Cardiovascular Benefit of Lowering LDL-C Below ~1 mmol/L (40 mg/dl)

Nicholas A. Marston, MD, MPH, Robert P. Giugliano, MD, SM, Jeong-Gun Park, PhD, Andrea Ruzza, MD, Peter S. Sever, PhD, Anthony Keech, MD, Marc S. Sabatine, MD, MPH

Nicholas A. Marston, MD, MPH
TIMI Study Group
Division of Cardiovascular Medicine
Brigham and Women’s Hospital
Harvard Medical School
### Risk Category vs. LDL-C Goal

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Risk ASCVD</strong></td>
<td>&lt;1.4 mmol/L (55 mg/dl) is recommended</td>
</tr>
<tr>
<td><strong>ASCVD with 2 CV events in 2 years (despite taking optimal statin therapy)</strong></td>
<td>&lt;1 mmol/L (40 mg/dl) may be considered</td>
</tr>
</tbody>
</table>

**2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk**

ESC Dyslipidemia Guidelines

ESC - European Society of Cardiology

ESC/EAS GUIDELINES - European Society of Cardiology and European Atherosclerosis Society

ESC CONGRESS 2021

THE DIGITAL EXPERIENCE

• The addition of PCSK9 inhibitors to statin therapy allows us to achieve LDL-C levels well below 1 mmol/L in many patients.

• However, the clinical benefit of LDL-C lowering beyond this level has recently been debated.

Evolocumab
59% mean reduction (95%CI 58-60), P<0.00001

Median achieved LDL-C
0.78 mmol/L (IQR 0.49-1.19 mmol/L)
30 mg/dl (IQR 19-45 mg/dl)

Placebo

1 mmol/L
Achieved LDL-C and Outcomes

• A post-hoc analysis from FOURIER showed a strong relationship between achieved LDL-C at 1 month & adjusted CV events, seen down to 0.2 mmol/L of LDL-C

• However, this was a post-randomization association
Aim

To determine whether there is continued cardiovascular benefit from lowering LDL-C below ~1 mmol/L (40 mg/dl) while maintaining randomization.
Methods

• We performed an exploratory analysis in the FOURIER trial

• FOURIER was a cardiovascular outcomes trial comparing evolocumab vs. placebo in patients with stable ASCVD on optimized statin therapy

• All 27,564 patients from FOURIER were included in this analysis

• The endpoint of major adverse cardiovascular event (MACE) was defined as CV death, MI, or stroke

• The median follow-up was 2.2 years
• Treatment benefit is directly proportional to the absolute amount of LDL-C reduction

• However, these data did not include many patients with achieved levels of LDL-C <1 mmol/L

Cholesterol Treatment Trialists Collaboration

Conceptual Approach

If there is no benefit to LDL-C lowering below 1 mmol/L

If there is the same benefit in LDL-C lowering <1 mmol/L

50% of LDL-C lowering is under 1 mmol/L

Relative risk reduction in MACE

20% 20% 10%

ESC CONGRESS 2021
THE DIGITAL EXPERIENCE
Pooled Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63 (9)</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>75</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>19</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use (%)</td>
<td>28</td>
</tr>
<tr>
<td>LDL-C, mmol/L, median (IQR)</td>
<td>2.4 (2.1-2.8)</td>
</tr>
<tr>
<td>LDL-C, mg/dl, median (IQR)</td>
<td>92 (80-109)</td>
</tr>
<tr>
<td><strong>Moderate or High Intensity Statin Use (%)</strong></td>
<td>99</td>
</tr>
</tbody>
</table>

Baseline characteristics were balanced between arms
65% of subjects achieved LDL-C <40 mg/dl (~1 mmol/L) with evolocumab
Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below ~1 mmol/L (<40 mg/dl) as a function of baseline LDL-C.

Results:
- Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below ~1 mmol/L (<40 mg/dl) as a function of baseline LDL-C.
- % of LDL-C lowering that is below 40 mg/dl:
  - Placebo: 62%
  - Evolocumab: 38%

Baseline LDL-C (mmol/L)
Achieved LDL-C (mmol/L)
Upper Panel: Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below 1 mmol/L (<40 mg/dl) as a function of baseline LDL-C.

Lower Panel: Hazard ratio for evolocumab vs. placebo for CV Death, MI, or Stroke per 1 mmol/L reduction in LDL-C as a function of baseline LDL-C.

P-interaction for treatment benefit = 0.78
Conclusions

• There is no evidence for attenuation of the clinical benefit of lowering LDL-C below 1 mmol/L (40 mg/dl)

• These data support the ESC/EAS Dyslipidemia Guideline recommendations and suggest lowering LDL-C below 1 mmol/L in a wider range of patients with ASCVD would further lower CV risk