Lipoprotein(a), PCSK9 Inhibition and Cardiovascular Risk: Insights from the FOURIER Trial

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Summary of Effects of PCSK9i Evolocumab

- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated

Placebo

Evolocumab (median 30 mg/dl, IQR 19-46 mg/dl)

59% reduction
P<0.00001

Absolute ↓ 56 mg/dl

KM Rate (%) at 3 Years

HR 0.85 (0.79-0.92)
P<0.0001

HR 0.80 (0.73-0.88)
P<0.0001

CVD, MI, stroke
UA, cor revasc

CVD, MI, stroke

Sabatine MS et al. NEJM 2017;376:1713-22
Lp(a) and Risk of MI

• Mendelian randomization data support a causal role for Lp(a) in risk of coronary heart disease

Risk of MI for Doubling in Lp(a) concentration

Kamstrup et al, JAMA. 2009;301(22):2331-2339
Methods

- Lp(a) was measured at baseline and weeks 12 and 48 at Medpace Reference Laboratories (Medpace Inc. Cincinnati, OH) using an isoform-independent immunoturbidometric assay (Polymedco, Cortlandt Manor, New York)

- Association between Lp(a) and CV risk
  - Examined in placebo arm
  - Unadjusted, and then adjusting for age, sex, race, weight, region, prior MI, history of stroke, PAD, HTN, DM, current smoking, baseline LDL-C

- Effect of evolocumab
  - On Lp(a) and LDL-C
  - CV outcomes by baseline Lp(a) concentration

- Association of achieved Lp(a), achieved LDL and CV risk

- Kaplan-Meier rates are reported at 3 years
Baseline Distribution of Lp(a)

Descriptive Statistics
N=25096
Median (IQR) = 37 (13-165) nmol/L
### Baseline Characteristics

#### Quartiles of baseline Lp(a)

<table>
<thead>
<tr>
<th></th>
<th>Q1 (&lt;14nM)</th>
<th>Q2 (14-37nM)</th>
<th>Q3 (38-165nM)</th>
<th>Q4 (&gt;165nM)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>62 (9.0)</td>
<td>63 (9.1)</td>
<td>62 (9.1)</td>
<td>63 (8.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Male sex</td>
<td>80%</td>
<td>76%</td>
<td>76%</td>
<td>68%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of CV disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>79%</td>
<td>79%</td>
<td>81%</td>
<td>83%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>21%</td>
<td>21%</td>
<td>20%</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV Risk Factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>81%</td>
<td>81%</td>
<td>79%</td>
<td>80%</td>
<td>0.055</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>41%</td>
<td>36%</td>
<td>36%</td>
<td>34%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current tobacco</td>
<td>30%</td>
<td>30%</td>
<td>29%</td>
<td>25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline LDL-C, mean (SD)</td>
<td>93 (25)</td>
<td>96 (27)</td>
<td>98 (31)</td>
<td>101 (27)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Baseline Lp(a) and CV Risk

Adjusted HR Q4:Q1 = 1.26 (95% CI 1.02-1.56)

KM rates at 3 years (%)

CHD death or MI

CV death, MI or stroke

Adjusted HR Q4:Q1 = 1.12 (95% CI 0.93-1.34)

MV model: Age, sex, race, weight, region, prior MI, history of stroke, PAD, HTN, DM, current smoking, baseline LDL-C

Restricted to placebo arm
Baseline Lp(a) and CV Risk

Adj HR Q4:Q1 = 1.31 (95% CI 1.04-1.66)

Adj HR Q4:Q1 = 0.92 (95% CI 0.63-1.33)

Adj HR Q4:Q1 = 1.23 (95% CI 0.81-1.89)

KM rates at 3 years (%)

Myocardial infarction

Stroke

Coronary death

MV model: Age, sex, race, weight, region, prior MI, history of stroke, PAD, HTN, DM, current smoking, baseline LDL-C

Restricted to placebo arm
Change in Lp(a) from Baseline to Week 48 with Evolocumab

Median absolute change in Lp(a): -11 nmol/L

Median % change in Lp(a): -26.9%

Placebo-controlled values
Absolute change in \( \text{Lp}(a) \) for patients on evolocumab

Descriptive Statistics

N = 11,864
Median (IQR) = -11 (-32, -1) nmol/L

Absolute change from baseline to 48 weeks
% change in Lp(a) for patients on evolocumab

Descriptive Statistics
N=11864
Median (IQR) = -26.9 (-46.7, -6.2) %
Change in Lp(a) by Quartile of Baseline Lp(a) with Evolocumab

Median absolute change in Lp(a)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Change (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>-1</td>
</tr>
<tr>
<td>Q2</td>
<td>-9</td>
</tr>
<tr>
<td>Q3</td>
<td>-24</td>
</tr>
<tr>
<td>Q4</td>
<td>-36</td>
</tr>
</tbody>
</table>

Median % change in Lp(a)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>-9.1</td>
</tr>
<tr>
<td>Q2</td>
<td>-16</td>
</tr>
<tr>
<td>Q3</td>
<td>-32.5</td>
</tr>
<tr>
<td>Q4</td>
<td>-41.9</td>
</tr>
</tbody>
</table>

*Reflects change from baseline to week 48 Placebo-controlled values
Absolute change in Lp(a) versus LDL for patients on evolocumab

\[ r = 0.21 \]

Change from baseline to week 48
% change in Lp(a) versus LDL for patients on evolocumab

$r = 0.37$

Change from baseline to week 48
Efficacy by Baseline Lp(a)

CV death, MI or stroke (3y KM rate, %)

HR 0.85  
(95% CI 0.73-0.97)  
ARR=1.26%  
NNT=79

HR 0.76  
(95% CI 0.66-0.86)  
ARR=2.8%  
NNT=36

P interaction=0.26
Achieved Lp(a), LDL and CV Risk

- CV death, MI or stroke beyond week 12 (%)
  - Lp(a) > median: 9.43%
  - Lp(a) <= median: 8.45%
  - LDL-C > median: 7.88%
  - LDL-C <= median: 6.57%

P < 0.001

KM rate at 3 years
Summary

• Evolocumab significantly reduces Lp(a) concentration

• Patients starting with higher Lp(a) levels appear to derive greater absolute benefit from PCSK9 inhibition.

• Patients who achieve lower levels of both LDL-C and Lp(a) have the lowest subsequent risk of CV events.