Advances in Treating Hyperlipidemia

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Disclosures

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- Founder and Shareholder of Epirium Bio

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  - Grants:
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    - Department of Homeland Security Grant (PI: Taub PR)
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Overview of Talk

- Review of residual risk despite Statin therapy
- Outcome Trial Results with PCSK9 Inhibitors
- Outcome Trial Results with Icosapent Ethyl
- Review of new agents
  - Bempedoic Acid
  - Inclisiran
Residual Risk Persists Despite Statin Therapy

Residual CVD Risk in Statin vs Placebo Trials
Many CHD Events Still Occur in Statin-Treated Patients

25-40% CVD Reduction Leaves High Residual Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Experiencing Major CHD Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Placebo 28.0, Statin 19.4 (P &lt; 0.001)</td>
</tr>
<tr>
<td>LIPID</td>
<td>Placebo 15.9, Statin 12.3 (P = 0.003)</td>
</tr>
<tr>
<td>CARE</td>
<td>Placebo 13.2, Statin 10.2 (P = 0.0001)</td>
</tr>
<tr>
<td>HPS</td>
<td>Placebo 11.8, Statin 8.7 (P &lt; 0.001)</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Placebo 7.9, Statin 5.5 (P &lt; 0.001)</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Placebo 10.9, Statin 6.8 (P &lt; 0.001)</td>
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</tbody>
</table>

References:
Aggressive LDL-C Lowering Therapy Does Not Eliminate CVD Risk

Significant Residual Risk Remains Untreated

IMPROVE-IT Study*

Residual risk: Due to increased triglycerides, elevated Lp(a), other untreated risk factors

Cannon et al NEJM 2015
Serial angiographic studies reveal culprit lesion of a future acute MI often does not cause significant stenosis.

Plaque can cause outward expansion of the artery wall which accommodates the growth of the plaque and minimizes luminal narrowing.

Luminal stenosis occurs late in the process of atherosclerosis.

Angiography is an assessment of luminal narrowing.
Low Grade Stenoses Cause Most Infarctions

Coronary StenosisSeverity Prior to MI

- 50-70% Stenosis: 18%
- >70% Stenosis: 14%
- <50% Stenosis: 68%

From Nissen NLA Presentation 3/19/16
Ischemia Trial

Trial enrolled 5,179 patients with stable CAD, preserved EF, and moderate-to-severe ischemia based on either stress imaging or exercise tolerance test. Results from ischemia trial reaffirm results from Courage and emphasize the importance of medical management.
CEN TRAL ILLUSTRATION: Schematic Diagram of the Mechanisms of Action of Statins, PCSK9 Inhibitors, PCSK9 Synthesis Inhibitors, and Bempedoic Acid

# Outcome Trials with PCSK9 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>ODYSSEY</th>
<th>FOURIER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Population</strong></td>
<td>Post ACS 2-4-52 Weeks from index event (median 2.6 months)</td>
<td>Stable ASCVD i.e. MI, stroke or PAD (median ~3 years from index event)</td>
</tr>
<tr>
<td><strong>Number of Patients</strong></td>
<td>18,924</td>
<td>27,564</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>58 (median)</td>
<td>63 (mean)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Patients with Diabetes</strong></td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>LDL-C entry criteria mg/dl (mmol/L)</strong></td>
<td>&gt; 70 (1.8)</td>
<td>&gt; 70 (1.8)</td>
</tr>
<tr>
<td><strong>Baseline LDL-C mg/dl (mmol/L)</strong></td>
<td>87 (2.3)</td>
<td>92 (2.4)</td>
</tr>
<tr>
<td><strong>High intensity statin</strong></td>
<td>89%</td>
<td>69%</td>
</tr>
<tr>
<td><strong>PCSK9 Inhibitor Dose Regimen</strong></td>
<td>Alirocumab 75 or 150mg every 2 weeks titrated to target LDL-C (25-50mg/dl) *75 mg dose was used 78% of the time</td>
<td>Evolocumab 140mg every 2 weeks or 420 mg every 4 weeks</td>
</tr>
<tr>
<td><strong>Duration of follow-up (years)</strong></td>
<td>2.8 (44% &gt; 3 years)</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>4-point MACE: CHD Death, MI, Ischemic stroke, Unstable angina requiring hospitalization</td>
<td>5-point MACE: CV Death, MI, Stroke Hospitalization for unstable angina, Coronary Revascularization</td>
</tr>
<tr>
<td><strong>Absolute Risk Reduction In Primary Endpoint</strong></td>
<td>1.6%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Significant Reductions in Secondary Lipid Parameters at Week 24

All patients on background of maximally-tolerated statin ± other lipid-lowering therapy

Alirocumab | Placebo
---|---
Non-HDL-C | | |
Apo B | | |
Lp(a) | | |

LS mean (SE) % change from baseline to Week 24:

-52% \( P<0.0001 \)
-54% \( P<0.0001 \)
-26% \( P<0.0001 \)

LS mean difference versus placebo:

Adjusted mean (SE) shown for Lp(a).
Triglycerides and CV Risk

- Multiple studies have shown elevated triglyceride levels are independently associated with increased risk of CV events [1]

- The recent REDUCE-IT trial is the first study to show targeting hypertriglyceridemia with isosapent ethyl (pure EPA) improves CV outcomes

- Fibrates do not reduce CV mortality [2]

1. Thompson et al., Arch Intern Med 2009;169:578
REDUCE-IT Population

Double-blind parallel group trial; median follow-up 4.9 years

8179 Patients

At High Risk for CV Events Due To:
- TG 150-499 mg/dL (median baseline 216 mg/dL), and
- Established CVD
  OR
- Diabetes mellitus + aged ≥50 years + ≥1 risk factor for CVD

Randomization 1:1

Stable Statin + icosapent ethyl (Vascepa) 4g/d

Stable Statin + Placebo

PRIMARY COMPOSITE (MACE) ENDPOINT
- CV Death
- Nonfatal MI
- Coronary Revascularization
- Nonfatal Stroke
- Unstable Angina requiring hospitalization
In patients with well controlled LDL on stable statin therapy with elevated triglycerides addition of icosapent ethyl resulted in a 4.8% absolute risk reduction and 25% relative risk reduction (P<0.001) in the composite endpoint of:

- CV death
- nonfatal MI
- nonfatal stroke
- coronary revascularization
- Unstable angina requiring hospitalization
Adding VASCEPA 4 g/d showed a 25% RRR in CV events.

Primary Composite Endpoint

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P = 0.00000001

No. at Risk
- Placebo: 4090, 3743, 3327, 2807, 2347, 1358
- VASCEPA: 4089, 3787, 3431, 2951, 2503, 1430

25% RRR
NNT = 21
# Bempedoic Acid Phase 3 CLEAR Program Design

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PATIENT POPULATION</th>
<th>NUMBER OF PATIENTS</th>
<th>BACKGROUND THERAPY</th>
<th>STUDY DURATION</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAR Harmony</td>
<td>ASCVD and/or HeFH on maximally tolerated statin therapy (LDL-C ≥70 mg/dL [1.8 mmol/L])</td>
<td>2230</td>
<td>Maximally tolerated statin therapy</td>
<td>52 weeks (+~78-weeks)</td>
<td>Safety (primary) and efficacy (secondary)</td>
</tr>
<tr>
<td>CLEAR Wisdom LDL-C Efficacy</td>
<td>ASCVD and/or HeFH on maximally tolerated statin therapy (LDL-C ≥100 mg/dL [2.6 mmol/L])</td>
<td>779</td>
<td>Maximally tolerated statin therapy</td>
<td>52 weeks</td>
<td>Efficacy and safety</td>
</tr>
<tr>
<td>CLEAR Serenity LDL-C Efficacy</td>
<td>Elevated LDL-C w/Statin Intolerance not Adequately Controlled with Current Lipid-Modifying Therapy</td>
<td>345</td>
<td>&lt; Low dose statin</td>
<td>24 weeks</td>
<td>Efficacy and safety in patients with statin intolerance</td>
</tr>
<tr>
<td>CLEAR Tranquility LDL-C Efficacy</td>
<td>Elevated LDL-C w/Statin Intolerance not Adequately Controlled with Current Lipid-Modifying Therapy</td>
<td>269</td>
<td>Ezetimibe ± ≤ Low dose statin</td>
<td>12 weeks</td>
<td>Efficacy and safety on a background of ezetimibe</td>
</tr>
</tbody>
</table>

ASCVD: atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; OLE, open-label extension.
CLEAR Wisdom Efficacy
Percent Change from Baseline to Week 12 in LDL-C (Background Statin Intensity)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean % Change from Baseline</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-15.1%*</td>
<td>253</td>
</tr>
<tr>
<td>Bempedoic Acid</td>
<td>-24.6%*</td>
<td>498</td>
</tr>
<tr>
<td>No Statin</td>
<td>-2.6%</td>
<td>29</td>
</tr>
<tr>
<td>Low/Moderate Intensity</td>
<td>-14.9%*</td>
<td>89</td>
</tr>
<tr>
<td>High Intensity</td>
<td>-14.4%*</td>
<td>135</td>
</tr>
</tbody>
</table>

*P < .001 for all comparisons

Mean = least squares mean (standard error).

Goldberg, AC et al. Presented at ACC 2019
Bempedoic Acid

- Studies show 15 to 25% LDL-C reduction on background statin
- Higher LDL reduction in patients not on statins

- Combination of bempedoic acid and ezetimibe lowers LDL-C about 35%

- Not active in muscle

- Overall good safety profile: uric acid increase, small incidence of tendon rupture
CLEAR Outcomes (1002-043) Global CVOT Study Design

A randomized, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major CV events in patients with, or at high risk for, CVD who are statin intolerant.

**Study Design**

**Week**

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Week</th>
<th>Study Phase</th>
<th>Screen Period</th>
<th>Single Blind Placebo Run in</th>
<th>Double Blind Treatment Period Evaluating MACE/LDL-C Reduction/Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>-5</td>
<td>Screen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>-4</td>
<td>Single Blind Placebo Run in</td>
<td>Bempedoic acid 180 mg (n=6302)</td>
<td>Placebo (n=6302)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0</td>
<td>Randomization</td>
<td></td>
<td></td>
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</tbody>
</table>

~4.75 years


CVOT, cardiovascular outcomes trial; PP, primary prevention; SP, secondary prevention.
Orion-10 Trial with Inclisiran

- 561 patients with ASCVD and elevated LDL cholesterol (≥ 70 mg/dL already on maximally tolerated statins to receive placebo or four injections of inclisiran over 18 months (days 1, 90, 270, and 450).

- At the end of the study, day 510, LDL cholesterol had been reduced by 56% (time-averaged) with inclisiran over placebo (P < 0.00001).

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ORION-10: Efficacy
Durable and potent with consistent effect over 18 months

Percent change in LDL-C over time – observed values in ITT patients

- Time-averaged Δ 56%
- Δ 58%

P-value for placebo – inclisiran comparison at each time point < 0.00001

1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points.
Conclusions

- Statins are the cornerstone of therapy in patients with hyperlipidemia
- PCSK9 inhibitors reduce LDL cholesterol and have favorable safety profile and also lower non HDL cholesterol, Lp(a) and may be an important tool in reducing residual risk
- EPA in the form of icosapent ethyl is associated with reduction in MACE
- Bempodoic acid and inclisiran are promising new agents for LDL lowering
- Get the LDL as low as you can for secondary prevention