Association Between Achieved LDL-Cholesterol and Long-term Cardiovascular and Safety Outcomes: An Analysis of the FOURIER and FOURIER-OLE Studies

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Disclosures

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Study Schema: FOURIER and FOURIER-OLE

Patients with stable ASCVD and LDL-C ≥70 mg/dl (~1.8mM) or non-HDL-C ≥100 mg/dl (~2.6mM) on optimized statin Rx

Evolocumab q2 or q4 wks

Matching placebo

Open-Label Evolocumab q2 or q4 wks

Parent FOURIER Trial
Median follow-up 2.2 yrs
N=27,564

FOURIER OLE Program
Median follow-up 5.0 yrs
N=6635

Sabatine et al. NEJM 2017; 376: 1713-1722.
O’Donoghue et al. Circulation 2022; 146:1109-1119.
Results of FOURIER and FOURIER-OLE – CV Outcomes

Primary Efficacy Endpoint

- **HR 0.85 [0.80-0.91]**

Key Secondary Efficacy Endpoint

- **HR 0.80 [0.74-0.87]**

O’Donoghue et al. *Circulation* 2022; 146:1109-1119.
Results of FOURIER-OLE - Safety

- **Serious Adverse Events**: 13% (Placebo Phase), 13% (Evolocumab Phase), 10% (Evolocumab Phase with OLE).
- **Injection Site Reactions**: 0.7% (Placebo), 0.8% (Evolocumab Phase), 0.4% (Evolocumab Phase with OLE).
- **Drug-Related Allergic Reactions**: 1.1% (Placebo), 1.1% (Evolocumab Phase), 0.8% (Evolocumab Phase with OLE).
- **Muscle-Related Event**: 1.9% (Placebo), 2.1% (Evolocumab Phase), 1.2% (Evolocumab Phase with OLE).
- **New Onset Diabetes**: 2.3% (Placebo), 1.8% (Evolocumab Phase), 1.2% (Evolocumab Phase with OLE).
- **Hemorrhagic Stroke**: 0.05% (Placebo), 0.00% (Evolocumab Phase), 0.04% (Evolocumab Phase with OLE).

O’Donoghue et al. Circulation 2022; 146:1109-1119.
Evidence Gap

The optimal achieved LDL-C level with regards to cardiovascular and safety outcomes in the long term remains unclear.
Objective

To explore the relationship between achieved LDL-C levels and the occurrence of long-term adverse cardiovascular and safety outcomes, down to very low (<20 mg/dL) achieved LDL-C levels.
Methods

• Patients divided into 6 categories based on achieved LDL-C
  – Used LDL-C at 4 wks in FOURIER (or 12 wks in OLE for pts who transitioned from placebo -> evolocumab)
  – LDL-C bins: <20, 20-<40, 40-<55, 55-<70, 70-<100, and ≥100 mg/dL

• CV outcomes
  – Primary: CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina
  – Key secondary: CV death, MI, or stroke

• Safety outcomes
  – Serious adverse events, muscle-related events, new-onset diabetes mellitus, cataract-related adverse events, neurocognitive events, hemorrhagic stroke, malignancy, and non-CV death
Methods (cont’d)

• Examined trends in baseline characteristics

• Annualized incidence rates and 95% confidence intervals were calculated for all cardiovascular and safety outcomes

• Multivariable models adjusted for baseline characteristics associated with achieved LDL-C, including age, BMI, sex, race, current smoker, prior MI, prior non-hemorrhagic stroke, history of diabetes, history of peripheral arterial disease, high-intensity statin use, ezetimibe use, and participation in OLE.
Cohort & Follow-Up

- 26,384 patients with achieved LDL-C levels in FOURIER and/or FOURIER-OLE
- 19,960 patients in FOURIER alone with a median follow-up 2.0 years
- 6,429 patients also participated in FOURIER-OLE with median follow-up 4.9 years
- Including FOURIER & FOURIER-OLE, maximum follow-up 8.6 years
Achieved LDL-C Categories

- LDL-C Category: <20
- LDL-C Category: 20-<40
- LDL-C Category: 40-<55
- LDL-C Category: 55-<70
- LDL-C Category: 70-<100
- LDL-C Category: ≥100

<table>
<thead>
<tr>
<th>LDL-C Category</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>3510</td>
</tr>
<tr>
<td>20-&lt;40</td>
<td>3587</td>
</tr>
<tr>
<td>40-&lt;55</td>
<td>2569</td>
</tr>
<tr>
<td>55-&lt;70</td>
<td>6182</td>
</tr>
<tr>
<td>70-&lt;100</td>
<td>3673</td>
</tr>
<tr>
<td>≥100</td>
<td>6863</td>
</tr>
</tbody>
</table>
Achieved LDL-C Over Time

- LDL-C (mg/dL)
  - <20
  - 20-<40
  - 40-<55
  - 55-<70
  - 70-<100
  - ≥100

Time (week):
- Achieved
- 48
- 96
- Last F/U
# Baseline Characteristics by Achieved LDL-C

<table>
<thead>
<tr>
<th>Achieved LDL-C level (mg/dL)</th>
<th>&lt;20</th>
<th>20-&lt;40</th>
<th>40-&lt;55</th>
<th>55-&lt;70</th>
<th>70-&lt;100</th>
<th>≥100</th>
<th>P_{trend}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), yrs</td>
<td>63.5±8.7</td>
<td>63.2±8.8</td>
<td>61.6±8.9</td>
<td>62.0±9.3</td>
<td>62.7±9.0</td>
<td>61.2±9.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>83.7%</td>
<td>78.9%</td>
<td>71.4%</td>
<td>71.4%</td>
<td>74.6%</td>
<td>70.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>28.4±4.4</td>
<td>29.1±4.7</td>
<td>30.3±5.7</td>
<td>30.1±5.7</td>
<td>29.4±5.3</td>
<td>29.5±5.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White race</td>
<td>84.0%</td>
<td>87.4%</td>
<td>87.0%</td>
<td>82.2%</td>
<td>82.5%</td>
<td>86.1%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Prior MI</td>
<td>82.2%</td>
<td>81.6%</td>
<td>81.0%</td>
<td>79.3%</td>
<td>81.7%</td>
<td>79.9%</td>
<td>0.037</td>
</tr>
<tr>
<td>Non-hemorrhagic CVA</td>
<td>18.9%</td>
<td>18.3%</td>
<td>18.8%</td>
<td>19.7%</td>
<td>19.8%</td>
<td>20.8%</td>
<td>0.0019</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34.9%</td>
<td>33.9%</td>
<td>40.6%</td>
<td>42.0%</td>
<td>35.8%</td>
<td>35.6%</td>
<td>0.051</td>
</tr>
<tr>
<td>Current smoker</td>
<td>26.6%</td>
<td>26.2%</td>
<td>28.0%</td>
<td>28.9%</td>
<td>28.7%</td>
<td>32.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High-intensity statin</td>
<td>65.8%</td>
<td>69.1%</td>
<td>72.5%</td>
<td>69.6%</td>
<td>68.2%</td>
<td>71.4%</td>
<td>0.0043</td>
</tr>
<tr>
<td>Baseline LDL-C, median (IQR), mg/dL</td>
<td>82 (75, 94)</td>
<td>90 (79, 103)</td>
<td>95 (81, 112)</td>
<td>85 (74, 107)</td>
<td>90 (81, 102)</td>
<td>115 (101, 137)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Primary endpoint: CV death, MI, stroke, coronary revascularization or hospitalization for unstable angina

Adj P-value <0.0001
CV Outcomes and Achieved LDL-C

Key secondary endpoint: CV death, MI, or stroke

Adj P-value <0.0001
Safety and Achieved LDL-C

### LDL-C Category:
- <20
- 20-<40
- 40-<55
- 55-<70
- 70-<100
- ≥100

**Serious Adverse Events**
- Adj $P_{\text{trend}} = 0.13$
- 16% 16% 17% 17% 15% 15%

**Muscle-related Events**
- Adj $P_{\text{trend}} = 0.06$
- 1.2% 1.2% 1.2% 1.2% 1.0% 1.0%

**New Onset Diabetes Mellitus**
- Adj $P_{\text{trend}} = 0.09$
- 1.7% 1.7% 1.6% 1.2% 1.5% 1.4%

**Cataract-related Adverse Events**
- Adj $P_{\text{trend}} = 0.17$
- 0.9% 0.8% 0.9% 0.9% 0.9% 0.6%

**Neurocognitive Events**
- Adj $P_{\text{trend}} = 0.63$
- 0.8% 0.9% 0.9% 1.0% 0.8% 0.8%

**Hemorrhagic Stroke**
- Adj $P_{\text{trend}} = 0.59$
- 0.07% 0.12% 0.06% 0.03% 0.09% 0.07%

**New or Progressive Malignancy**
- Adj $P_{\text{trend}} = 0.71$
- 1.5% 1.5% 1.7% 1.8% 1.3% 1.6%

**Non-cardiovascular Death**
- Adj $P_{\text{trend}} = 0.03$
- 0.4% 0.2% 0.5% 0.6% 0.4% 0.5%
MACE & Safety w/ LDL-C <10 vs ≥100 mg/dL

A. Cardiovascular Outcomes

- **Primary efficacy endpoint**
  - LDL-C <10 mg/dL: 3.4%
  - LDL-C ≥100 mg/dL: 5.7%
  - Relative Risk (RR): 0.60 (0.46, 0.79)
  - P-value <0.001

- **Key secondary efficacy endpoint**
  - LDL-C <10 mg/dL: 2.4%
  - LDL-C ≥100 mg/dL: 4.3%
  - Relative Risk (RR): 0.55 (0.40, 0.77)
  - P-value <0.001

B. Safety

- **Serious Adverse Events**
  - LDL-C <10 mg/dL: 15.4
  - LDL-C ≥100 mg/dL: 14.2
  - P-value = 0.58
Limitations

- All patients enrolled in FOURIER had stable ASCVD with baseline LDL-C ≥70 mg/dL and non-HDL ≥ 100 mg/dL on GDMT, and thus findings may not be applicable to all patients in general practice.

- Comparisons based on a post-randomization variable and, despite multivariable analysis, may be subject to residual confounding.
Summary & Conclusions

• Monotonic relationship between lower achieved LDL-C levels, down to very low LDL-C levels <20 mg/dL, and a lower risk of cardiovascular events up to 8.6 years of follow-up

• No serious safety concerns with low LDL-C during the extended follow-up period

• Altogether, these data suggest that targeting a very low LDL-C level is both effective and safe for patients with atherosclerotic cardiovascular disease