Relationship Between Baseline LDL-C and %LDL-C Reduction with Evolocumab in the FOURIER Trial

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Background

• Statins, ezetimibe and PCSK9 inhibitors are commonly used to lower LDL-C and therefore to lower ASCVD risk

• Intensity of lipid lowering therapy is defined by %LDL-C reduction

• It is commonly assumed %LDL-C lowering is intrinsic to a drug with little variation by patient characteristics

Objective

• To evaluate association between baseline LDL-C and %LDL-C reduction with a statin, ezetimibe and a PCSK9 inhibitor
Methods and Materials

3 double-blind, placebo-controlled RCTs of lipid-lowering therapies

- 4497 patients w/in 5 days of ACS
  Total chol <250 mg/dl + statin-naive
  - Analyses restricted to patients on study drug with LDL-C values at baseline and follow-up timepoint (1 month for simvastatin & ezetimibe; 3 months for evolocumab).

- 18,144 patients w/in 10 days of ACS
  LDL-C 50-125mg/dl
  - Analyses restricted to patients on study drug with LDL-C values at baseline and follow-up timepoint (1 month for simvastatin & ezetimibe; 3 months for evolocumab).

- 27,564 w/ stable ASCVD on statin
  LDL-C ≥70 or non-HDL-C ≥100mg/dl
  - Analyses restricted to patients on study drug with LDL-C values at baseline and follow-up timepoint (1 month for simvastatin & ezetimibe; 3 months for evolocumab).

%LDL-C calculated as follows: used generalized linear regression to model achieved LDL-C as function of baseline LDL-C in each arm of each trial; %LDL-C reduction estimated from the difference between treatment and placebo achieved LDL-C.
## Study Population

<table>
<thead>
<tr>
<th>Lipid Lowering Agent</th>
<th>A to Z – TIMI 21</th>
<th>IMPROVE-IT</th>
<th>FOURIER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>3187</td>
<td>10,680</td>
<td>25,847</td>
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<tr>
<td>Ezetimibe</td>
<td></td>
<td></td>
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<tr>
<td>Evolocumab</td>
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</tbody>
</table>

| N in analysis population | 3187             | 10,680     | 25,847  |

| Age, median (IQR), yrs   | 61               | 62         | 63      |

| Female (%)               | 23               | 23         | 24      |

| Caucasian (%)            | 86               | 83         | 85      |

| Diabetes Mellitus (%)    | 20               | 21         | 36      |

| Baseline LDL-C, median (IQR), mg/dL | 113 (95-131) | 83 (67-99) | 91.5 (79.5-108.5) |

| Achieved LDL-C in placebo arm, median (IQR), mg/dL | 124 (105-145) | 62 (51-76) | 88 (75-106) |

| Achieved LDL-C in treatment arm, median (IQR), mg/dL | 67 (53 – 82) | 45 (36-57) | 28 (19-43) |
%LDL-C Lowering By Baseline LDL-C

- Ezetimibe: Δ 1.2%
- Simvastatin: Δ 3.2%
- Evolocumab: Δ 6.6%
FOURIER %LDL-C Lowering, Stratified By Statin

%LDL-C Reduction

High-intensity statin

Moderate-intensity statin
Possible Mechanism

- In the setting of lower intrahepatic LDL-C, SREBP-2 is upregulated.
- Higher levels of SREBP-2 → ↑ synthesis of both the LDL receptor and, as a counter-regulatory brake, PCSK9.
- In that setting, PCSK9 inhibition may lead to particularly greater LDL receptor activity.
Limitations

• A-to-Z and IMPROVE-IT both enrolled immediately post-ACS, whereas FOURIER did not

• Although baseline LDL-C associated with magnitude of % LDL-C reduction, cannot prove causality; other factors could also be at play

• Observations should be repeated in studies with other PCSK9 inhibitors to confirm class-effect
Conclusion

- Lower baseline LDL-C is associated with 6.6% absolute greater LDL-C reduction for evolocumab

- These data are encouraging for reaching the progressively lower LDL-C targets that are being set