HDL mimetics for ACS treatment: What’s new?

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ACS patients experience a high rate of recurrent cardiovascular (CV) events in the subacute period.

Figure adapted from PLATO Trial
Cornel JH et al. Am Heart J 2012;164:334-342
Novel Approaches to Modify Lipids and Lipoproteins

- Low Density Lipoprotein
- High Density Lipoprotein
- Triglyceride Rich Lipoproteins
- Inflammation
- Lipoprotein a
New Approaches for Raising HDL

What is in development?

• Cholesterol Ester Transfer Protein (CETP) inhibitors
• ER-Niacin / Laropiprant combination
• ApoA1 based strategies
• LCAT replacement strategies
• ABCA1 agonists / miR-33 inhibition
• LCAT agonists
• Bile-acid based strategies
New Approaches for Raising HDL

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ApoA1 Based Therapies

- ApoA1 Mimetics, such as APL-180 Novartis
- Full-length ApoA1, such as ApoA1 Cerenis Therapeutics
- Pre-Beta HDL, as generated by delipidation, HDL Therapeutics Inc.
- Reconstituted HDL, CSL Ltd.
- ApoA1 Milano MDCO216, The Medicines Company
- Trimeric ApoA1, Borean Pharma and now Roche
- RVX-208, as developed by Resverlogix
- Fx-5A, as developed by Kinemed Inc.
ApoA1-Milano
Percent Change in Atheroma Volume with IVUS LDL-C Reduction vs. HDL-C Increasing Therapy

Nissen SE et al. JAMA. 2003 and 2004

Prava 40 mg 18 months
Atorva 80 mg 18 months
Rosuva 40 mg 24 months
ApoA-1 Milano 5 weeks

2.7*
P=0.02

Median change in TAV (%)

Progression From no change to regression

REVERSAL ASTEROID

ApoA-1 Milano

5 weeks
ApoA1 Milano

- Manufacturing changes require a full re-start of the development of MDCO-216 (= ApoA1 Milano)
- Toxicology programme has been completed
- Discussion with regulatory agencies on the clinical development are ongoing
- Clinical development of MDCO-216 is expected soon and an IVUS trial, DRIVE is in the planning stage.
Delipidation
Step 1
Collected ~1 litre of plasma

Step 2
Plasma enriched through process

Step 3
Re-infused preβ enriched plasma

- Used patients own HDL
- Cholesterol removed from αHDL to yield preβ-HDL
- Preβ enriched plasma is re-infused into patient

IVUS Clinical Trial Using Selective Delipidated HDL

Treatment arm (N=14)

1:1 randomization

Control arm (N=14)

(N=28)

Day 0 1 2 3 4 5 6 7 8

Week

IVUS

Treatment or control plasma infusion

Results of the IVUS Clinical Trial Using Selective Delipidated HDL

CSL112: A novel, reconstituted HDL for infusion

- CSL112 is apoA-I, the chief protein component of HDL, purified from human plasma and reconstituted with phospholipids to form HDL particles suitable for IV infusion
- CSL112 is an efficient acceptor of cholesterol via ABCA1 and LCAT activator \textit{in vitro}
- CSL112 is similar in size, organization and function to native HDL
**Why CSL112 in ACS?**

*An MOA-based medical rationale*

Hypothesis: Rapid CV event reduction can be achieved based on immediate effects of apoA-I Infusion*

- **↓** Atherogenic burden (IVUS; rapid dilipidation of femoral plaque)
- **↑** Endothelial function (NO promoting)
- **↑** Circulating endothelial progenitor cells
- **↓** Circulating inflammatory and adhesion molecules
- **↓** Platelet aggregation
- **↑** Glucose homeostasis (metabolism, skeletal muscle uptake, insulin secretion)

Rapid CV event reduction during the transition period from acute to chronic stable CV risk “The ACS Treatment Gap”

Cholesterol Efflux Capacity, High-Density Lipoprotein Function, and Atherosclerosis

Amit V. Khera, M.D., Marina Cuchel, M.D., Ph.D., Margarita de la Llera-Moya, Ph.D., Amrith Rodrigues, M.S., Megan F. Burke, B.A., Kashif Jafri, B.A., Benjamin C. French, Ph.D., Julie A. Phillips, Ph.D., Megan L. Mucksavage, M.Sc., Robert L. Wilensky, M.D., Emile R. Mohler, M.D., George H. Rothblat, Ph.D., and Daniel J. Rader, M.D.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
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<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>1.30 (0.95–1.73)</td>
<td>0.10</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>

Figure 1. 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.
CSL112 elevates cholesterol efflux capacity

- Infusion of CSL112 in healthy volunteers elevated the ability of plasma to remove cholesterol from cells. Elevation is higher and faster than any previous therapy
  - Statins do not elevate cholesterol efflux
- Elevation of apoA-I, the chief protein of HDL, is higher and faster than any previous therapy
  - >100% increase with CSL112 in 2 h vs:
    - 2.9% increase after 4 weeks for niacin
    - 6.8% after 24 months for dalcetrapib

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1Khera AV et al. NEJM 2011;364:127-135
3Tawakol et al. Presented at Eur Soc Cardiol 2012, Munich, Germany. Figure is placebo corrected
Summary of CSL 112

• CSL112 is human apoA-I formulated as a reconstituted HDL
• CSL112 promotes cholesterol efflux and LCAT activation
• Addition of CSL112 to plasma dramatically enhances efflux activity
  • Human serum in vitro and rabbit serum ex vivo
• Efflux is elevated regardless of lipid phenotype
• CSL112 is rapidly remodeled to small particles reactive with anti-preBeta1 antibody
• CSL112 preferentially enhances efflux through the ABCA1 pathway
• CSL112 may thus provide a novel option for rapid reduction of atherosclerotic burden
  • The speed of action makes it well suited for treatment of ACS patients
  • First patient randomised last week in AEGIS-I, a safety study of CSL 112 in ACS patients (1200)
Conclusion

• HDL is capable of rapidly removing cholesterol from plaques
• The speed of action of apo A1 based therapies may be suited for the early post ACS period
• Imaging studies are underway or planned with a number of different compounds that will assess the potential clinical utility of these agents