LDL Cholesterol Lowering with Evolocumab and Outcomes in Patients with Peripheral Artery Disease: Insights from the FOURIER Trial


for the FOURIER Steering Committee & Investigators

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

Evolocumab SC 140 mg Q2W or 420 mg QM
RANDOMIZED DOUBLE BLIND

Placebo SC Q2W or QM

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

PEP: CVD, MI, Stroke, UA, Coronary Revascularization
Key Secondary EP: CVD, MI, Stroke

Summary of Effects of PCSK9i Evolocumab

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

<table>
<thead>
<tr>
<th>KM Rate (%) at 3 Years</th>
<th>CVD, MI, stroke</th>
<th>CVD, MI, stroke UA, cor revasc</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 0.85 (0.79-0.92)</td>
<td>0.80 (0.73-0.88)</td>
<td></td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

59% reduction
P<0.00001

Absolute ↓ 56 mg/dl

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

Placebo

Sabatine MS et al. NEJM 2017;376:1713-22
Background & Objectives

Patients with lower extremity PAD are at heightened risk of adverse cardiovascular (MACE) and limb events (MALE)

Statin vs. Placebo reduces CV risk and peripheral revascularization & observational studies suggest reductions in amputations

In patients with PAD on statins:

- Does further reducing LDL-C reduce CV risk?
- Does lowering LDL-C reduce the risk of MALE?

We investigated:

- CV risk and the absolute benefit of evolocumab in patients with PAD
- MALE risk and whether it was modified by evolocumab
Methods

• Patients qualified with PAD if either:
  – Intermittent claudication and ABI < 0.85
  – Prior peripheral revascularization or amputation for ischemia

• Primary analysis in prespecified PAD subgroup with sensitivity excluding patients with prior MI or stroke to see if benefits extend to PAD alone

• **MALE** defined as composite of acute limb ischemia (ALI), major amputation (AKA or BKA), or urgent revascularization; **MACE** defined as composite of CVD, MI or stroke
Patients with Peripheral Artery Disease

- 27,564 Patients with Atherosclerosis Randomized
- 57% Peripheral Revascularization (Median 3.7 years prior)
- 3,642 Patients with Symptomatic Lower Extremity Peripheral Artery Disease
- 69% Intermittent Claudication & ABI < 0.85 at Baseline
- 1,505 Patients with Symptomatic Lower Extremity Peripheral Artery Disease and no prior MI or Stroke
- 26% 955
- 27% 1,044
- 42% 1,517
- 4% 39
- Amputation for Ischemia
- 41
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MI or Stroke and no PAD N=23,922</th>
<th>PAD N=3,642</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>63 (56, 69)</td>
<td>64 (58, 69)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>History Hypertension (%)</td>
<td>79</td>
<td>85</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td>History of Diabetes (%)</td>
<td>36</td>
<td>43</td>
</tr>
<tr>
<td>History of Stroke (%)</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>History of Myocardial Infarction (%)</td>
<td>86</td>
<td>50</td>
</tr>
<tr>
<td>Statin, High/Moderate (%)</td>
<td>69 / 30</td>
<td>69 / 31</td>
</tr>
<tr>
<td>Antiplatelet therapy (%)</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>Anticoagulant therapy (%)</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>ACE-I or ARB use at baseline (%)</td>
<td>78</td>
<td>76</td>
</tr>
</tbody>
</table>

All p-values < 0.05 except statin use/intensity (p=0.57)
Statin dose at baseline missing in 10 (0.0%) without PAD and 3 (0.1%) with PAD
Peripheral Artery Disease and Risk in Placebo Patients

CVD / MI / Stroke adjusted age, sex, race, BMI, diabetes, hypertension, smoking, eGFR, CHF, prior MI, CABG/PCI, and history of stroke or TIA.

Adjusted HR
1.81
(1.53 – 2.14)
P<0.001
CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease

**Placebo**

- **N=3,642**
- **27% RRR**
- **HR 0.73 (0.59 – 0.91)**
- **P=0.0040**

**Evolocumab**

- **N=23,922**
- **HR 0.81**
- **95% CI (0.73 – 0.90)**
- **P<0.001**

**P-Interaction = 0.41**

**ARR**

- **PAD**
  - **3.5%**
  - **NNT_{2.5y} = 29**
- **No PAD**
  - **1.4%**
  - **NNT_{2.5y} = 72**
CV Death, MI or Stroke in Patients with PAD and no MI or Stroke

43% RRR
HR 0.57
(0.38 – 0.88)
P=0.0095

PAD 4.8% ARR
NNT<sub>2.5y</sub> 21

5.5%

Outcome MACE HR 95% CI
CV Death 0.78 (0.39–1.57)
MI 0.66 (0.38–1.14)
Stroke 0.30 (0.11–0.82)
Major Adverse Limb Events

All Patients
N=27,564

42% RRR

HR 0.58
(0.38 – 0.88)
P=0.0093

Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>0.58</td>
<td>(0.38 – 0.88)</td>
</tr>
<tr>
<td>ALI or major amputation</td>
<td>0.52</td>
<td>(0.31 – 0.89)</td>
</tr>
<tr>
<td>ALI</td>
<td>0.55</td>
<td>(0.31 – 0.97)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>0.57</td>
<td>(0.17 – 1.95)</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>0.69</td>
<td>(0.38 – 1.26)</td>
</tr>
</tbody>
</table>
Major Adverse Limb Events in Patients with and without Known PAD

Known PAD
HR 0.63
95% CI (0.39 – 1.03)

No Known PAD
HR 0.37
95% CI (0.16 – 0.88)

P-interaction 0.29
Major Adverse Limb Events in Patients with PAD and no MI or Stroke

- Placebo
- Evolocumab

PAD (no MI/stroke, N=1505)

57% RRR

HR 0.43
(0.19 - 0.99)

P=0.042

1.3% ARR

1.3%

2.6%
Achieved LDL-C and Major Adverse Limb Events

P=0.026 for beta coefficient

adjusted for significant (p<0.05) predictors of LDL-C cholesterol at 1 month after randomization including age, BMI, LDL-C at baseline, male sex, race, randomized in North America, current smoker, high intensity statin.
MACE or MALE
In Patients with and without PAD

Placebo
Evolocumab

PAD
N=3,642
27% RRR
HR 0.73
(0.60 – 0.88)
P=0.0014

No PAD
N=23,922
7.8%
7.8%
No PAD
N=23,922
HR 0.80
95% CI (0.72 – 0.89)
P<0.001
p-interaction = 0.39

PAD 4.1% ARR
NNT_{2.5y} 25

No PAD 1.5% ARR
NNT_{2.5y} 67
MACE or MALE
In Patients with PAD and no MI or Stroke

Placebo
Evolocumab

PAD
(no MI/stroke, N=1505)

48% RRR
HR 0.52
(0.35 – 0.76)
P=0.0006

12.8%
6.3% ARR
NNT_{2.5y} 16
6.5%

Days from Randomization

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

- Patients with PAD are at heightened risk of MACE and MALE

- LDL-C lowering with evolocumab in patients with PAD:
  - Reduces major adverse CV events with robust ARR
  - Reduces major adverse limb events

- Benefits extend to PAD without prior MI or stroke with an ARR for MACE or MALE of 6.3% (NNT 16) at 2.5 years
Conclusion

LDL-C reduction to very low levels should be considered in patients with PAD, regardless of history of MI or stroke, to reduce the risk of MACE and MALE

For more information see simultaneous publication in:

**Circulation**

 оригинальное исследовательское статьи

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)