cholesterol Quintile (mg/dl)

- Placebo
- Dalcetrapib

HDL Cholesterol at Baseline by Quintile (mg/dl)

2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0

NEJM, Nov 2012
Anacetrapib Effects on LDL-C and HDL-C

**LDL-C**

- Baseline 80
- Week 6: 716
- Week 12: 716
- Week 18: 687
- Week 24: 646
- Week 30: 604
- Week 46: 568
- Week 62: 540

- Anacetrapib
- Placebo

  - Anacetrapib n = 804 771 716 687 646 604 568 540
  - Placebo n = 803 759 741 743 735 711 691 666

  - **-39.8% (P<0.001)**

**HDL-C**

- Baseline 30
- Week 6: 83
- Week 12: 86
- Week 18: 86
- Week 24: 84
- Week 30: 83
- Week 46: 82
- Week 62: 81
- Week 76: 80

- Anacetrapib
- Placebo

  - Anacetrapib n = 776 757 718 687 647 607 572 543
  - Placebo n = 766 761 741 744 736 711 691 666

  - **+138.1% (P<0.001)**

Serum Cholesterol Efflux Capacity

\[ ^3\text{H}-\text{Cholesterol labeled} \]
\[ + \text{ACAT Inhibitor} \]

J774 MACROPHAGES

\[ \text{cAMP} + 0.2\% \text{ BSA} \]

apoB-depleted sera

% FC Efflux

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

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>
</table>

*Non-fatal myocardial infarction*
HDL of dialysis patients has impaired capacity to elicit cholesterol efflux

Yamamoto et al JACC 2012
Dialysis patients have dysfunctional HDL irrespective of HDL-C

HDL of dialysis patients has impaired capacity to abrogate inflammatory cell chemotaxis.
Conclusions

• Aggressive LDL reduction halts progression but only induces minimal regression

• Residual risk reduction may derive from “appropriate” HDL maneuvers

• No studies thus far have confirmed the HDL hypothesis. Niacin on its way out. CETP inhibitors?

• Shifting strategy to improvement of HDL function depends on reliable diagnostics