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

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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

![Graph showing LDL cholesterol levels over time]

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

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>
<tr>
<td>&lt;2 yrs</td>
<td>9.7%</td>
<td>23%</td>
<td>2.0%</td>
</tr>
<tr>
<td>≥2 yrs</td>
<td>7.9%</td>
<td>4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>≥2 MI’s</td>
<td>15.2%</td>
<td>15%</td>
<td>1.6%</td>
</tr>
<tr>
<td>1 MI</td>
<td>7.8%</td>
<td>17%</td>
<td>1.2%</td>
</tr>
<tr>
<td>MVD</td>
<td>9.4%</td>
<td>19%</td>
<td>1.6%</td>
</tr>
<tr>
<td>No MVD</td>
<td>8.6%</td>
<td>12%</td>
<td>0.9%</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
Prior MI Overall

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>≥2 N=5285 (24%)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>60 (9)</td>
<td>63 (9)</td>
<td>62 (9)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>77</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75</td>
<td>81</td>
<td>81</td>
</tr>
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<td>31</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>28</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>High-intensity statin (%)</td>
<td>76</td>
<td>69</td>
<td>75</td>
</tr>
<tr>
<td>LDL-C, mg/dL (IQR)</td>
<td>90 (79-106)</td>
<td>93 (80-110)</td>
<td>92 (81-105)</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>30 (19-46)</td>
</tr>
</tbody>
</table>
Risk of CV Death, MI or Stroke with Each Risk Factor

![Bar chart showing the risk of CVD, MI, or Stroke (3-yr KM) in Pbo](image)

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

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

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

Analyses in placebo arm
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
- NNT 35
- Placebo: 10.8% 7.9%
- Evolocumab: 13% 9.3%
- Δ 2.9%
- Δ 1.0%
- **P_interaction=0.18**

**Qualifying MI ≥2 yrs ago**

- **13% RRR**
- HR 0.87 (95% CI 0.76-0.99)
- P=0.04
- NNT 101
- Placebo: 13.0%
- Evolocumab: 8.3%
- Δ 8.3%
- Δ 1.0%
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

1 Prior MI

16% RRR

HR 0.84
(95% CI 0.74-0.96)
P=0.008

12.4%

P_interaction = 0.57

Evolocumab

Placebo

CV Death, MI, or Stroke

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
- ∆ 3.4%
- NNT 29
- 0% 6% 12% 18% 24% 30% 36%

**No Multivessel Disease**

- 11% RRR
- HR 0.89
  - (95% CI 0.79-1.00)
  - P=0.055
- ∆ 1.3%
- NNT 78
- 0% 6% 12% 18% 24% 30% 36%

CV Death, MI, or Stroke
Overlap Between Factors

22,351 patients w/ prior MI

8402 Pts <2 y from MI
5618 Pts w/ MVD
5285 Pts ≥2 MIs

An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School
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)
 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)

Months after Randomization
Landmark Analyses in Pts w/ a High-Risk MI Feature

- **CV Death, MI, Stroke**

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

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

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

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

- **2% absolute risk reduction over 2 years**

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

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

**Graph:****
- CV Death, MI, Stroke vs. Months from Randomization
- Placebo vs. Evolocumab
- Evolution of risk over time
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.*