Clinical Benefit of Evolocumab in Patients with a History of MI: An Analysis from FOURIER

Marc S. Sabatine, Gaetano M. De Ferrari, Robert P. Giugliano, Kurt Huber, Basil S. Lewis, Jorge Ferreira, Julia F. Kuder, Sabina A. Murphy, Stephen D. Wiviott, Christopher Kurtz, Narimon Honarpour, Anthony C. Keech, Peter S. Sever, and Terje R. Pedersen, for the FOURIER Steering Committee & Investigators

American Heart Association – Annual Scientific Session
Late-Breaking Science in Prevention
November 13, 2017
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

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

Placebo SC
Q2W or QM

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 UA, cor revasc

HR 0.85 (0.79-0.92)
P<0.0001

HR 0.80 (0.73-0.88)
P<0.0001

CVD, MI, stroke

Sabatine MS et al. NEJM 2017;376:1713-22
Patients at higher CV risk may derive greater benefit from PCSK9 inhibition

Within the broad subgroup of patients w/ prior MI in FOURIER, we investigated if readily ascertainable clinical features of the CAD history identified patients:

1) At higher CV risk

2) Who derived greater benefit from PCSK9 inhibition
High-Risk Features in Patients with History of MI

21,162 patients with prior MI randomized to ticagrelor vs. placebo on a background of aspirin

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo Arm 3-yr KM Rate of CVD/MI/Stroke</th>
<th>Relative Risk Reduction</th>
<th>Absolute Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>9.0%</td>
<td>16%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Dellborg M et al. *ESC* 2017
Bonaca MP et al. *JACC* 2017;70:1368-75
Bansilal S et al. *JACC* 2016;67(Suppl):2146
Methods

- Analyses restricted to 22,351 Pts w/ prior MI
- Divided into subgroups on basis of 3 factors (all of which were prespecified enrichment risk factors):
  - Time from qualifying MI
  - # of prior MI’s at baseline
  - Presence of residual multivessel disease at baseline
- Outcome of interest: CV death, MI, or stroke
- Analyses
  - Risk of CV events in placebo arm in patients w/ or w/o a specific high-risk feature
  - Efficacy of evolocumab vs. placebo within each subgroup
22,351 patients (81% of overall trial)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>62 (9)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>78</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>79</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>28</td>
</tr>
<tr>
<td>High-intensity statin (%)</td>
<td>71</td>
</tr>
<tr>
<td>LDL-C, mg/dL (IQR)</td>
<td>92 (80-109)</td>
</tr>
<tr>
<td>LDL-C w/ EvoMab at 48 wk, mg/dL (IQR)</td>
<td>30 (19-46)</td>
</tr>
</tbody>
</table>

Hazard ratio 0.82 (95% CI, 0.74-0.91)  
P<0.001
# High-Risk Features and Other Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Time from Qualifying MI</th>
<th># Prior MIs</th>
<th>Residual Multivessel CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2 y ago N=8402 (38%)</td>
<td>≥2 y ago N=13,918 (62%)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>60 (9)</td>
<td>63 (9)</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>77</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75</td>
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<td>69</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL (IQR)</td>
<td>90 (79-106)</td>
<td>93 (80-110)</td>
<td></td>
</tr>
<tr>
<td>LDL-C w/ EvoMab at 48 wk, mg/dL (IQR)</td>
<td>29 (19-45)</td>
<td>30 (18-46)</td>
<td></td>
</tr>
</tbody>
</table>
Risk of CV Death, MI or Stroke with Each Risk Factor

- **Years from Qualifying MI**
  - <2 yrs: 10.8% (HR 1.19, 1.04-1.37, P=0.01)
  - ≥2 yrs: 9.3%

- **# of Prior MIs**
  - ≥2: 15.0% (HR 2.04, 1.78-2.35, P<0.001)
  - 1: 8.2%

- **Multivessel Disease**
  - Yes: 12.6% (HR 1.47, 1.27-1.70, P<0.001)
  - No: 8.9%

Analyses in placebo arm

An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School
## Multivariable Adjusted Analyses of All 3 Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted HR (95% CI) for CV death, MI or stroke</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying MI &lt;2 y ago</td>
<td>1.36 (1.18-1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2 Prior MIs</td>
<td>1.90 (1.65-2.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Residual multivessel CAD</td>
<td>1.34 (1.16-1.55)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Model in placebo arm of trial includes all 3 risk factors plus the following covariates: age, sex, weight, race, region, h/o stroke, h/o PAD, HTN, DM, current smoking, eGFR ≥60, high-intensity statin use, and LDL-C at baseline.
Benefit of EvoMab Based on Time from Qualifying MI

**Qualifying MI <2 yrs ago**

- **24% RRR**
- **HR 0.76**
  (95% CI 0.64-0.89)
- **P<0.001**
- **Δ 2.9%**
- **NNT 35**

**Placebo**

**Evolocumab**

**Qualifying MI ≥2 yrs ago**

- **13% RRR**
- **HR 0.87**
  (95% CI 0.76-0.99)
- **P=0.04**
- **Δ 1.0%**
- **NNT 101**

**P_{interaction}=0.18**

Months after Randomization
Benefit of EvoMab Based on # of Prior MIs

≥2 Prior MIs

21% RRR

HR 0.79

(95% CI 0.67-0.94)

P=0.006

15.0%

Δ 2.6%

NNT 38

Placebo

Evolocumab

1 Prior MI

16% RRR

HR 0.84

(95% CI 0.74-0.96)

P=0.008

16.4%

Δ 1.7%

NNT 60

Pinteraction = 0.57

CV Death, MI, or Stroke

0% 2% 4% 6% 8% 10% 12% 14% 16%

0 6 12 18 24 30 36

Months after Randomization
Benefit of EvoMab Based on Multivessel Disease

**Multivessel Disease**

- **30% RRR**
- **HR 0.70**
- **(95% CI 0.58-0.84)**
- **P<0.001**
- **Δ 3.4%**
- **NNT 29**

**No Multivessel Disease**

- **11% RRR**
- **HR 0.89**
- **(95% CI 0.79-1.00)**
- **P=0.055**
- **Δ 1.3%**
- **NNT 78**

**Placebo**

- 9.2%

**Evolocumab**

- 12.6%

**P_interaction = 0.03**
Overlap Between Factors

22,351 patients w/ prior MI

8402 Pts <2 y from MI

5285 Pts ≥2 MIs

5618 Pts w/ MVD
Overlap Between Factors

37% of the population

63% of the population w/ at least 1 risk factor
Benefit of EvoMab Based on # of High-Risk MI Features

High-risk feature: <2 yrs from qualifying MI, ≥2 prior MIs, or residual multivessel disease

Placebo
Evolocumab

N=8343 (37% of prior MI trial population)
0 Features
6% RRR
0.5% ARR

Months after Randomization
Benefit of EvoMab Based on # of High-Risk MI Features

High-risk feature: <2 yrs from qualifying MI, ≥2 prior MIs, or residual multivessel disease

- Placebo
- Evolocumab

≥1 Feature
- 22% RRR
- 2.5% ARR

P_{interaction} = 0.11

N=13,973 (63% of prior MI trial population)
Landmark Analyses in Pts w/ a High-Risk MI Feature

19% RRR
HR 0.81 (95% CI 0.68-0.95)
P = 0.01

27% RRR
HR 0.73 (95% CI 0.62-0.86)
P < 0.001

Placement

Evolocumab

CV Death, MI, Stroke

Months from Randomization

High-risk feature: <2 yrs from qualifying MI, ≥2 prior MIs, or multivessel disease
Landmark Analyses in Pts w/ a High-Risk MI Feature

19% RRR
HR 0.81 (95%CI 0.68-0.95)  
P=0.01

27% RRR
HR 0.73 (95%CI 0.62-0.86)  
P<0.001

If same pattern continues, would extrapolate to 5% ARR over 5 years

NNT<sub>5y</sub> of ~20

Evolocumab

Placebo

CV Death, MI, Stroke

Months from Randomization
Summary

• Patients (1) closer to their most recent MI, (2) with multiple prior MIs, or (3) with multivessel disease are at 34-90% ↑ risk for major vascular events.

• These patients experience substantial:
  - relative risk reductions (21-30%) and
  - absolute risk reductions (2.6-3.4% over 3 yrs)
with intensive LDL-C lowering w/ the PCSK9i evolocumab

These readily ascertainable clinical features offer one approach to tailoring therapy.