Reduction with Evolocumab in Complex Coronary Revascularization: Insights from the FOURIER Trial

Kazuma Oyama,1 Remo H.M. Furtado,1,2 Antonio Fagundes Jr.,1 Thomas A. Zelniker,1,3 Minao Tang,1 Julia Kuder,1 Sabina A. Murphy,1 Andrew Hamer,4 Huei Wang,4 Anthony C. Keech,5 Terje R. Pedersen,6 Robert P. Giugliano,1 Marc S. Sabatine,1 Brian A. Bergmark1

1TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA
2Hospital Israelita Albert Einstein, Sao Paulo, Brazil
3Division of Cardiology, Vienna General Hospital and Medical University of Vienna, Austria
4Amgen, Thousand Oaks, CA, USA
5National Health and Medical Research Council Clinical Trials Centre, Sydney Medical School, University of Sydney, Sydney, Australia
6Medical Faculty, Oslo University Hospital Aker, Oslo, Norway

Disclosures: The FOURIER trial was supported by Amgen. K.O. was supported by a grant from JSPS (Japan Society for the Promotion of Science) Overseas Research Fellowships. B.A.B. reports grant support: Pfizer, AstraZeneca, Abbott Vascular; Consulting fees: Philips, Abbott Vascular, Servier, Daiichi-Sankyo, Janssen, Quark. B.A.B. is a member of the TIMI Study Group, which has received institutional grant support through the Brigham and Women’s Hospital from: Abbott, Amgen, Arena, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Elsi, GlaxoSmithKline, Intarcia, Janssen, Medimmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences.
PCSK9 inhibitors induce plaque regression and reduce the risk of coronary revascularization overall. The objective of this analysis was to investigate the coronary anatomical complexity at the time of revascularization and assess the effect of evolocumab on the risk of complex coronary revascularization procedures.
Methods

- FOURIER was a randomized trial of the PCSK9 inhibitor evolocumab vs. placebo in 27,564 patients with stable atherosclerosis on statin therapy followed for a median of 2.2 years.

- Clinical documentation of revascularization events was blindly reviewed to assess coronary anatomy and procedural characteristics.

- **Complex revascularization** was the composite of:
  - CABG, or
  - **Complex PCI** (GLOBAL LEADERS definition)
    - At least one of:
      1. Multivessel PCI
      2. ≥3 stents implanted
      3. ≥3 lesions treated
      4. bifurcation PCI with ≥2 stents
      5. total stent length >60 mm

# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Any complex revascularization (N=632)</th>
<th>Simple PCI only (N=1,092)</th>
<th>No revascularization (N=25,840)</th>
<th>P for trend (Any complex revasc vs. simple PCI vs. no revasc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62</td>
<td>61</td>
<td>63</td>
<td>0.23</td>
</tr>
<tr>
<td>Female, %</td>
<td>18</td>
<td>20</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>88</td>
<td>92</td>
<td>81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of nonhemorrhagic stroke, %</td>
<td>13</td>
<td>13</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of PAD, %</td>
<td>17</td>
<td>14</td>
<td>13</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>82</td>
<td>82</td>
<td>80</td>
<td>0.092</td>
</tr>
<tr>
<td>DM, %</td>
<td>43</td>
<td>38</td>
<td>36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of PCI, %</td>
<td>76</td>
<td>85</td>
<td>61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CABG, %</td>
<td>20</td>
<td>25</td>
<td>19</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>95</td>
<td>94</td>
<td>92</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Angiographic Characteristics by Procedure Type

- **CABG (N=296, 17%)**
  - LMCA stenosis \(\geq 50\%\) (N=209, 12%)
  - Prox. LAD stenosis \(\geq 50\%\) (N=629, 36%)
  - Multivessel Disease (N=832, 48%)
  - Bypass graft stenosis \(\geq 50\%\) (N=254, 16%)
  - CTO (N=613, 36%)
  - ISR \(\geq 50\%\) (N=463, 27%)

- **Complex PCI (N=336, 19%)**

- **Simple PCI (N=1,092, 63%)**

Proportion of Patients

- LMCA stenosis \(\geq 50\%\)
  - Simple PCI: 26% (P<0.001)
  - Complex PCI: 43% (P<0.001)
  - CABG: 15% (P<0.001)

- Prox. LAD stenosis \(\geq 50\%\)
  - Simple PCI: 31% (P<0.001)
  - Complex PCI: 47% (P<0.001)
  - CABG: 17% (P<0.001)

- Multivessel Disease
  - Simple PCI: 65% (P=0.950)
  - Complex PCI: 64% (P<0.001)
  - CABG: 17% (P<0.001)

- Bypass graft stenosis \(\geq 50\%\)
  - Simple PCI: 21% (P<0.001)
  - Complex PCI: 15% (P=0.035)
  - CABG: 7% (P=0.009)

- CTO
  - Simple PCI: 33% (P=0.003)
  - Complex PCI: 34% (P=0.009)
  - CABG: 21% (P=0.786)

- ISR \(\geq 50\%\)
  - Simple PCI: 23% (P=0.950)
  - Complex PCI: 27% (P=0.950)
  - CABG: 26% (P=0.950)
Effect of Evolocumab on Complex Revascularization

Complex revascularization
HR 0.71 (95% CI 0.61-0.84)
P value < 0.001

CABG
HR 0.76 (95% CI 0.60-0.96)
P value = 0.019

Complex PCI
HR 0.67 (95% CI 0.54-0.84)
P value < 0.001
# Effect of Evolocumab on Complex Revascularization

<table>
<thead>
<tr>
<th>Event</th>
<th>3-Year KM Rate (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex revascularization</td>
<td>2.4</td>
<td>0.71 (0.61-0.84)</td>
</tr>
<tr>
<td>CABG</td>
<td>1.2</td>
<td>0.76 (0.60-0.96)</td>
</tr>
<tr>
<td>Complex PCI</td>
<td>1.2</td>
<td>0.67 (0.54-0.84)</td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>0.8</td>
<td>0.67 (0.51-0.87)</td>
</tr>
<tr>
<td>≥3 stents implanted</td>
<td>0.5</td>
<td>0.70 (0.49-0.98)</td>
</tr>
<tr>
<td>≥3 lesions treated</td>
<td>0.3</td>
<td>0.59 (0.40-0.87)</td>
</tr>
<tr>
<td>Bifurcation PCI with ≥2 stents</td>
<td>0.1</td>
<td>0.55 (0.30-0.99)</td>
</tr>
<tr>
<td>Total stent length &gt;60 mm</td>
<td>0.3</td>
<td>0.70 (0.46-1.06)</td>
</tr>
</tbody>
</table>

![Graph showing the effect of Evolocumab on complex revascularization events](image)
Landmark Analyses for Complex Revascularization

0-12 months
RRR 20%
HR 0.80 (95% CI 0.64-0.99)

12-24 months
RRR 36%
HR 0.64 (95% CI 0.49-0.84)

24-36 months
RRR 41%
HR 0.59 (95% CI 0.37-0.96)
Limitations

• Granular coronary anatomic information was not available at baseline, precluding comparison to pre-randomization status.

• Anatomic detail is only known for patients who underwent revascularization during the trial.

• Individual coronary angiograms were not available; review depended on clinical documentation from revascularization procedures.
Conclusion

• Adding evolocumab to statin therapy reduced the risk of developing complex coronary artery disease requiring revascularization, including complex PCI and CABG individually.

• Together with prior coronary imaging findings, these data suggest very aggressive LDL-C lowering may have beneficial effects on coronary atherosclerosis burden, anatomical complexity, and the need for coronary revascularization.