Triple Trouble: treatment of dyslipidemia with PCSK-9 Inhibitors in patients with diabetes and previous acute coronary syndrome

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The Lower The Better ⇒ Even Lower even better
Reduction of LDL-C below vs above 50 mg/dL reduces CV risk by a further 10%.

Adjusted* HR 0.90 (0.85–0.96)

\[ p=0.002 \]


*Model covariates: age, BMI, sex, race, region, Hx diabetes, current smoker, Hx hypertension, Hx MI, Hx PCI
BMI, body mass index; HR, hazard ratio; Hx, family history of; MI, myocardial infarction; PCI, percutaneous coronary intervention.

ACS patients with:
* Diabetes
* Age > 75y
* Previous CABPG

Risk Indicators
- CHF
- HTN
- Age≥75
- DM
- Prior Stroke
- Prior CABG
- PAD
- eGFR<60
- Current Smoking
“Real Word” Populations with an Unmet Need for LDL-C Lowering

**CURRENT LIPID LOWERING STRATEGIES (Statins±Ezetimibe) Targeting LDL-C**

**UNMET CLINICAL NEEDS**

Emerging therapies → PCSK9 inhibitors

- Safety
- Treat to target
- The lower the better

**Familial Hypercholesterolemia**
- 70% “not at goal”

**Statin-Intolerant Population**
- 100% “not at goal”

**Very High CV Risk Population (>3%/y)**
- 59% “not at goal”
The mode of action are complementary. The effects are additives.

LDL – 130%

(LDL -60%)

(LDL -50%)

(LDL -20%)

(LDL -50%)

(LDL -20%)
### ODYSSEY OUTCOMES & FOURIER Study Designs

<table>
<thead>
<tr>
<th>ALIROCUMAB</th>
<th>ODYSSEY OUTCOMES</th>
<th>FOURIER</th>
<th>EVOLOOCUMAB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>Patients with recent ACS on maximally tolerated statin ± other LLT LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL or apolipoprotein B ≥80 mg/dL 18,000 pts (9000 vs 9000)</td>
<td>27,500 Patients with MI, stroke, or PAD and additional risk factors (1 major or 2 minor) + on optimal background lipid therapy (effective statin dose ± ezetimibe) LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL</td>
<td>Time to Cardiovascular Death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for Unstable Angina or coronary revascularization</td>
</tr>
<tr>
<td><strong>Primary End Point</strong></td>
<td>Time to Coronary Heart Disease death, non-fatal myocardial infarction, ischemic stroke, Unstable Angina requiring hospitalization</td>
<td>Time to Coronary Heart Disease death, non-fatal myocardial infarction, ischemic stroke, Unstable Angina requiring hospitalization</td>
<td>Time to Cardiovascular Death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for Unstable Angina or coronary revascularization</td>
</tr>
<tr>
<td><strong>LDL-C reduction</strong></td>
<td>Treat-to-target approach Patient started on 75Q2W (~50% LDL-C reduction) up-titration to 150Q2W if LDL-C ≥50 mg/dL</td>
<td>Lower-the-better approach with one dose fits all Patients on 140Q2W/420QM ≥60% LDL-C reduction</td>
<td>No down-titration or switch to placebo if low LDL-C level</td>
</tr>
<tr>
<td><strong>Management of Low LDL-C</strong></td>
<td>With down-titration from 150Q2W to 75Q2W if 2 consecutive LDL-C &lt;25mg/dL, or from 75Q2W to placebo if 2 consecutive LDL-C &lt;15 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDL-C</strong></td>
<td>86.5mg/dL (median)</td>
<td>91.5mg/dL (median)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean Exposure to Study Drug and Follow-up</strong></td>
<td>Mean 3 years 2-to-5 years follow-up</td>
<td>Mean 2 years 1-to-3.5 years follow-up</td>
<td></td>
</tr>
</tbody>
</table>
Evolocumab Outcomes Trial: Study Design Overview

**Screening**
- Age 40–85 years
- MI, stroke, or PAD
- Additional risk factors (one major or two minor)
- Optimal background lipid therapy (including effective dose of statin ± ezetimibe)
- LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL

**Evolocumab SC**
- 140 mg Q2W or 420 mg QM
- (per subject preference)
- n ~ 13,750

**Placebo SC**
- Q2W or QM
- (per subject preference)
- n ~ 13,750

**Maximum approximately 15 weeks**
- D1, W4, W12, W24, Q24W

**End of Study (EOS)**

**27,500 Patients**

**1630 events**
- RRR > 15%

**PRIMARY END-POINT:**
- CV Death, MI, Stroke, Hosp. or UA, or Coronary Revascularization

**SECONDARY END-POINT:**
- CV death, MI, Stroke

**CTTC END-POINT:**
- Coronary and Vascular Events

**Legend:**
- D = day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol;
- MI = myocardial infarction; PAD = peripheral artery disease; Q2W = every 2 weeks; Q24W = every 24 weeks; QM = every month; SC = subcutaneous; W = week.

Median LDL-C Levels Over Time: All Patients

LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group.

Data shown are median values with 95% confidence intervals in the two arms; ITT.

Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization

HR 0.85 (95% CI 0.79 to 0.92); P < 0.001

**HR** = Hazard ratio
**CV** = Cardiovascular; **MI** = Myocardial infarction; **UA** = Unstable angina


<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Placebo</th>
<th>Evolocumab</th>
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<tbody>
<tr>
<td>13,780</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13,278</td>
<td>6</td>
<td>6.0</td>
<td>5.3</td>
</tr>
<tr>
<td>12,825</td>
<td>12</td>
<td>10.7</td>
<td>9.1</td>
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<tr>
<td>11,871</td>
<td>18</td>
<td>14.6</td>
<td>12.6</td>
</tr>
<tr>
<td>7,610</td>
<td>24</td>
<td>14.6</td>
<td>12.6</td>
</tr>
<tr>
<td>3,690</td>
<td>30</td>
<td>12.6</td>
<td>12.6</td>
</tr>
<tr>
<td>686</td>
<td>36</td>
<td>9.1</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Key Secondary Endpoint:
Composite of CV Death, MI, or Stroke

CV = Cardiovascular; MI = Myocardial infarction; HR = Hazard ratio
Figure 1. Distribution of achieved LDL-cholesterol concentrations at 4 weeks in patients who did not have a primary efficacy or prespecified safety event before the study.
Red bars are evolocumab (median 0.0 mmol/L, IQR 0.5-1.2). Blue bars are placebo (median 2.2 mmol/L, IQR 1.9-2.7).
Safety

LDL-C (mM) at 0, 5, 10, 15, 20, 25 weeks

LDL-C (mM) at 4 weeks

SAE, AE->Discon, New DM, Cancer, Cataract

Neurocog, AST/ALT↑, CK↑, Non-CV death, Hem stroke
Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] mM = 7 [5-9] mg/dL

**Cardiovascular Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>≥2.6 mM</th>
<th>&lt;0.26 mM</th>
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<tbody>
<tr>
<td>CVD, MI, Stroke, UA, Cor</td>
<td>HR 0.69 (0.49-0.97)</td>
<td>P=0.03</td>
</tr>
<tr>
<td></td>
<td>HR 0.59 (0.37-0.92)</td>
<td>P=0.02</td>
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</tbody>
</table>

**Safety**

<table>
<thead>
<tr>
<th></th>
<th>≥2.6 mM</th>
<th>&lt;0.26 mM</th>
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</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>HR 0.94 (0.74-1.20)</td>
<td>P=0.61</td>
</tr>
<tr>
<td></td>
<td>HR 1.08 (0.63-1.85)</td>
<td>P=0.78</td>
</tr>
<tr>
<td>AE -&gt; drug discontinued</td>
<td>3,4</td>
<td>3,4</td>
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</table>

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017
Primary and secondary composite endpoint results were consistent across all key subgroups

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT: 3-yr KM rate (%)</th>
<th>KEY SECONDARY ENDPOINT: 3-yr KM rate (%)</th>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Evo</td>
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<tr>
<td>OVERALL</td>
<td>27564</td>
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<tr>
<td>Age</td>
<td></td>
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<tr>
<td>&lt;65</td>
<td>15310</td>
</tr>
<tr>
<td>≥65</td>
<td>12254</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6769</td>
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<tr>
<td>Male</td>
<td>20795</td>
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<tr>
<td>Caucasian</td>
<td>23458</td>
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<td>Non-Caucasian</td>
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<td>Region</td>
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<td>Latin America</td>
<td>1823</td>
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<td>Asia/Pacific</td>
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Sabatine MS, et al. *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoia1615664 (Supplementary Figure S5)
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 Deswal, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ileana Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Nariman Ronenpour, Anthony C Keech, Peter S Sever, Terje A Pedersen

1. EFFICACY of Evolocumab in pts with and without Diabetes

   ↓ LDL

2. SAFETY of Evolocumab

   Glycaemia, HbA1c

   New-onset Diabetes
Prediabetes

New-onset Diabetes in Non Diabetes-Group

Kaplan-Meier rate (%)

End of year 1
End of year 2
End of year 3

p=0.32
11.6% 10.9%

p=0.43
4.0% 3.8%

p=0.64
7.3% 7.0%

HbA1c (%)
A Diabetes

- Evolocumab
- Placebo

LDL cholesterol (mmol/L)

Reduction at 48 weeks of 57% (95% CI 56-58); p<0.0001

B No diabetes

LDL cholesterol (mmol/L)

Reduction at 48 weeks of 60% (95% CI 60-61); p<0.0001
Primary End-point

A Diabetes

\[ \text{Evolocumab} \quad \text{Placebo} \]

Cumulative incidence (%)

NNT = 37

HR 0.83 (95% CI 0.75-0.93); p=0.0008
Absolute risk reduction 2.7% (95% CI 0.7-4.8)

Number of patients

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>5191</td>
<td>5184</td>
</tr>
<tr>
<td>5071</td>
<td>5006</td>
</tr>
<tr>
<td>4616</td>
<td>4727</td>
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<td>3048</td>
<td>3020</td>
</tr>
<tr>
<td>1804</td>
<td>1693</td>
</tr>
<tr>
<td>340</td>
<td>335</td>
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</tbody>
</table>

B No diabetes

Cumulative incidence (%)

NNT = 62

HR 0.87 (95% CI 0.79-0.96); p=0.0002
Absolute risk reduction 1.6% (95% CI 0.1-3.2)

Number of patients

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>8264</td>
<td>8269</td>
</tr>
<tr>
<td>7998</td>
<td>8049</td>
</tr>
<tr>
<td>7763</td>
<td>7821</td>
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<tr>
<td>7320</td>
<td>7410</td>
</tr>
<tr>
<td>4817</td>
<td>4974</td>
</tr>
<tr>
<td>2407</td>
<td>2473</td>
</tr>
<tr>
<td>545</td>
<td>577</td>
</tr>
</tbody>
</table>

Key Secondary End-point

CV Death:

- 3.6%
- 3.5%

NNT = 50

CV Death:

- 10.2%
- 12.2%

NNT = 50

CV Death:

- 6.4%
- 8.4%
### CV – Mortality in FOURIER

#### Mean Follow-up: 2.2y

Optimal Medical Therapy

Mortality Low Rate

Event-drive Trial

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<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>More Intensive Rx Arm</th>
<th>Less Intensive Rx Arm</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>2004</td>
<td>27</td>
<td>36</td>
<td>0.74 (0.45-1.22)</td>
</tr>
<tr>
<td>A2Z</td>
<td>2004</td>
<td>86</td>
<td>111</td>
<td>0.76 (0.57-1.01)</td>
</tr>
<tr>
<td>TNT</td>
<td>2005</td>
<td>101</td>
<td>127</td>
<td>0.80 (0.61-1.03)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>2005</td>
<td>223</td>
<td>218</td>
<td>1.03 (0.85-1.24)</td>
</tr>
<tr>
<td>SEARCH</td>
<td>2010</td>
<td>565</td>
<td>572</td>
<td>0.99 (0.88-1.11)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2015</td>
<td>538</td>
<td>537</td>
<td>1.00 (0.89-1.13)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td><strong>1540</strong></td>
<td><strong>1601</strong></td>
<td><strong>0.96 (0.90-1.03)</strong></td>
</tr>
</tbody>
</table>

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Landmark Analyses

First Primary End-Point

A. Diabetes

Evolocumab

Placebo

HR 0.77 (95% CI 0.67-0.89), P=0.0004

B. No diabetes

Evolocumab

Placebo

HR 0.84 (95% CI 0.73-0.97), P=0.0135

Key Secondary End-Point

A. Diabetes

Evolocumab

Placebo

HR 0.75 (95% CI 0.63-0.89), P=0.0012

B. No diabetes

Evolocumab

Placebo

HR 0.75 (95% CI 0.63-0.89), P=0.0017

# of patients
Placebo Evolocumab

365 548 730 913 1095

5388 4823 3084 1442 266

5395 4909 3080 1424 270

5388 4896 3161 1495 279

5395 4965 3143 1465 274

58136 7595 4871 2314 433

8153 7645 4987 2374 437

8136 7668 4961 2381 448

8153 7716 5080 2437 448
Conclusion - 1

• Among patients with previous/recent ACS the presence of diabetes, but not prediabetes, was independently associated with a substantially increased risk of cardiovascular morbidity and mortality, despite statin therapy.

• PCSK9-I lowered LDL cholesterol and significantly reduced cardiovascular risk with similar efficacy in patients with and without diabetes. However, because of their heightened baseline risk of cardiovascular events, patients with diabetes tended to have a greater absolute risk reduction with PCSK9-I treatment.

• Recent guidelines have recommended identifying people with diabetes and established atherosclerotic cardiovascular disease as having an extreme risk requiring more intensive treatment to achieve lower LDL goals (< 55 mg/dl).

• PCSK9-I added to statins are safe, and did not increase the risk of new-onset diabetes, nor did it worsen glycaemia and HbA$_{1c}$.
Conclusion - 2

• The use of PCSK-9 Inhibitors in patients with diabetes and recent or previous ACS might be particularly attractive from a cost-effectiveness standpoint (NNT 60 → 32)

• In patients with recent ACS, CV-event risk > 3%/y and LDL-C > 140 mg/dl a PCSK-9I may be considered

• Risk stratification and individualization of therapy among patients with recent or previous ACS are emerging as growing needs in the context of the increasing number of “intensive” therapies

• The “Risk-Score” strategy offers an opportunity to select candidates with the potential for the greatest absolute gains
Effects of ezetimibe by TRAP 2P risk score in IMPROVE-IT

Bohula EA et al. (2016)

$NNT = 16$

$NNT = 45$