Characterization of Types and Sizes of Myocardial Infarction Reduced with Evolocumab in FOURIER

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On behalf of the FOURIER Investigators

American Heart Association Scientific Sessions
November 13, 2017
Decades of lipid-lowering trials have shown that LDL reduction with statins reduces myocardial infarction.

The FOURIER trial compared the PCSK9 inhibitor evolocumab to placebo in patients on statin therapy and showed a significant reduction in cardiovascular events proportional to LDL reduction and time.

We sought to further characterize the effects of evolocumab on myocardial infarction.
Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL (1.8 mmol/L) or
non-HDL-C ≥100 mg/dL (2.6 mmol/L)

Randomized Double Blind

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks; Median f/up 2.2 yrs

Primary Endpoint: CVD/MI/Stroke/UA/Coronary Revasc
Key Secondary Endpoint: CVD/MI/Stroke

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

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

**Placebo**

59% reduction
P<0.00001

Absolute ↓ 56 mg/dl

**KM Rate (%) at 3 Years**

- **CVD, MI, stroke**
  - HR 0.85 (0.79-0.92)
  - P<0.0001
  - Absolute 56 mg/dl

- **UA, cor revasc**
  - HR 0.80 (0.73-0.88)
  - P<0.0001
  - Absolute 9.9 mg/dl

Sabatine MS et al. *NEJM* 2017;376:1713-22
## Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD, MI, stroke, UA, or revasc</strong></td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td><strong>CV death, MI, or stroke</strong></td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td><strong>4.4</strong></td>
<td><strong>6.3</strong></td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td><strong>Hosp for unstable angina</strong></td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td><strong>Coronary revasc</strong></td>
<td>7.0</td>
<td>9.2</td>
<td>0.78 (0.71-0.86)</td>
</tr>
</tbody>
</table>
Hypothesis

We hypothesized that:

1. In this stable population, spontaneous MI would predominate
2. PCSK9 inhibition with evolocumab would reduce spontaneous MI and more severe MIs
3. Longer durations of treatment would result in greater MI reduction
Methods

- Myocardial Infarction (MI) was identified locally and adjudicated centrally by the independent TIMI Clinical Events Committee using source documentation.
- MI definition was based on the 3rd Universal MI definition.
- MI was further categorized by:
  - ECG Type (STEMI/ NSTEMI)
  - Size (peak troponin “fold” elevation) vs to local report ULN
- Universal MI Type:
  - Type 1 – Spontaneous Atherothombotic
  - Type 2 – Ischemic Imbalance (secondary)
  - Type 3 – Death due to MI without evaluation*
  - Type 4 – PCI Related MI (types A-C collapsed)
  - Type 5 – CABG related MI*

^Thygesen K et al. Circulation 2012

*Due to small numbers, these data are not presented individually.
1288 total myocardial infarctions occurred in the trial

Universal MI Type

- Type 1 Spontaneous: 68%
- Type 2 Secondary: 15%
- Type 3: 1%
- Type 4 PCI-Related: 15%
- Type 5 <1%

*25 Type 4a, 99 Type 4b, 70 Type 4c

ECG Categorization

- NSTEMI: 78%
- STEMI: 18%
- Unknown: 4%
Effect of Evolocumab by Universal MI Type

Due to small numbers, Types 3 and 5 are not presented individually.
Effect of Evolocumab by MI Type: NSTEMI and STEMI

**NSTEMI**

- HR 0.77 (95% CI 0.68-0.88)
- P<0.001

**STEMI**

- HR 0.64 (95% CI 0.49-0.84)
- P<0.001
MI Size
1288 total MI, 1150 with Tn Size Data

60% ≥10x ULN

Proportion of MI Events (%) vs. Fold Elevation of Tn

- 1-<3: 22%
- 3-<5: 10%
- 5-<10: 9%
- 10-<25: 23%
- 25-<100: 17%
- >=100: 20%
Effect of Evolocumab by MI Size Based on Peak Tn/ULN*

- Total: HR 0.73
- ≥1: HR 0.72
- ≥3: HR 0.70
- ≥5: HR 0.69
- ≥10: HR 0.66
- ≥25: HR 0.64
- ≥50: HR 0.66
- ≥100: HR 0.71

*No Tn/ULN: HR 0.79 (0.56-1.11)
Effect of Evolocumab on Total and Spontaneous MI

**Total MI**
- HR 0.73
- (95% CI 0.65-0.82)
- P<0.001

**Spontaneous MI**
- HR 0.68
- (95% CI 0.59-0.79)
- P<0.001
Effect of Evolocumab By Timing
All MI by Months of Treatment

Total
HR 0.73

0 to < 6
HR 0.92

6 to <12
HR 0.69

12 to <18
HR 0.66

≥ 18
HR 0.65
Summary

- MI was the commonest of the first primary composite outcomes in this population with stable atherosclerosis
- Type 1 (spontaneous) and NSTEMI categories predominated
- Addition of the PCSK9 inhibitor evolocumab to statin therapy reduced MI, with consistent reductions of:
  - Larger MI
  - Spontaneous & PCI-related MI [w/ no effect on Type 2 (ischemic mismatch)]
  - STEMI and NSTEMI
- MI reduction tended to be greater after the 1st 6 months of therapy. The relatively short trial period may, therefore have limited the overall effect.
Conclusions/Implications

- LDL-C reduction with the PCSK9 inhibitor evolocumab resulted in substantial and consistent reductions in MI, including the most severe events.

- These data underscore the importance of LDL lowering in prevention of MI.

- For future trials of lipid lowering therapy, particularly with shorter time horizons, MI evaluation may wish to focus on spontaneous events.