DEBATE: Lowering LDL-C Levels With Statins And PCSK9 inhibitors in At Risk Patients with PAD Prevents Cardiovascular Events And Deaths

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Disclosure Statement of Financial Interest
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship Company
Grant/Research Support
- Boston Scientific
- Biotronik
- Biosensors
- Abbot Vascular
- Amgen
- Boston Scientific
- Biotronik
- Biosensors
Consulting Fees/Honoraria

Trial Design
27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL (1.8 mmol/L) or non-HDL-C ≥100 mg/dL (2.6 mmol/L)

Follow-up Q 12 weeks
Median f/up 2.2 yrs

Randomized
Double Blind

Summary of Effects of PCSK9i Evolocumab
- ↓ LDL-C by 59% to a median of 30 mg/dL
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated

Primary Endpoint
Hazard ratio 0.85 (95% CI 0.79-0.92) P=0.0001
**Landmark Analysis**

- **16% RRR**
  - HR 0.84 (95% CI 0.74-0.96)
  - P=0.018
- **25% RRR**
  - HR 0.75 (95% CI 0.66-0.85)
  - P=0.00001

**Summary for Evolocumab**

- **↓ LDL-C by 59%**
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)
- **CV outcomes in patients already on statin therapy**
  - 15% ↓ broad primary endpoint: 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C
- **Safe and well-tolerated**
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed

**Patients with Peripheral Artery Disease**

- **27,564 Patients with Atherosclerosis Randomized**
  - 3,642 Patients with Symptomatic Lower Extremity Peripheral Artery Disease
  - 1,955 Patients with Symptomatic Lower Extremity Peripheral Artery Disease and no prior MI or Stroke

- **57% Intermittent Claudication & ABI = <0.90 at Baseline**
  - 42% CABG 1517
  - 26% PCI 915
  - 27% Evolocumab 1,946
  - 4% Amputation for Ischemia

**MACE or MALE in Patients with PAD and no MI or Stroke**

- **48% RRR**
  - HR 0.52 (0.35 – 0.76)
  - P=0.0006

**Major Adverse Limb Events in Patients with and without Known PAD**

- **Known PAD**
  - HR 0.43
  - 95% CI (0.30 - 1.00)
  - P-interaction 0.29
  - 1.6% known PAD
  - 0.82% Evolocumab
  - 0.80% Placebo

- **No Known PAD**
  - HR 0.37
  - 95% CI (0.16 - 0.88)
  - 5.16% no known PAD
  - 0.76% Evolocumab
  - 0.16% Placebo

**CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease**

- **37% RRR**
  - HR 0.63
  - 95% CI (0.43 – 0.91)
  - P=0.02
  - 5.3% CR:F: 0.00
  - 6.0% Evolocumab
  - 0.16% Placebo
Patients with PAD are at heightened risk of MACE and MALE.

- LDL-C lowering with evolocumab in patients with PAD:
  - Reduces major adverse CV events with robust ARR
  - Reduces major adverse limb events
- Benefits extend to PAD without prior MI or stroke with an ARR for MACE or MALE of 6.3% (NNT 16) at 2.5 years.

Just published a week ago in *NEJM*...

**ORIGINAL ARTICLE**

**Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome**


**ODYSSEY**

** Patients with ACS**

- High intensity or maximum tolerable dose of atorvastatin or rosuvastatin
  - At least one lipid entry criterion met:
    - LDL-C ≥70 mg/dL
    - Non-HDL-C ≥100 mg/dL
    - ApoB ≥80 mg/dL

**Placebo SC**

**Q2W**

**Alirocumab SC**

**Q2W**

**Primary endpoint**: Time to first occurrence of CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization. All-cause and cardiovascular death were secondary endpoints, analyzed in a hierarchy of secondary endpoints.

**Double-blind randomization**: 1-12 months after ACS

**N=18,924**

**Median follow-up**: 2.8 years; ascertainment complete for >99% of potential patient-years of follow-up for CV events and death

*Blinded adjustment of alirocumab dose to target achieved LDL-C 25-50 mg/dL and avoid sustained levels <15 mg/dL.

**Primary Efficacy Endpoint: MACE**

To prevent one primary endpoint event would require 49 (95% CI 28 to 164) patients to be treated for 4 years

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

**HR 0.85**

**95% CI 0.78, 0.93**

**P<0.001**

**ODYSSEY**

**All-Cause Death**

<table>
<thead>
<tr>
<th>Years Since Randomization</th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
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<tbody>
<tr>
<td>2000</td>
<td>1813</td>
<td>1813</td>
</tr>
<tr>
<td>2001</td>
<td>1716</td>
<td>1716</td>
</tr>
<tr>
<td>2002</td>
<td>1619</td>
<td>1619</td>
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<td>2003</td>
<td>1522</td>
<td>1522</td>
</tr>
<tr>
<td>2004</td>
<td>1425</td>
<td>1425</td>
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</table>

**HR 0.85**

**95% CI 0.78, 0.96**

**Value-Based Price**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Annual price of alirocumab to be cost effective</th>
</tr>
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<tbody>
<tr>
<td>Base</td>
<td>$500,000/QALY</td>
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<tr>
<td>Sensitivity analysis</td>
<td>$4,510</td>
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<tr>
<td>Baseline LDL-C 110 mg/dL</td>
<td>$33,957</td>
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<tr>
<td>Baseline LDL-C 110 mg/dL</td>
<td>$2,083</td>
</tr>
</tbody>
</table>

**In Unprecedented Move, Amgen Cuts Price Of Cholesterol Drug Repatha By 60% to $5,850**
Conclusion

LDL-C reduction to very low levels should be considered in patients with PAD, regardless of history of MI or stroke, to reduce the risk of MACE and MALE

For more information see simultaneous publication in:

Circulation

Original Research Article
Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 inhibition in Subjects With Elevated Risk)