Novel HDL Targeted Therapies: The Search Continues
Assoc. Prof. K.Kostner, Univ. of Qld, Brisbane

“Is anti-atherosclerosis the next big thing”

Baseline
Rest
Stress

Rest
Stress

COURAGE Trial
1 Year Later

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LDL Target depends on your level of Risk

Acute Plaque Rupture ACS (UA/NSTEMI/STEMI)

Stable CAD

Familial HL

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How low can we go?

Cholesterol and TG can be reduced by 99%

Kostner K et al.

Kostner, 2008
Benefit of intensive LDL-C lowering: Accumulating evidence

Event (%) vs. LDL cholesterol (mg/dL)

- Statin
- Placebo

77 mg/dl (1.9)

HPS
CARE
LIPID
4S

TNT (80 mg atorvastatin)

HDL

Anti-oxidant

Anti-Thrombotic
- antiplatelet
- protein C activation

Pro-fibrinolytic

Enhanced Reverse Cholesterol Transport

Anti-Atherothrombotic Effect
TNT:MCVE Frequency by HDL level in group with LDL-C < 70 mg/dL (Adjusted for baseline LDL)

<table>
<thead>
<tr>
<th>Quintile of HDL-C (mg/dL)</th>
<th>No of Patients</th>
<th>No of Events</th>
<th>HR (95% CI) vs Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;37)</td>
<td>473</td>
<td>57</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>(37-42)</td>
<td>525</td>
<td>50</td>
<td>0.85 (0.57-1.25)</td>
</tr>
<tr>
<td>(42-47)</td>
<td>550</td>
<td>34</td>
<td>0.57 (0.36-0.88)</td>
</tr>
<tr>
<td>(47-52)</td>
<td>569</td>
<td>34</td>
<td>0.55 (0.35-0.86)</td>
</tr>
<tr>
<td>(&gt;52)</td>
<td>544</td>
<td>35</td>
<td>0.61 (0.38-0.97)</td>
</tr>
</tbody>
</table>

Barter et al, NEJM 2007; 357; 13, 1301-1310.
Primary (Genetic) Causes of Low HDL-C

- ApoA-I
  - Complete apoA-I deficiency
  - ApoA-I mutations (e.g., ApoA-I\textsubscript{Milano})
- LCAT
  - Complete LCAT deficiency
  - Partial LCAT deficiency (fish-eye disease)
- ABC1
  - Tangier disease
    - Homozygous
    - Heterozygous
  - Familial hypoalphalipoproteinemia
  - Familial combined hyperlipidemia with low HDL-C
  - Metabolic syndrome

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STRATEGIES FOR RAISING HDL IN HUMANS

Lifestyle

• Weight reduction
• Increased physical activity
• Stop smoking
• ??? alcohol

Drugs

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CD Advance Data No. 347 + October 27, 2004

PNAS April 27, 2004;101:6659
Effects of Lipid-Modifying Drugs on HDL-C Levels

Niacin  ↑  15–35%
Fibrates  ↑  10–15%
Estrogens  ↑  10–15%
Statins  ↑  5–10%


Kostner 2008
Extended-Release Niacin: The Lipid Poly Pill


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A Working Hypothesis for Niacin-Induced HDL Elevation

Kostner, 2008
# Niacin and Atherosclerosis: A Positive Effect on Clinical Outcomes

<table>
<thead>
<tr>
<th>Trial (reference)</th>
<th>Treatment (mean dose)</th>
<th>Number of participants</th>
<th>Change in lipids in treatment group</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>Placebo</td>
<td>T-C</td>
</tr>
<tr>
<td>CLAS [17]</td>
<td>Niacin (4.3 g/day) + colestipol (30 g/day)</td>
<td>80</td>
<td>82</td>
<td>↓26%</td>
</tr>
<tr>
<td>FATS [18]</td>
<td>Niacin (4 g/day) + colestipol (30 g/day)</td>
<td>48</td>
<td>52</td>
<td>↓23%</td>
</tr>
<tr>
<td>HATS [19]</td>
<td>Niacin (2.4 g/day) + simvastatin (13 mg/day)</td>
<td>73</td>
<td>73</td>
<td>↓29%</td>
</tr>
<tr>
<td>Stockholm [23]</td>
<td>Niacin (4.5 g/day) + clofibrate (1.5 g/day)</td>
<td>279</td>
<td>276</td>
<td>↓13%</td>
</tr>
<tr>
<td>CDP [2,3]</td>
<td>Niacin (3 g/day)</td>
<td>1119</td>
<td>2789</td>
<td>↓10%</td>
</tr>
</tbody>
</table>

T-C, total cholesterol; TG, triglyceride; CLAS, Cholesterol-Lowering Atherosclerosis Study; FATS, Familial Atherosclerosis Treatment Study; HATS, HDL Atherosclerosis Treatment Study; CDP, Coronary Drug Project; NR, not recorded. \(^a\)Coronary death, stroke, revascularization, myocardial infarction, worsening ischemia.
ARBITER 2: Carotid Intima Media Thickness

Within-group Comparison

Change in CIMT (mm ± SEM) at 12 Months vs Baseline

- Statin + ERN: 0.014 (P=0.23)
- Statin + Placebo: 0.044 (P<0.001)

Between-group comparison P=0.08.
Intent-to-treat analysis of placebo > extended-release niacin, P=0.048.
Coronary Drug Project
Long-Term Mortality Benefit of Niacin in Post-MI Patients (8341 men)

1119 pat. niacin (3g/day)

Survival (%)

Years of follow-up

CHD deaths + non-fat. MI - 15% (p < 0.05)

2789 pat. placebo

151 pat. niacin (3g/day)

TG - 26%
Tot-C - 10%

Total mortality - 11% (p = 0.0012)

Canner PL et al. J Am Coll Cardiol 1986;8:1245–1255

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Nicotinic Acid Receptor (GPR109A): Locations and Effects


+ 300 mg niacin

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Properties of Laropiprant (MK-0524)

- Potent antagonist of DP₁ (not DP₂).
- Blocks PGD₂ binding without inhibiting PGD₂ synthesis
  - Functional potency at the platelet thromboxane A₂ receptor (TP) IC₅₀ 770 nM; at 40 mg dose no evidence of meaningful inhibition of platelet aggregation.
- At relevant systemic exposures, preclinical program did not reveal significant toxicities attributable to laropiprant
- In phase I and II studies, tested at doses up to 900 in single and 450 mg in multiple dose studies and up to 150 mg with niacin for up to 11 months and was well-tolerated

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Purpose:

- To evaluate the lipid-altering efficacy and flushing profile of ERN/LRPT administered as monotherapy
- or added to ongoing statin therapy in patients with primary hypercholesterolemia or mixed dyslipidemia.

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Study Design

This was a worldwide, multicenter, double-blind, randomized, placebo-controlled, parallel study with a 24-week double-blind treatment period. Endpoints: lipids, flushing and safety

**Figure 1. Study Design**

- Patients were randomized to ERN/LRPT 1g, ERN 1g or placebo in a 3:2:1 ratio (stratified by on-going statin use and study site).
- After 4 weeks, the active treatment doses were doubled, increasing the ERN/LRPT doses to 2g/40 mg (designated ERN/LRPT 2g) and ERN dose to 2g
Results (Lipid Efficacy)

- ERN/LRPT 2g produced significantly (p<0.001) greater % reductions from baseline in LDL-C relative to placebo across weeks 12 to 24

Mean percent change from baseline in low-density lipoprotein cholesterol (LDL-C) over time. *LS mean percent change from baseline (average of weeks 12 through 24).

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ERN/LRPT 2g produced significantly (p<0.001) greater % changes from baseline in HDL-C & TG.

Efficacy of ERN/LRPT 2g was similar when administered alone or when added to ongoing statin therapy.

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Initiation Phase of Therapy (Week 1):
• Patients treated with ERN/LRPT 1g experienced significantly (p<0.001) less flushing compared with patients treated with ERN 1g, as measured by maximum GFSS.
Pooled Safety Profile

Methods

- Pooled data from 3 active or placebo controlled Phase 3 and 3 phase 2 one year extension studies
- 4747 patients exposed: ERN/LRPT (n=2548), ERN (1268) Simv/Pbo(931)
## Pooled Safety Profile

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>SIMVA/Pbo N=931</th>
<th>ERN N=1268</th>
<th>ERN/LRPT N=2548</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related* AEs (n [%])</td>
<td>156 (16.8)</td>
<td>501 (39.5)</td>
<td>901 (35.4)</td>
</tr>
<tr>
<td>Drug-related* serious AEs (n [%])</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Discontinuations due to drug-related* AEs (n [%])</td>
<td>28 (3.0)</td>
<td>204 (16.1)</td>
<td>328 (12.9)</td>
</tr>
<tr>
<td>Pre-specified parameters of interest:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed adjudicated cardiovascular events (n/N [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consecutive or presumed consecutive ALT/AST elevations ≥3 x ULN (n/N [%])</td>
<td>8/920 (0.9)</td>
<td>6/1221 (0.5)</td>
<td>25/2465 (1.0)</td>
</tr>
<tr>
<td>Drug-related hepatitis (n)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myopathy** (n/N [%])</td>
<td>0</td>
<td>1/1221 (0.08)</td>
<td>1/2465 (0.04)</td>
</tr>
<tr>
<td>CK elevations ≥10 x ULN (n/N [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New onset diabetes$ \dagger$ (n/N [%])</td>
<td>1/888 (0.1)</td>
<td>3/1094 (0.3)</td>
<td>12/2276 (0.5)</td>
</tr>
</tbody>
</table>

*Drug-related events are those considered related to the investigator.

**Myopathy** events are muscle-related AEs and/or changes in creatine kinase.

$\dagger$ New onset diabetes was defined as a change of ≥10 mmol/L from baseline in a patient with a normal baseline.
HPS2- THRIVE Study Overview

- **Objective:**
  - To assess the effect of ER niacin/laropiprant 2 g/40 mg vs placebo on CV events, on a background of simvastatin 40 mg

- **Patient Population:**
  - 20,000 high risk atherosclerosis patients (a) MI, (b) peripheral or cerebrovascular disease, (c) diabetes + atherosclerotic vascular disease. One third in category (c)

- **Primary Study Endpoints:**
  - Major vascular events (MVE)

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Unblinded active run-in

<table>
<thead>
<tr>
<th>Weeks</th>
<th>ERN/LRPT 1g*</th>
<th>ERN/LRPT 2g*</th>
</tr>
</thead>
<tbody>
<tr>
<td>-12 to-16</td>
<td>-8</td>
<td>-4</td>
</tr>
</tbody>
</table>

ER niacin/laropiprant 2 g/40 mg

- Simvastatin 40 ± EZ (background) - 2300 MVE

Placebo

*Patients enter on a background of either simvastatin 40 mg or ezetimibe (EZ)/simvastatin 10/40 mg. Ezetimibe/simvastatin 10/40 mg initiated at week -8 if TC levels >3.5 mmol/L (LDL-C 76 mg/dL)

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ACS Patients

Baseline

EEM-14.3 mm²

Lumen Area 6.27 mm²

Atheroma Area 8.1 mm²

Side Branch

5 weeks Later

EEM-11.5 mm²

Lumen Area 6.23 mm²

Atheroma Area 5.35 mm²

Side Branch

Apo A-1 Milano
Phospholipid complex
JAMA Nov 5, 2003;290:2292
Anacetrapib

- Anacetrapib is an orally active, potent and selective CETP inhibitor.

- In preclinical models, anacetrapib consistently increased HDL-C concentrations with no observed effects on either blood pressure or heart rate and was well tolerated up to the maximal feasible dose.

- Preliminary studies in healthy subjects showed that single and multiple doses of anacetrapib for 2 weeks produced CETP inhibition and favorable HDL-C, LDL-C and apolipoprotein effects, and was generally well tolerated without an effect on blood pressure.

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Percent Changes from Baseline in LDL-C

Monotherapy

Weeks on Treatment

Placebo
Anacetrapib 10 mg
Anacetrapib 40 mg
Anacetrapib 150 mg
Anacetrapib 300 mg

Co-administration

Weeks on Treatment

Atorva 20 mg
Anacetrapib 10 mg + Atorva 20 mg
Anacetrapib 40 mg + Atorva 20 mg
Anacetrapib 150 mg + Atorva 20 mg
Anacetrapib 300 mg + Atorva 20 mg

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Percent Change from Baseline in Apo B

Monotherapy

Co-administration

Weeks on Treatment

Percent Change from Baseline in Apo B

Placebo
Anacetrapib 10 mg
Anacetrapib 40 mg
Anacetrapib 150 mg
Anacetrapib 300 mg

Atorva 20 mg
Anacetrapib 10 mg + Atorva 20 mg
Anacetrapib 40 mg + Atorva 20 mg
Anacetrapib 150 mg + Atorva 20 mg
Anacetrapib 300 mg + Atorva 20 mg

Kostner, 2008
Percent Changes from Baseline in HDL-C

**Monotherapy**

- Placebo
- Anacetrapib 10 mg
- Anacetrapib 40 mg
- Anacetrapib 150 mg
- Anacetrapib 300 mg

**Co-administration**

- Atorva 20 mg
- Anacetrapib 10 mg + Atorva 20 mg
- Anacetrapib 40 mg + Atorva 20 mg
- Anacetrapib 150 mg + Atorva 20 mg
- Anacetrapib 300 mg + Atorva 20 mg

Kostner, 2008
Percent Change from Baseline in Apo A-I

Monotherapy

- Placebo
- Anacetrapib 10 mg
- Anacetrapib 40 mg
- Anacetrapib 150 mg
- Anacetrapib 300 mg

Co-administration

- Atorva 20 mg
- Anacetrapib 10 mg + Atorva 20 mg
- Anacetrapib 40 mg + Atorva 20 mg
- Anacetrapib 150 mg + Atorva 20 mg
- Anacetrapib 300 mg + Atorva 20 mg

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Safety and Tolerability

- Anacetrapib as monotherapy and co-administered with atorvastatin was generally well tolerated.
- The incidences for all AE categories were similar across pooled treatment groups, with no dose response relationships.
- Most treatment-related AEs were mild or moderate, with constipation, diarrhea, dyspepsia and myalgia being the most common.
- There were no treatment-related serious AEs or deaths.
- Treatment-related discontinuations were rare and no patient discontinued due to serious treatment-related AEs.
- There were sparse and non-dose-related incidences of clinically important elevations in ALT, AST and CK.
- There were no hepatitis-related AEs, myopathy (unexplained muscle symptoms and CK elevations > 10 x upper limit of normal) or rhabdomyolysis.

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Blood Pressure

Systolic

Diastolic

Placebo
Anacetrapib 10 mg
Anacetrapib 40 mg
Anacetrapib 150 mg
Anacetrapib 300 mg

LS Mean % Change from Baseline (±SE)

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Future Paradigm:
Lower Targets, earlier and more specific Treatment (HDL, TG etc)

Risk is a continuous variable

- Treat LDL to target
- Lower TG and Lp(a)
- Raise HDL

Risk Factors

CV Risk

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