CARDIOVASCULAR BENEFIT OF LOWERING LDL-C BELOW 40 mg/dl

Nicholas Marston, MD, MPH
TIMI Study Group
Brigham and Women’s Hospital
Harvard Medical School
## ESC Dyslipidemia Guidelines

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

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Risk ASCVD</td>
<td>&lt;55 mg/dl is recommended</td>
</tr>
<tr>
<td>ASCVD with 2 CV events in 2 years (despite taking optimal statin therapy)</td>
<td>&lt;40 mg/dl may be considered</td>
</tr>
</tbody>
</table>
The addition of PCSK9 inhibitors to statin therapy allows us to achieve LDL-C levels well below 40 mg/dl in many patients.

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

59% mean reduction (95%CI 58-60)
56 mg/dl absolute reduction (95%CI 55-57)
- A post-hoc analysis from FOURIER showed a strong relationship between achieved LDL-C at 1 month & adjusted CV events, seen down to 10 mg/dl of LDL-C

- However, this was a post-randomization association

To determine whether there is continued cardiovascular benefit from lowering LDL-C below 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 <40 mg/dl.
Conceptual Approach

- **80 mg/dl**
- **60 mg/dl**
- **20 mg/dl**
- **40 mg/dl**

If there is no benefit to LDL-C lowering below 40 mg/dl, the relative risk reduction in MACE is **10%**.

If there is the same benefit in LDL-C lowering <40 mg/dl, the 50% of LDL-C lowering is under 40 mg/dl.

Relative risk reduction in MACE:
- **20%**
Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below 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 40 mg/dl as a function of baseline LDL-C.
Achieved LDL-C (mg/dl)

Upper Panel: Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below <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.

If consistent benefit of LDL-C lowering regardless of how low

If no benefit of lowering LDL-C below 40 mg/dl

No attenuation of benefit even when more than 1/3 of LDL-C lowering is below 40 mg/dl
Conclusions

➢ There is no evidence for attenuation of the clinical benefit of lowering LDL-C below 40 mg/dl

➢ These data support the ESC/EAS Dyslipidemia Guideline recommendations and suggest lowering LDL-C below 40 mg/dl in a wider range of patients with ASCVD would further lower CV risk
THANK YOU