Agents to Raise HDL

*Do we have the right Biomarker of HDL function?*

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McGill University Health Center
The Case for HDL

- The clinical equipoise
- HDL-C as a biomarker of CAD, CVD
- HDL Functions and biomarkers
- Where do we go from here?
Hazard Ratios for Coronary Heart Disease or Ischemic Stroke Across Quantiles HDL-C

Figure 3. Hazard Ratios for Coronary Heart Disease Across Fifths of Usual Lipids or Apolipoproteins

<table>
<thead>
<tr>
<th>Quintile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean usual level, mg/dL</td>
<td>125</td>
<td>145</td>
<td>159</td>
<td>173</td>
<td>198</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>85</td>
<td>99</td>
<td>108</td>
<td>118</td>
<td>137</td>
</tr>
<tr>
<td>Apo B</td>
<td>37</td>
<td>44</td>
<td>49</td>
<td>55</td>
<td>66</td>
</tr>
<tr>
<td>HDL-C</td>
<td>126</td>
<td>139</td>
<td>148</td>
<td>158</td>
<td>178</td>
</tr>
</tbody>
</table>


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Human Serum Lipoproteins

Yin and Yang of HDL

The epidemiological association between HDL-C and CVD is strong and coherent.

HDL-C still predicts events if LDL-C is low

Animal data is unequivocal: HDL protect against atherosclerosis

Strong biological plausibility for HDL as a therapeutic target

Mendelian Randomization does not support HDL-Cholesterol as a causal risk factor

The Clinical trial data is neutral (and, in some cases, there is harm)
Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events Among

A

Boekholdt MS. *Circulation*. 2013;128:1504-1512
HDL Modulators

- Fibrates. (Fenofibrate: Accord)
- Niacin (Aim High, HPS-2 THRIVE)
- CETP \emph{inh.} Torcetrapib; Dalcetrapib
- rHDL: CER, CSL-112
- Apolipoprotein mimetics
- BET modulators (RVX208; 222)
Fibrates

- Gemfibrozil, Bezafibrate
- Fenofibrate
Effects of Combination Lipid Therapy on Cardiovascular Events in Type 2 Diabetes Mellitus: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial

Henry C. Ginsberg, MD
College of Physicians & Surgeons, Columbia University, New York

For The ACCORD Study Group

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus
The ACCORD Study Group
Published at www.nejm.org March 14, 2010 (10.1056/NEJMoa1001282)
Niacin

- Aim-HIGH
- HPS2-THRIVE
AIM-HIGH : Results

P=0.79 by log-rank best

No. à risque
Placebo plus statine  1695  1581  1381  910  436
Niacin plus statine  1718  1606  1366  903  428
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

<table>
<thead>
<tr>
<th>Condition</th>
<th>ERN/LRPT</th>
<th>Placebo</th>
<th>Excess</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic complication</td>
<td>3.7%</td>
<td>0%</td>
<td>3.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>1.8%</td>
<td>0%</td>
<td>1.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infection</td>
<td>1.4%</td>
<td>0%</td>
<td>1.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.0%</td>
<td>0%</td>
<td>1.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0.7%</td>
<td>0%</td>
<td>0.7%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.4%</td>
<td>0%</td>
<td>0.4%</td>
<td>0.05</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.7%</td>
<td>0%</td>
<td>0.7%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Skin</td>
<td>0.3%</td>
<td>0%</td>
<td>0.3%</td>
<td>0.0026</td>
</tr>
</tbody>
</table>
CEPT<em>inh</em>

- Torcetrapib; Dalcetrapib
- Anacetrapib, Evacetrapib
# Lipid efficacy of CETP inhibitors (% change from baseline)

<table>
<thead>
<tr>
<th>CETP inhibitor</th>
<th>Dose mg/d</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>0</td>
</tr>
<tr>
<td>Dalecetrapib</td>
<td>600</td>
<td>31</td>
<td>2</td>
<td>3</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>-17</td>
</tr>
</tbody>
</table>

Adapted from Cannon C, JAMA 306:2154; 2011
Inhibiting CETP

- Anacetrapib (REVEAL TIMI 55)
- Evacetrapib (ACCELERATE)
Anacetrapib: Effects on LDL-C and HDL-C

**LDL-C**

![Graph showing LDL-C levels over study weeks with Anacetrapib and Placebo, with a decrease of -39.8% (p<0.001).](image)

**HDL-C**

![Graph showing HDL-C levels over study weeks with Anacetrapib and Placebo, with an increase of +138.1% (p<0.001).](image)
Evacetrapib

**HDL-C**
- Placebo: -3.0%
- 30 mg: 53.6%
- 100 mg: 94.6%
- 500 mg: 128.8%*

**LDL-C**
- Placebo: 3.9%
- 30 mg: -13.6%
- 100 mg: -22.3%
- 500 mg: -35.9%*

* P<0.001 compared with placebo
Increasing Apo AI and HDL Biogenesis

- Reconstituted HDL infusions in man
HDL Metabolism

Intestine

ABCA1

ApoA-I

ABCG5/8

rHDL

Bile acid

SR-BI

LDLR

LDL

TG

VLDL

CETP

PLTP

HDL2

HDL3

Cholesterol bilary excretion

Kidney

Lipid-poor ApoA-I

Nascent HDL

ABCG1

LCAT

ABCA1

Macrophages
Apo AI Proteoliposomes

POPC:Chol:Apo Al
200:20:2
Cholesterol Efflux

ApoA-I

Discoidal HDL

ABCA1

ABCG1

Mitochondria

Nucleus

Cholesterol pool

Passive Diffusion

LCAT

SR-BI

RXR

LXR

+ABCA1 +ABCG1

Oxysterol

Cholesterol Efflux

Hafiane A. Cholesterol 2013
Nascent HDL structure and Composition

rHDL: Lipid composition resembles raft domains.
*Sorci-Thomas MG JLR 2012*
Physicochemical properties and lipid class composition of HDL particle subpopulations.

Specifically, the content of phosphatidylserine revealed positive correlations with all metrics of HDL functionality, reflecting enrichment of phosphatidylserine in small, dense HDL3.
ERASE Trial: Primary Endpoint

The primary endpoint of percent change in atheroma volume from baseline to 6 weeks did not differ between treatment groups (-3.4% in the CSL-111 group vs. -1.6% in the placebo group, p=0.48).

ACC 2007
HDL Mimetics

Phase 2a Findings Demonstrate that CSL112, A Novel Apolipoprotein A-I Infusion Therapy, Has a Favorable Safety Profile, is Well Tolerated and Increases Cholesterol Efflux Capacity in Stable Atherothrombotic Patients

Dallas, TX — 20 November 2013

Cerenis Reports Top-Line Phase II Results for its HDL Mimetic CER-001

TOULOUSE, France and ANN ARBOR, Michigan, 2 January 2014 - Cerenis Therapeutics, the biopharmaceutical company, today announced that its Phase IIb CHI-SQUARE (Can HDL Infusions Significantly Quicken Atherosclerosis Regression?) study did not reach its primary endpoint in post-Acute Coronary Syndrome (ACS) patients.

The Phase IIb efficacy and safety trial randomized 507 patients with ACS at 53 centers in the US, Canada, France and The Netherlands. The trial, conducted by Principal Investigator Jean-Claude Tardif, MD, FRCPC, FACC of the Montreal Heart Institute, was a double-blind, randomized, placebo-controlled dose-ranging study to assess the efficacy of

HDL Mimetic Fails to Regress Plaque in CHI-SQUARE ACS Trial

Shelley Wood
January 03, 2014
Apolipoprotein Mimetics

- D-4F, rD-4F
- 5A, 6F
- FAMPS, ELK-2A2K2E
- ATI-5261, CS-6253
HDL Mimetic Peptide ATI-5261 Promotes Nascent HDL Formation and Reverse Cholesterol Transport in vitro

The purpose of this study is to investigate apolipoprotein-mimetic peptides for their ability to mimic the functionality of HDL particles.

We therefore investigated compound ATI-5261 in the process of HDL biogenesis.
Creation of α-helix peptide ATI-5261

Major lipid-binding motif

Acidic residues
Hydrophobic segment

apoE

N 50 100 150 200 250 299

P

P

P

216 237 260 299

238

270

aa238-266

ATI-5261

EVRASKLEEWFAAFREFAEFLEFLARLKS

Cholesterol efflux in BHK-ABCA1 cells

ATI-5261 (squares)
Km= 1.04±0.16 ug/ml (0.37±0.05 uM)
Vmax=14.48±0.29% efflux/6h
Vmax/Km=13.92

CS-6253 (triangles)
Km= 2.27±0.16 ug/ml (0.37±0.18 uM)
Vmax=15.25±0.25% efflux/6h
Vmax/Km= 6.71

ApoA-I (circles)
Km= 4.53±0.67 ug/ml (0.15±0.02 uM)
Vmax=14.85±0.02% efflux/6h
Vmax/Km=3.27
Increasing Apo AI and HDL Biogenesis

❖ RVX-208
RVX-208 (BET Bromodomain inh.)

LIPID/METABOLIC

ASSURE: No success for oral apoA1 booster

SEPTEMBER 2, 2013  Sue Hughes

ESC Amsterdam, NL - A novel drug that induces production of the HDL precursor protein apolipoprotein A1 (apoA1) failed to show significant regression of atherosclerosis vs placebo in the ASSURE study.

Presenting the results at the European Society of Cardiology (ESC) 2013 Congress today, Dr Stephen Nicholls (Royal Adelaide Hospital, Australia) said the results with RVX-208 (Resverlogix) were "disappointing and surprising, given promising earlier findings."

However, he stressed that because of an unusually large placebo effect, no significant difference in lipoprotein changes were seen with the new drug, meaning that the study had not tested the HDL hypothesis.

"With just a 26-week treatment period, this was a short study for an oral agent. As HDL infusions have shown impressive atherosclerosis regression in just a few weeks, we were hoping to see similar effects with this first oral agent to induce hepatic synthesis of apoA1, the precursor to new HDL particles. But this was not to be the case."
Conclusion: In ASSURE potentially more favorable effects of the apoA-I inducer, RVX-208, on coronary disease progression and MACE were observed in patients with higher levels of systemic inflammation.
Why does this NOT work?

HDL might not be causal in protection against atherosclerosis

This does not fit the biology

HDL-cholesterol is a biomarker of CV health

Most likely

Need for better biomarkers of HDL function

Yes, but which one?
The Challenge

Develop *Biomarkers of HDL Function*

- Cellular Cholesterol Efflux
- Anti-oxidant
- Anti-inflammatory
- Vascular Endothelial function
- Anti-thrombotic

That can be tested in outcome studies, be reproducible and brought to high throughput.
The Need to Study HDL Function: Potential Novel Therapeutic Approaches

- LXR agonists
- FXR agonists
- BAR agonists
- PPARα agonists
- Apo AI Prod RVX208
- Dalcetrapib
- Anacetrapib
- Evacetrapib
- Niacin

VLDL
LDL
Cholesterol pool
ABCA1
Cholesterol pool
CD36
Arterial-wall macrophage
LPL
LPL
CETP inhibition with torcetrapib
LDL receptor
Hepatocyte
ABCA1
SR-B1
ABCG1
FC
CE
Bile acids
FC and PL
ApoA-I
ApoA-I
Lipid-poor apoA-I
Nascent pre-β HDL
LxR agonists
PPARα agonists (Fibrates)
Conclusions

- The HDL pathway remains a sound therapeutic target.
- HDL-C is not a good biomarker of therapeutic success.
- HDL biogenesis, lipidome and proteome may hold the key to novel therapies.