HDL Therapeutics: The Start of a New Era

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Major Anti-Atherosclerotic Functional Roles of HDL With Available Clinical Measures

- Macrophage cholesterol efflux
- Anti-oxidative effects
- Anti-inflammatory effects
- Endothelial function
- Glucose homeostasis

Percentage of HDL-C Synthesized by the Liver, Intestine, and Peripheral Cells

Liver

Intestine

Plasma

Preβ-HDL (HDL-VS)

αHDL (HDL-S, HDL-M, & HDL-L)

75%

Peripheral Tissues

Macrophages

Preβ-HDL (HDL-VS)

αHDL (HDL-S, HDL-M, & HDL-L)

20%

Intestine

ABCA1

ABCA1

ABCG1

Cholesterol Pool

HDL Particle Subclasses And Cholesterol Efflux From Cholesterol-Loaded Cells

Validation of HDL Functional Measures in the Evaluation of Atherosclerosis and Cardiovascular Events

Biomarker of HDL Functionality

Surrogate Measure of Atherosclerosis

Atherosclerosis Volume and Composition

Surrogate Measure of Cardiovascular Events

Cardiovascular Events

Odds Ratios for CAD According to the Efflux Capacity and Selected Risk Factors

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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.92 (1.26–2.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.80 (1.31–2.47)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.10 (0.95–1.73)</td>
<td>1.78</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.01 (0.86–1.18)</td>
<td>0.93</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.85 (0.70–1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>Efflux capacity</td>
<td>0.75 (0.63–0.90)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Cholesterol Efflux Capacity and Incident CHD Events in EPIC-Norfolk

Nested case-control sample within a prospective study of 25,639 individuals aged 40-79 years examined in 1993-1997 and followed up to 2009.

Efflux capacity was quantified in 1,895 incident CHD cases and 2,474 control participants free of any cardiovascular disorders.

Validated ex vivo radiotracer assay that involved incubation of J774 macrophages with apoB-depleted serum from study participants.

Association of Cholesterol Efflux and Incident CHD Events – EPIC Norfolk

Figure. Association of cholesterol efflux levels in association with incident CHD events (1895 cases & 2474 controls)

Progressive adjustment

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjustment</td>
<td>0.56 (0.43, 0.69)</td>
</tr>
<tr>
<td>plus age &amp; sex</td>
<td>0.62 (0.47, 0.78)</td>
</tr>
<tr>
<td>plus diabetes, hypertension</td>
<td>0.64 (0.48, 0.80)</td>
</tr>
<tr>
<td>plus smoking</td>
<td>0.66 (0.49, 0.84)</td>
</tr>
<tr>
<td>plus WHR &amp; BMI</td>
<td>0.69 (0.51, 0.87)</td>
</tr>
<tr>
<td>plus LDL-C &amp; triglycerides</td>
<td>0.67 (0.49, 0.84)</td>
</tr>
<tr>
<td>plus HDL-C</td>
<td>0.75 (0.53, 0.97)</td>
</tr>
<tr>
<td>or plus apo(a1)</td>
<td>0.65 (0.41, 0.90)</td>
</tr>
</tbody>
</table>

Kaplan–Meier Curves and Hazard Ratios for Cardiovascular Events, According to Quartile of Cholesterol Efflux Capacity

**B Total Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Hazard Ratio Unadjusted</th>
<th>Hazard Ratio Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q2</td>
<td>0.75 (0.51–1.10)</td>
<td>0.74 (0.50–1.09)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.65 (0.44–0.97)</td>
<td>0.56 (0.37–0.85)</td>
</tr>
<tr>
<td>Q4</td>
<td>0.52 (0.34–0.80)</td>
<td>0.42 (0.27–0.65)</td>
</tr>
</tbody>
</table>

P = 0.02 by log-rank test

<table>
<thead>
<tr>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
</tr>
<tr>
<td>Q2</td>
</tr>
<tr>
<td>Q3</td>
</tr>
<tr>
<td>Q4</td>
</tr>
</tbody>
</table>

Functionality of HDL in AIM-HIGH

Percent Change in Cholesterol Efflux by Treatment

Percent Change in Global Cholesterol Efflux by Treatment

- Placebo Mean
- EVA Monotherapy Mean
- Statin Alone Mean
- Combination Mean

Mean Percent Change

Placebo Mean
EVA Monotherapy Mean
Statin Alone Mean
Combination Mean

Error bars represent 90% CI

*p<.05 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

**p<.001 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

Percent Change in ABCA1 Mediated Cholesterol Efflux by Treatment

Percent Change in Non-ABCA1 Mediated Cholesterol Efflux by Treatment

Abbreviations: ABCA1=ATP Binding Cassette transporter A1 pathway; CI=confidence interval, EVA=evacetrapib

Nicholls S, et al JACC 2015 in press
Percent Change in Prebeta-1 HDL by Immunofixation

Error bars represent 90% CI
*p<.05 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

Abbreviations: CI=confidence interval; EVA=evacetrapib; HDL=high-density lipoprotein

Nicholls S, et al JACC 2015 in press
**Percent Change in HDL Subclasses by 2D-gel**

* p<.05 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

** p<.001 compared with placebo (for EVA monotherapy and statin monotherapy groups) or compared with statin alone for combination therapy group

Nicholls S, et al JACC 2015 in press

Abbreviations: 2D=two dimensional; EVA=evacetrapib; HDL=high-density lipoprotein; preβ-1=prebeta-1
• Using zirconium-89 labeled CER-001, pre-beta HDL mimetic, preferentially targets atherosclerotic plaques as evaluated by PET/CT scanning.

• CER-001 infusion increased plasma mediated cholesterol efflux capacity. After one hour of CER-001 infusion, plasma mediated cholesterol efflux increased by 13.8% and mean plasma apoA-I levels increased by 9.9 mg/dL.

Stroes E, et al. ESC 2015
Cerenis Therapeutics press release
Conclusions

• Therapeutic interventions directed towards increased cholesterol loading of the HDL particle have been based on epidemiological studies that have established HDL-C as a biomarker of CVD risk

• The advent of clinical tools to assess HDL functionality has changed the paradigm for HDL therapeutics

• Key mechanistic criteria for clinical outcomes trials with an HDL–based therapy include the generation of HDL particles that improve the efficiency of macrophage cholesterol efflux, and compositional change in the proteome and lipdome of the HDL particle, and improves anti-oxidant and anti-inflammatory properties

Rosenson RS and Brewer HB, Cardiovasc Drugs Ther 2015