Clinical Efficacy and Safety of Achieving Very Low LDL-C Levels With the PCSK9 Inhibitor Evolocumab in the FOURIER Outcomes Trial

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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Amgen, Bristol Myers Squibb, Merck, Pfizer, Daiichi Sankyo, GlaxoSmithKline)
- Research contracts (Amgen)
Summary of FOURIER

- ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
- ↓ CV outcomes in patients already on statin therapy
- Evolocumab was safe and well-tolerated

**Change in LDL-C over time**
- **Placebo**
  - Median 0.78 mM
  - IQR [0.49-1.27]
- **Evolocumab**
  - 59% mean decline
  - P<0.00001
  - Absolute ↓ 1.45 mM (1.42-1.47)

**KM Rate (%) at 3 Years**
- **Placebo**
  - HR 0.80 (0.73-0.88)
  - P<0.00001
- **Evolocumab**
  - HR 0.85 (0.79-0.92)
  - P<0.0001

**Figure Legend**
- CV death, MI, stroke
- UA, cor revasc

**Graphs**
- LDL-C (mM) vs. Weeks after randomization
- KM Rate (%) at 3 Years

**References**
Methods

- LDL-C assessed at 4 wks (ultracentrifugation if <1 mM)
- Analyzed 5 groups by achieved LDL-C at 4 weeks
  1) <0.5 mM (20 mg/dL)
  2) 0.5-1.3 mM (20-49 mg/dL)
  3) 1.3-1.8 mM (50-69 mg/dL)
  4) 1.8-2.6 mM (70-99 mg/dL)
  5) ≥2.6 mM (≥100 mg/dL) was the referent group
- Pooled results across 2 Rx groups (evo, placebo)
- Prespecified 1° and 2° efficacy composite endpoints
- 10 safety adverse events evaluated:
  - Cognition¹ assessed by CANTAB and pt survey of everyday cognition

1582 pts with events in first 4 wks or no LDL-C at week 4 were excluded
CV Death, MI, or Stroke

<table>
<thead>
<tr>
<th>LDL-C (mM)</th>
<th>Adj HR (95% CI)</th>
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<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>0.5-1.3</td>
<td>0.75 (0.64-0.86)</td>
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<tr>
<td>1.3-1.8</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>0.90 (0.78-1.04)</td>
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<tr>
<td>≥ 2.6</td>
<td>referent</td>
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</tbody>
</table>

P = 0.0001

LDL-C (nM) at 4 weeks
Safety Events

% pts pt

LDL-C (mM) at
- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥2.6

Adj P-values for trend >0.10 for each comparison

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017
Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] nM = 7 [5-9] mg/dL

Cardiovascular Efficacy

- CVD, MI, Stroke, UA, Cor Revasc
  - HR 0.69 (0.49-0.97)
  - HR 0.59 (0.37-0.92)

Safety

- Serious adverse event
  - HR 0.94 (0.74-1.20)
  - HR 1.08 (0.63-1.85)
- AE -> drug discontinued
  - 3.4

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017
Conclusions

- LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i ($< 1$ mM)

- A strong linear relationship of achieved LDL-C and CV events seen, down to an LDL $< 0.26$ mM

- No excess in safety events with very low achieved LDL-C $< 20$ mg/dL at 2.2 years

These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with atherosclerotic CV disease