Cardiovascular Efficacy & Safety of Evolocumab in Diabetes, and Risk of Development of Diabetes: An Analysis from the FOURIER Trial

MS Sabatine, LA Leiter, SD Wiviott, RP Giugliano, P Deedwania, GM De Ferrari, SA Murphy, JF Kuder, AC Keech, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

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Clinical Trial Update
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Disclosures

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Amgen; AstraZeneca; Daiichi-Sankyo; Eisai; GlaxoSmithKline; Intarcia; Janssen Research Development; Medicines Company; MedImmune; Merck; Novartis; Pfizer; Poxel; Takeda

Scientific Advisory Boards:
Amgen; CVS Caremark; Esperion; Intarcia; Janssen Research Development; MedImmune; Merck; Novartis
**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 \( \geq 70 \text{ mg/dL (1.8 mmol/L)} \) or non-HDL-C \( \geq 100 \text{ mg/dL (2.6 mmol/L)} \)

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

### Overall Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63 (9)</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>75</td>
</tr>
<tr>
<td><strong>Weight, kg, mean (SD)</strong></td>
<td>85 (17)</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>19</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus per patient hx</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>28</td>
</tr>
</tbody>
</table>

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms

Sabatine MS et al. *NEJM* 2017;376:1713-1722
## Overall Lipid Lowering Therapy & Lipid Levels at Baseline

### Characteristic

<table>
<thead>
<tr>
<th>Statin use (%)*</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-intensity</td>
<td>69</td>
</tr>
<tr>
<td>Moderate-intensity</td>
<td>30</td>
</tr>
</tbody>
</table>

| Ezetimibe use (%) | 5 |

<table>
<thead>
<tr>
<th>Median lipid measures (IQR)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>92 (80-109) 2.4 (2.1-2.8)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>168 (151-189) 4.3 (3.9-4.9)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (37-53) 1.1 (1.0-1.4)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>133 (100-182) 1.5 (1.1-2.1)</td>
</tr>
</tbody>
</table>

*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent. 1% were on low intensity or intensity data were missing. Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines. Pooled data; no differences between treatment arms.

Sabatine MS et al. *NEJM* 2017;376:1713-1722
Overall Effects on LDL Cholesterol

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

Placebo

59% mean reduction (95%CI 58-60), P<0.00001

Absolute reduction: 56 mg/dl (95%CI 55-57)

1.4 mmol/L

Evolocumab (median 0.78 mmol/L, IQR 0.5-1.2 mmol/L)

0 12 24 36 48 60 72 84 96 108 120 132 144 156 168

LDL Cholesterol (mg/dl)

Weeks

Sabatine MS et al. *NEJM* 2017;376:1713-1722
Primary & Key Secondary Endpoints

Primary Endpoint: CV Death, MI, Stroke, Hosp for UA, or Cot Revasc

- Hazard ratio 0.85 (95% CI, 0.79-0.92)
- P<0.0001

- Evolocumab
- Placebo

Key Secondary Endpoint: CV Death, MI, or Stroke

- Hazard ratio 0.80 (95% CI, 0.73-0.88)
- P<0.00001

- Evolocumab
- Placebo

Sabatine MS et al. *NEJM* 2017;376:1713-1722
## Overall Safety

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>77.4</td>
<td>77.4</td>
</tr>
<tr>
<td>Serious</td>
<td>24.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Treatment-related and led to d/c of study drug</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Laboratory results (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding Ab</td>
<td>0.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Neutralizing Ab</td>
<td>none</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Sabatine MS et al. *NEJM* 2017;376:1713-1722
Diabetes Substudy Objectives

- Investigate the efficacy of evolocumab in patients with and without diabetes at baseline
- Investigate the safety profile of evolocumab, particularly with respect to glycemia and the development of new-onset diabetes
Methods

• Baseline Diabetes Subgroups
  – **Diabetes**: either clinical history per patient; CEC review of baseline medical records; or baseline HbA1c ≥6.5% or FPG ≥126 mg/dL (7.0 mmol/L)
  – **No diabetes**
    • **Prediabetes**: baseline HbA1c 5.7-6.4% or FPG 100-125 mg/dL (5.5-6.9 mmol/L)
    • **Normoglycemia**: none of the above

• Outcomes
  – Primary endpoint: CV death, MI, stroke, hospitalization for UA, coronary revasc
  – Key secondary endpoint: CV death, MI, stroke
  – Adverse events in general; new-onset diabetes; glycemia

• TIMI Clinical Events Committee (CEC)
  – Adjudicated all efficacy endpoints & new-onset diabetes (per ADA definitions)
  – Members unaware of treatment assignment & lipid levels
Analyses

• Comparison of CV outcomes in patients w/ diabetes vs. w/o diabetes at baseline
  – Adjusted for: age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, high-intensity statin use

• Efficacy of evolocumab vs. placebo
  – Lipids
  – Clinical outcomes
  – In patients w/ and w/o diabetes at baseline

• Safety of evolocumab vs. placebo
  – New-onset diabetes in those w/o diabetes at baseline
  – Glycemia in patients w/ & w/o diabetes at baseline; weight
  – In patients w/ and w/o diabetes at baseline
Diabetes at Baseline

- **Normoglycemia**: N=6189 (22%)
- **Prediabetes**: N=10344 (38%)
- **Diabetes**: N=11031 (40%)

**Diagnosis of diabetes:**
- Patient history (91%)
- CEC review of baseline lab measurements (7%)
- Baseline lab measurement (2%)

Median duration: 5.7 y (IQR 1.9-11.9)

25% taking insulin
# Diabetes vs. No Diabetes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetes (N=11,031)</th>
<th>No Diabetes (N=16,533)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63 (9)</td>
<td>62 (9)</td>
</tr>
<tr>
<td><strong>Female sex (%)</strong></td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td><strong>White race (%)</strong></td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td><strong>Weight, kg, mean (SD)</strong></td>
<td>88 (19)</td>
<td>83 (16)</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>87</td>
<td>75</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td><strong>eGFR, mL/min per 1.73 m(^2) (SD)</strong></td>
<td>75 (21)</td>
<td>76 (17)</td>
</tr>
</tbody>
</table>

All P values <0.0001 apart from age (P=0.55)
## Diabetes vs. No Diabetes

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<th>Characteristic</th>
<th>Diabetes (N=11,031)</th>
<th>No Diabetes (N=16,533)</th>
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<tbody>
<tr>
<td><strong>Statin use (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-intensity</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>Moderate-intensity</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td><strong>Ezetimibe use (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><strong>Median lipid measures, mmol/L (IQR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.3 (2.0-2.8)</td>
<td>2.4 (2.1-2.8)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.3 (3.9-4.8)</td>
<td>4.4 (3.9-4.9)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.1 (0.9-1.3)</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.7 (1.3-2.3)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
</tbody>
</table>

Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines. All P values <0.0001
Risk of Primary Endpoint with Diabetes

Adj Hazard Ratio 1.26 (95% CI 1.13-1.40)   P<0.0001

Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.
Risk of Key Secondary Endpoint with Diabetes

Adj Hazard Ratio 1.40 (95% CI 1.23-1.60)  
P<0.0001

Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.
LDL-C Reduction with Evolocumab

**Patients w/ Diabetes at Baseline**

- **Placebo**: 2.2 mmol/L
- **Evolocumab**: 0.8 mmol/L

57% mean reduction

\[ P < 0.00001 \]

**Patients w/o Diabetes at Baseline**

- **Placebo**: 2.4 mmol/L
- **Evolocumab**: 0.8 mmol/L

60% mean reduction

\[ P < 0.00001 \]
Effect of Evolocumab on Other Lipid Parameters

Patients w/ Diabetes at Baseline

- Non-HDL-C: Placebo (P<0.0001), Evolocumab (0.3)
- ApoB: Placebo (P<0.0001), Evolocumab (2.7)
- Triglycerides: Placebo (P<0.0001), Evolocumab (0.0)
- Lp(a): Placebo (P<0.0001), Evolocumab (0.0)

Patients w/o Diabetes at Baseline

- Non-HDL-C: Placebo (P<0.0001), Evolocumab (0.3)
- ApoB: Placebo (P<0.0001), Evolocumab (2.6)
- Triglycerides: Placebo (P<0.0001), Evolocumab (0.0)
- Lp(a): Placebo (P<0.0001), Evolocumab (0.0)
Effect of Evolocumab on Primary Endpoint

Patients w/ Diabetes at Baseline

- Hazard Ratio 0.83 (95% CI 0.75-0.93)
- P=0.0008
- Placebo: 17.1%
- Evolocumab: 14.4%
- Δ 2.7%
- NNT 37

Patients w/o Diabetes at Baseline

- Hazard Ratio 0.87 (95% CI 0.79-0.96)
- P=0.0052
- Placebo: 13.0%
- Evolocumab: 11.4%
- Δ 1.6%
- NNT 62

Pinteraction = 0.60
Effect of Evolocumab on Key Secondary Endpoint

**Patients w/ Diabetes at Baseline**

- **Hazard Ratio 0.82** (95% CI 0.72-0.93)  
  - P=0.0021
- **12.2%**
- **Δ 2.0%**
- **NNT 50**

**Patients w/o Diabetes at Baseline**

- **Hazard Ratio 0.78** (95% CI 0.69-0.89)  
  - P=0.0002
- **8.4%**
- **Δ 2.0%**
- **NNT 50**

**CV Death, MI, Stroke**

- **Evolocumab**
- **Placebo**
- **P_{interaction} = 0.65**
## Individual CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Patients with Diabetes at Baseline</th>
<th>Patients without Diabetes at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EvoMab (N=5515)</td>
<td>Placebo (N=5516)</td>
</tr>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>14.4</td>
<td>17.1</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>10.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>MI</td>
<td>5.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Hosp for Unstable Angina</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.4</td>
<td>10.0</td>
</tr>
</tbody>
</table>
Landmark Analysis in Patients with Diabetes at Baseline

1st Year: 13% RRR
HR 0.87 (95% CI 0.73-1.04)

After 1st Year: 25% RRR
HR 0.75 (95% CI 0.63-0.89)
In all patients w/o diabetes at baseline (1294 incident cases in 16,510 patients):

HR 1.05 (95% CI 0.94-1.17)

In patients w/ prediabetes at baseline (1163 incident cases in 10,338 patients):

HR 1.00 (95% CI 0.89-1.13)
Glycemic Parameters

Values are median (IQR)

**HbA₁c**

**Placebo**

**Fasting Plasma Glucose**

Diabetes at baseline

No diabetes at baseline
Glycemic Parameters in Prediabetes

Values are median (IQR)
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with diabetes</td>
<td>-0.1 (-2.1, 1.6)</td>
<td>-0.1 (-2.0, 1.7)</td>
</tr>
<tr>
<td>Patients without diabetes</td>
<td>0.3 (-1.3, 2.0)</td>
<td>0.3 (-1.3, 2.0)</td>
</tr>
<tr>
<td>Patients with prediabetes</td>
<td>0.2 (-1.4, 2.0)</td>
<td>0.3 (-1.4, 2.0)</td>
</tr>
<tr>
<td>Patients with normoglycemia</td>
<td>0.3 (-1.3, 2.0)</td>
<td>0.3 (-1.3, 2.0)</td>
</tr>
</tbody>
</table>

Bodyweight in kg. Values are median (IQR) of time-weighted average for post-baseline measurements.
Strengths & Limitations

- Largest trial of PCSK9i
- ~3× # of events (CV and new-onset diabetes) than prior studies
- CV events and new-onset DM adjudicated
- Serial glycemia measurements
- Median trial duration 2.2 years
- All patients on background statin therapy
- No glucose tolerance testing
Summary

- Patients w/ diabetes at substantially higher risk of CV events
- Evolocumab efficacious in ASCVD patients w/ & w/o diabetes
  - 57-60% ↓ in LDL-C
  - 18-22% relative risk reductions in CVD/MI/stroke; benefit ↑ over time
  - Given higher baseline risk, larger absolute risk reduction in CV events with evolocumab in patients with diabetes (particularly coronary revasc)
- Evolocumab safe and well-tolerated
  - No increased risk of diabetes, even in patients with prediabetes
  - No worsening of glycemia
Use of evolocumab is particularly clinically efficacious in ASCVD patients with diabetes, and evolocumab does not cause diabetes or worsen glycemia in patients with or without diabetes in the timeframe we studied.
Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Joanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen

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