The FOURIER & EBBINGHAUS Trials:
Clinical Efficacy & Safety of Evolocumab in Patients with Cardiovascular Disease

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Brigham and Women’s Hospital
Cardiovascular Grand Rounds
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Disclosures

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) Mutations

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Affected family members with:
- Total chol in 90th percentile
- Tendon xanthomas
- CHD, Early MI
- Stroke

PCSK9 Regulates the Surface Expression of LDL-Rs by Targeting Them for Lysosomal Degradation

**PCSK9 Mutations**

**PCSK9 Gain-of-Function Mutations**
- ↓ hepatic LDL receptors
- ↑ circulating LDL-C
- Familial hypercholesterolemia phenotype

**PCSK9 Loss-of-Function Mutations**
- ↑ hepatic LDL receptors
- ↓ circulating LDL-C
- Protected from CV disease
**PCSK9 Loss-of-Function Mutations:**
Effect of Lifelong Low LDL-C on CHD

# Impact of PCSK9 Loss of Function Mutation on Risk of MI

Lifelong Impact of 16% Lower LDL translates into 60% Lower Risk

<table>
<thead>
<tr>
<th>Site</th>
<th>Study</th>
<th>OR for MI</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>FINRISK</td>
<td></td>
<td>0.30 (0.11, 0.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sweden</td>
<td>Malmo Diet and Cancer Study CV cohorts</td>
<td></td>
<td>0.32 (0.07, 1.61)</td>
<td>0.17</td>
</tr>
<tr>
<td>Spain</td>
<td>Registre Gironi del Cor (REGICOR)</td>
<td></td>
<td>0.35 (0.15, 0.82)</td>
<td>0.02</td>
</tr>
<tr>
<td>Seattle</td>
<td>Heart Attack Risk in Puget Sound</td>
<td></td>
<td>0.45 (0.21, 0.98)</td>
<td>0.049</td>
</tr>
<tr>
<td>Boston</td>
<td>MGH Premature CAD Study</td>
<td></td>
<td>0.59 (0.21, 1.69)</td>
<td>0.46</td>
</tr>
<tr>
<td>Combined analysis</td>
<td></td>
<td></td>
<td>0.40 (0.26, 0.61)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

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Two Healthy Individuals w/ Inactivating Mutations in Both PCSK9 Alleles

<table>
<thead>
<tr>
<th>PCSK9 Genotype</th>
<th>PCSK9&lt;sup&gt;Y142X/ΔR97&lt;/sup&gt;</th>
<th>PCSK9&lt;sup&gt;C679X/C679X&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>96 mg/dL (2.5 mmol/L)</td>
<td>85 mg/dL (2.2 mmol/L)</td>
</tr>
<tr>
<td>LDL</td>
<td>14 mg/dL (0.4 mmol/L)</td>
<td>15 mg/dL (0.4 mmol/L)</td>
</tr>
<tr>
<td>TG</td>
<td>119 mg/dL (1.3 mmol/L)</td>
<td>71 mg/dL (0.8 mmol/L)</td>
</tr>
<tr>
<td>HDL</td>
<td>65 mg/dL (1.7 mmol/L)</td>
<td>54 mg/dL (1.4 mmol/L)</td>
</tr>
<tr>
<td>Plasma [PCSK9]</td>
<td>Undetectable</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical</td>
<td>• Apparent good health</td>
<td>• Apparent good health</td>
</tr>
<tr>
<td></td>
<td>• Normal fertility (mother)</td>
<td>• Normal fertility (mother)</td>
</tr>
<tr>
<td></td>
<td>• No developmental abnl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• College graduate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Aerobics instructor</td>
<td></td>
</tr>
</tbody>
</table>

Hooper AJ et al.. *Atherosclerosis*. 2007;193:445-8
PCSK9 Inhibition with a Monoclonal Antibody

Benefit of Statins & Estab Non-Statin Rx that Work via LDL-C Receptor Upregulation

25 Statin Trials
177,088 patients
20,962 major vascular events

RRR per 1 mmol/L reduction in LDL-C:
23% (95% CI 16-29%)
P<0.001

8 Trials of Diet, Resins, Ileal Bypass, or Ezetimibe
26,969 patients
6,480 major vascular events

RRR per 1 mmol/L reduction in LDL-C:
25% (95% CI 16-29%)
P<0.001

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Silverman MG et al. & Sabatine MS. JAMA 2016;316:1289
Mendelian Randomization in *PCSK9* and *HMGCR*

- 112,772 participants from 14 studies
- 14,120 major cardiovascular events
- 7 variants in *PCSK9*
- 6 variants in *HMGCR*

![Graph showing standardized difference in LDL cholesterol and odds ratio for myocardial infarction or death from CHD per decrease in LDL cholesterol of 10 mg/dl.](image)

<table>
<thead>
<tr>
<th></th>
<th>Standardized Difference in LDL Cholesterol</th>
<th>Odds Ratio for Myocardial Infarction or Death from CHD (95% CI) per Decrease in LDL Cholesterol of 10 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSK9 genetic score</td>
<td>-10.0</td>
<td>0.81 (0.74–0.89)</td>
</tr>
<tr>
<td>HMGCR genetic score</td>
<td>-10.0</td>
<td>0.81 (0.72–0.90)</td>
</tr>
</tbody>
</table>

Ference BA et al. & Sabatine MS. *NEJM* 2016;375:2144-53
Study Design

78 centers
5 countries

Screening and Placebo Run-in Period

Subcutaneous injection of 6 mL placebo

Fasting LDL-C 5-10 days before randomization

Maximum 6 weeks

Randomization (n=631)

70 mg AMG 145 SC Q2W
78 Subjects

105 mg AMG 145 SC Q2W
79 Subjects

140 mg AMG 145 SC Q2W
78 Subjects

Placebo SC Q2W
78 Subjects

Placebo SC Q4W
77 Subjects

280 mg AMG 145 SC Q4W
79 Subjects

350 mg AMG 145 SC Q4W
79 Subjects

420 mg AMG 145 SC Q4W
80 Subjects

934 screened → 631 random. → 629 treated

( *2 subjects assigned placebo Q4W received no study drug)

End of Study: 4 weeks after last dose

Optional Enrollment in Extension Study

Visits: Day 1 Week 2 Week 4 Week 6 Week 8 Week 10 Week 12 Week 14

Q2W:

Q4W:

Primary Endpoint:
AMG 145 Reduced LDL-C at 12 wks

- AMG 145 Reduced LDL-Cat 12 wks
- LDL-C measured using ultracentrifugation

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>AMG 145 Q2W</th>
<th>AMG 145 Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>140</td>
<td>N = 79</td>
<td>N = 78</td>
</tr>
<tr>
<td>280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>420</td>
<td>N = 80</td>
<td></td>
</tr>
</tbody>
</table>

- * p < 0.0001 for each dose vs placebo

<table>
<thead>
<tr>
<th>LDL-C at 12 wks</th>
<th>Mean (mg/dL)</th>
<th>(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>26</td>
</tr>
</tbody>
</table>

% Reduction in LDL with Top 2 AMG 145 Doses: Major Subgroups

140 mg Q2W dose of AMG 145 reduced LDL at 12 weeks ranging from 56-74% in key subgroups

-66% (-71, -61)

Baseline Characteristics

All patients

Men

Women

Age < 65 Years
Age ≥ 65 Years
BMI < 25 Kg/M2
BMI 25-30 Kg/M2
BMI ≥ 30 Kg/M2

Baseline UC LDL-C < 100 mg/dL
Baseline UC LDL-C 100-130 mg/dL
Baseline UC LDL-C ≥ 130 mg/dL

Baseline PCSK9 < median
Baseline PCSK9 ≥ median

Intensive statin regimen
Non-intensive statin regimen

Concomitant ezetimibe
No concomitant ezetimibe

420 mg Q4W dose of AMG 145 reduced LDL at 12 weeks ranging from 38-57% in key subgroups

-50% (-56, -45)

UC = Ultra centrifugation

Reduction in Lp(a)

**Mean % Change in Lp(a) at Week 12 Compared to Placebo**

**AMG 145 Q2W**
- 70mg (n=75): -18
- 105mg (n=76): -32.1
- 140mg (n=73): -32.3

**AMG 145 Q4W**
- 280mg (n=78): -18.2
- 350mg (n=79): -22.8
- 420mg (n=77): -23.1

*P<0.001 for each dose v. placebo*

**Achieved Lp(a) at week 12, nmol/L, median (IQR)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Lp(a)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>19.2</td>
<td>(9-116)</td>
</tr>
<tr>
<td>70mg</td>
<td>30.0</td>
<td>(9-116)</td>
</tr>
<tr>
<td>105mg</td>
<td>27.0</td>
<td>(7-148)</td>
</tr>
<tr>
<td>140mg</td>
<td>29.0</td>
<td>(7-97)</td>
</tr>
<tr>
<td>280mg</td>
<td>21.5</td>
<td>(7-125)</td>
</tr>
<tr>
<td>350mg</td>
<td>17.0</td>
<td>(7-155)</td>
</tr>
<tr>
<td>420mg</td>
<td>40.0</td>
<td>(9-167)</td>
</tr>
</tbody>
</table>

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Durability of LDL-C Reduction

[Graph showing median change in LDL-C level from baseline with different study phases and risk numbers]

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JAMA Cardiology 2017;epub ahead of print
GLAGOV

968 high risk patients with symptomatic CAD and 20-50% stenosis by invasive coronary angiography in a “target vessel”

Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features

Intravascular ultrasound at baseline

Statin Monotherapy (n=484) 18 months treatment Statin plus evolocumab 420 mg QM (n=484)

423 statin completers 423 evolocumab completers

Follow-up IVUS of originally imaged “target” vessel (n=846)
Percent Change in LDL-C During Treatment

- **Mean LDL-C 93.0 mg/dL**
  - Change from baseline 3.9%
- **Mean LDL-C 36.6 mg/dL**
  - Change from baseline -59.8%

**Study Week**

LDL-C Percentage Change from Baseline (%)
Primary Endpoint: Percent Atheroma Volume

Change in Percent Atheroma Volume (%)

-0.12
-0.1
-0.08
-0.06
-0.04
-0.02
0
0.02
0.04
0.06
0.08
0.1
0.12

Statin monotherapy
Statin-evolocumab

P = NS
P < 0.0001

P < 0.001

0.05

-0.95

JAMA 2016;316:2373-84
Mean On-Treatment LDL-C vs. Change in PAV

Locally Weighted Polynomial Regression (LOESS) Plot with 95% confidence limits

On-Treatment LDL-C (mg/dL)

Change Percent Atheroma Volume (%)

JAMA 2016;316:2373-84
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)

\[
\text{LDL-C} \geq 70 \text{ mg/dL or non-HDL-C} \geq 100 \text{ mg/dL}
\]

Randomized Double Blind

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

Endpoints

• **Efficacy**
  – Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc
  – Key secondary: CV death, MI or stroke

• **Safety**
  – AEs/SAEs
  – Events of interest incl. muscle-related, new-onset diabetes, neurocognitive
  – Development of anti-evolocumab Ab (binding and neutralizing)

• **TIMI Clinical Events Committee (CEC)**
  – Adjudicated all efficacy endpoints & new-onset diabetes
  – Members unaware of treatment assignment & lipid levels
Follow-up

Randomized 27,564 patients

Evolocumab (N=13,784)

Placebo (N=13,780)

Follow-up median 26 months (IQR 22-30)

2907 patients experienced primary endpoint
1829 experienced key secondary endpoint

Premature perm. drug discontinuation

5.6%/yr 5.8%/yr

Withdrew consent

0.29%/yr 0.35%/yr

Lost to follow-up

5 patients 13 patients

Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up
## Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>75</td>
</tr>
<tr>
<td>White race (%)</td>
<td>85</td>
</tr>
<tr>
<td>Region (%)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>17</td>
</tr>
<tr>
<td>Europe</td>
<td>63</td>
</tr>
<tr>
<td>Latin America</td>
<td>7</td>
</tr>
<tr>
<td>Asia Pacific &amp; South Africa</td>
<td>14</td>
</tr>
</tbody>
</table>

Pooled data; no clinically meaningful differences between treatment arms

Sabatine MS et al. *NEJM* 2017;epub ahead of print
## Baseline CV Disease

### Characteristic

<table>
<thead>
<tr>
<th>Type of cardiovascular disease</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction (%)</td>
<td>81</td>
</tr>
<tr>
<td>Median time from MI – y (IQR)</td>
<td>3.3 (1.0-7.5)</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic) (%)</td>
<td>19</td>
</tr>
<tr>
<td>Median time from stroke – y (IQR)</td>
<td>3.3 (1.1-7.2)</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
</tbody>
</table>

### Cardiovascular risk factor (%)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>28</td>
</tr>
</tbody>
</table>

Pooled data; no clinically meaningful differences between treatment arms

Sabatine MS et al. *NEJM* 2017;epub ahead of print
## Baseline CV Meds

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA and/or P2Y$_{12}$ Inhibitor (%)</td>
<td>92</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>76</td>
</tr>
<tr>
<td>ACE inhibitor or ARB and/or aldosterone antagonist (%)</td>
<td>78</td>
</tr>
</tbody>
</table>

Pooled data; no clinically meaningful differences between treatment arms

Sabatine MS et al. *NEJM* 2017; epub ahead of print
# Lipid Lowering Therapy & Lipid Levels at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statin use (%)</strong>*</td>
<td></td>
</tr>
<tr>
<td>High-intensity</td>
<td>69</td>
</tr>
<tr>
<td>Moderate-intensity</td>
<td>30</td>
</tr>
<tr>
<td><strong>Ezetimibe use (%)</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Median lipid measures (IQR) – mg/dL</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>92 (80-109)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>168 (151-189)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (37-53)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>133 (100-182)</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 clinically meaningful differences between treatment arms

Sabatine MS et al. *NEJM* 2017;epub ahead of print
LDL Cholesterol

**Placebo**

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

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

**Evolocumab**

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

Sabatine MS et al. *NEJM* 2017;epub ahead of print
Primary Endpoint

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

Placebo

Evolocumab

Sabatine MS et al. NEJM 2017;epub ahead of print
Key Secondary Endpoint

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

CV Death, MI, or Stroke

Placebo

Evolocumab

Sabatine MS et al. NEJM 2017;epub ahead of print
### Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-yr Kaplan-Meier rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Death due to acute MI</td>
<td>0.26</td>
<td>0.32</td>
<td>0.84 (0.49-1.42)</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>0.29</td>
<td>0.30</td>
<td>0.94 (0.58-1.54)</td>
</tr>
<tr>
<td>Other CV death</td>
<td>1.9</td>
<td>1.8</td>
<td>1.10 (0.90-1.35)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
</tbody>
</table>

Sabatine MS et al. *NEJM* 2017;epub ahead of print
Benefit on mortality was not apparent early, even in trials in which it was the primary endpoint.

4S

LIPID

Lancet 1994;344:1383-89
NEJM 1998;339:1349-57
More Intensive LDL-C Lowering & CV Death

No clear benefit on CV mortality

<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>1540</td>
<td>1601</td>
<td>0.96 (0.90-1.03)</td>
</tr>
</tbody>
</table>

*NEJM* 2004;350:1495-504  
*JAMA* 2004;292:1307-16  
*NEJM* 2005;352:1425-35  
*JAMA* 2005;294:2437-45  
*Lancet* 2010;376:1658-69  
*NEJM* 2015;372:2387-97
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-yr Kaplan-Meier rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Hosp for unstable angina</td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.0</td>
<td>9.2</td>
<td>0.78 (0.71-0.86)</td>
</tr>
<tr>
<td>Urgent</td>
<td>3.7</td>
<td>5.4</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Elective</td>
<td>3.9</td>
<td>4.6</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.8</td>
<td>4.3</td>
<td>1.04 (0.91-1.19)</td>
</tr>
</tbody>
</table>

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Sabatine MS et al. *NEJM* 2017;epub ahead of print
### Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>1° Endpoint HR (95% CI)</th>
<th>Key 2° Endpoint HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>27564</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI alone</td>
<td>19113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke alone</td>
<td>3366</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD alone</td>
<td>1505</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyvascular disease</td>
<td>3563</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDL-C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;80 mg/dl)</td>
<td>6961</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (80-&lt;92 mg/dl)</td>
<td>6886</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 (92-109 mg/dl)</td>
<td>6887</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 (&gt;109 mg/dl)</td>
<td>6829</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline statin intensity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not high</td>
<td>8461</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ezetimibe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1440</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26124</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Dosing Regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 2 weeks</td>
<td>24774</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>2790</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm

P<0.0001
Timing of Benefit of LDL-C Lowering

Data from CTTC Meta-Analysis of Statin Trials

<table>
<thead>
<tr>
<th>Total number of MVEs</th>
<th>Annual event rate in control arm (% per year)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>3.8</td>
<td>0.91 (0.85–0.97)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>3.4</td>
<td>0.78 (0.73–0.85)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>3.6</td>
<td>0.76 (0.70–0.82)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>3.6</td>
<td>0.72 (0.66–0.79)</td>
</tr>
<tr>
<td>4-5 years</td>
<td>3.7</td>
<td>0.78 (0.71–0.87)</td>
</tr>
<tr>
<td>≥5 years</td>
<td>3.9</td>
<td>0.76 (0.65–0.87)</td>
</tr>
<tr>
<td>All years</td>
<td>3.6</td>
<td>0.80 (0.78–0.82)</td>
</tr>
<tr>
<td>Years 1–≥5</td>
<td>3.6</td>
<td>0.76 (0.74–0.79)</td>
</tr>
</tbody>
</table>

Landmark Analysis

16% RRR
HR 0.84 (95% CI 0.74-0.96)
P = 0.008

25% RRR
HR 0.75 (95% CI 0.66-0.85)
P < 0.00001

Placebo
Evolocumab

CV Death, MI, Stroke

0% 2% 4% 6% 8%
0 3 6 9 12 12 18 24 30 36

Months from Randomization

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Sabatine MS et al. NEJM 2017;epub ahead of print
Fatal or Nonfatal MI or Stroke

- **19% RRR**
  - HR 0.81 (95% CI 0.70-0.93)
  - P = 0.003

- **33% RRR**
  - HR 0.67 (95% CI 0.59-0.77)
  - P < 0.00001

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Sabatine MS et al. NEJM 2017; epub ahead of print
Comparison to Cholesterol
Treatment Trialists Collaboration

Hazard Ratio (95% CI) per 1 mmol/L reduction in LDL-C

- **Major Coronary Events**
  - CTTC Meta-analysis Year 2: 0.78 (0.70-0.86)
  - FOURIER Year 2: 0.80 (0.71-0.90)

- **Stroke**
  - CTTC Meta-analysis Year 2: 0.77 (0.66-0.91)
  - FOURIER Year 2: 0.77 (0.63-0.94)

- **Coronary revascularization**
  - Urgent: 0.75 (0.67-0.84)
  - Elective: 0.84 (0.73-0.98)

- **Major Vascular Events**
  - 0.77 (0.73-0.82)
  - 0.83 (0.76-0.90)

CTTC data from *Lancet* 2010;376:1670-81
Relative Risk Reduction per mmol/L \( \downarrow \) LDL-C as a Function of Time

Observed Overall RRR (95% CI) with Statins in CTTC Meta-analysis (median duration of follow-up 5 yrs)

CTTC Estimated RRR over Time

FOURIER Estimated RRR over Time

Major vascular events for CTTC and coronary heart death, MI or stroke for FOURIER. Estimates based on year 1 RRR and then application of year 2 RRR going forward. 

*Lancet* 2016;388:2532-61; *NEJM* 2017;epub ahead of print

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# Absolute Risk Reductions

*In stable secondary prevention setting*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Absolute ↓ in MACE</th>
<th>Follow-up</th>
<th>NNT over 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE</td>
<td>Statin vs. placebo in Pts w/ avg LDL-C</td>
<td>3.0-4.2%</td>
<td>5.0 yrs</td>
<td>24-34</td>
</tr>
<tr>
<td>LIPID</td>
<td>Statin vs. placebo in Pts w/ avg LDL-C</td>
<td>3.6-4.4%</td>
<td>6.1 yrs</td>
<td>28-34</td>
</tr>
<tr>
<td>TNT</td>
<td>High vs. moderate intensity statin Rx</td>
<td>2.2%</td>
<td>4.9 yrs</td>
<td>45</td>
</tr>
<tr>
<td>FOURIER</td>
<td>PCSK9i vs. placebo in Pts on statin Rx</td>
<td>2.0%</td>
<td>3.0 yrs</td>
<td>25-30</td>
</tr>
</tbody>
</table>

MACE defined as composite of coronary or CV death, MI or stroke.
Range provided when trials did not report triple composite.
For FOURIER, lower range of NNT based on extrapolating RRR for MACE beyond first year to subsequent years.

<table>
<thead>
<tr>
<th>Adverse events (%)</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory results (%)</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding Ab</td>
<td>0.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Neutralizing Ab</td>
<td><em>none</em></td>
<td>n/a</td>
</tr>
<tr>
<td>Adverse events (%)</td>
<td>Evolocumab (N=13,769)</td>
<td>Placebo (N=13,756)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes (new-onset)</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Laboratory results (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotransferase &gt;3× ULN</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Creatine kinase &gt;5× ULN</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC.

Sabatine MS et al. *NEJM* 2017; epub ahead of print
Cognition and Statins

– Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits

– In 2012 FDA added risk of adverse cognitive effects to label of all statins

– However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects.

*The National Lipid Association
Brain synthesizes cholesterol locally

mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

EBBINGHAUS Trial Design

**RANDOMIZED DOUBLE BLIND**

**Placebo SC Q2W or QM**

**Evolocumab SC 140 mg Q2W or 420 mg QM**

2442 patients screened for EBBINGHAUS

1974 Enrolled (Full Analysis Pop)
Median F/U 19.8 months

Primary Analysis Cohort (N=1204)
Baseline cognitive testing on/before 1st dose of study drug and had f/u cognitive testing post dosing*

Additional 770 pts w/ baseline assessment before week 12 visit

**MAJOR EXCLUSIONS**
1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study

Endpoints

1. Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform. Assessed at baseline, 6, 12, 24, 48 mos and study end.
   – Primary: Spatial working memory strategy index of executive function
   – Secondary: Spatial working memory between errors
     Paired associates learning
     Reaction time
   – Exploratory: Global score (combines above 4 tests)

2. Patient survey of everyday cognition* at study end

3. Investigator report of cognitive AEs

*Memory and executive function domains

Owen 1990 PMID: 2267054; Sahakian 1988, PMID: 3382917; Owen 1996 PMID: 8714706; Kollins PMID: 21476931
CANTAB - Spatial Working Memory (SWM)

- Search for the blue token hidden within a red box
- Number of red boxes increases each round (3, 4, 6, 8).
- Critical instruction: *Do not return to a box where a blue token was found.*

SWM strategy index: = # inefficient searches started. Range 4-28.

Lower scores represent better performance.
Primary Endpoint
Spatial Working Memory Strategy Index

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Treatment Difference in Z score (Placebo minus Evolocumab)
Favors Evolocumab  Favors Placebo

\[ P_{\text{non-inferiority}} < 0.001 \]

Non-inferiority boundary 0.19

Raw Scores
Baseline  Post baseline  Change
Placebo   Evolocumab
17.8 17.8  17.6 17.5

Mean Number of boxes

-5  0  5  10  15  20  25

P_{NI} is from fixed estimate
## Secondary Endpoints

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Task description</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial Working Memory Between Errors Score</td>
<td>Find the hidden blue token (3-card Monty)</td>
<td># times a box is revisited in which a blue token had already been found</td>
</tr>
<tr>
<td>Paired Associates Learning</td>
<td>Memory matching game (Concentration)</td>
<td># times errors made in finding a match</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>Touch yellow dot quickly after it appears on screen</td>
<td>Time in milliseconds until dot touched</td>
</tr>
</tbody>
</table>

Lower scores (fewer errors, faster time) are better
Secondary Endpoint Results

Spatial Working Memory Between Errors Score

- **Placebo**: Baseline 21.0, Post baseline 20.9
- **Evolocumab**: Baseline 20.1, Post baseline 20.3

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21.0</td>
<td>20.1</td>
</tr>
<tr>
<td>Post baseline</td>
<td>20.9</td>
<td>20.3</td>
</tr>
</tbody>
</table>

**Trt diff of Δ in Z-scores**

- Placebo: 0.033
- Evolocumab: 0.36

Paired Associates Learning

- **Placebo**: Baseline 25.2, Post baseline 26.5
- **Evolocumab**: Baseline 23.6, Post baseline 24.9

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>25.2</td>
<td>23.6</td>
</tr>
<tr>
<td>Post baseline</td>
<td>26.5</td>
<td>24.9</td>
</tr>
</tbody>
</table>

**Trt diff of Δ in Z-scores**

- Placebo: 0.023
- Evolocumab: 0.49

Median 5-Choice Reaction Time

- **Placebo**: Baseline 355, Post baseline 357
- **Evolocumab**: Baseline 356, Post baseline 362

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>355</td>
<td>356</td>
</tr>
<tr>
<td>Post baseline</td>
<td>357</td>
<td>362</td>
</tr>
</tbody>
</table>

**Trt diff of Δ in Z-scores**

- Placebo: 0.073
- Evolocumab: 0.06

Lower raw scores (fewer errors, faster time) are better
Cognitive Assessments by Nadir
Achieved LDL-C and Treatment (Full Pop)

Primary CANTAB Endpoint*: Average Change from Baseline

- Mean Δ of boxes
  - Placebo
  - Evolocumab
  - # pts 0 661 13 206 969 115
  - LDL values achieved:
    - <25 mg/dL
    - <0.65 mM/L
    - ≥ 40 mg/dL
    - ≥1.03 mM/L

P=NS across LDL values achieved and also between treatments

Composite Global Score: Average Change from Baseline

- Mean Δ -Z score
  - Placebo
  - Evolocumab
  - LDL values achieved:
    - <25 mg/dL
    - <0.65 mM/L
    - ≥ 25-39 mg/dL
    - 0.65-1.0 mM/L
    - ≥ 40 mg/dL
    - ≥1.03 mM/L

Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score
## Patient Self-Report: 23 Questions Regarding Everyday Cognition

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Placebo (N=781) Mean (SD)</th>
<th>Evolocumab (N=800) Mean (SD)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td>1.16 (0.39)</td>
<td>1.17 (0.39)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Executive functioning total score</strong></td>
<td>1.11 (0.32)</td>
<td>1.12 (0.32)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Planning</strong></td>
<td>1.08 (0.31)</td>
<td>1.10 (0.32)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Organization</strong></td>
<td>1.09 (0.32)</td>
<td>1.10 (0.33)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Divided attention</strong></td>
<td>1.15 (0.42)</td>
<td>1.16 (0.41)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>1.13 (0.33)</strong></td>
<td><strong>1.14 (0.33)</strong></td>
<td><strong>0.42</strong></td>
</tr>
</tbody>
</table>

Patient self-report at end of study as compared to randomization, graded as:

1. Better or no change
2. Questionable / occasionally worse
3. Consistently a little worse
4. Consistently much worse

Lower scores represent better cognition

Results shown are in the full study population

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Neurocognitive Summary

In patients with known cardiovascular disease on background statin followed for 20 months

1. No differences btw evolocumab vs placebo
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL
Summary for Evolocumab

• ↓ LDL-C by 59%
  – Consistent throughout duration of trial
  – Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)

• ↓ CV outcomes in patients already on statin therapy
  – 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  – Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  – 25% reduction in CV death, MI, or stroke after 1\textsuperscript{st} year
  – Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

• Safe and well-tolerated
  – Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  – Rates of EvoMab discontinuation low and no greater than pbo
  – No neutralizing antibodies developed
A Quarter of a Century of Treating LDL-C

High is bad
Average is not good
Lower is better
Even lower is even better
Lowest is best

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Optimal Physiologic LDL-C?

A Receptor-Mediated Pathway for Cholesterol Homeostasis

Michael S. Brown and Joseph L. Goldstein

The LDL-receptor studies lend experimental support to the epidemiologists’ suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (9). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (28). In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (118). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16) (119). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25 to 60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings.

Lower Risk of Cardiovascular Events via Multiple Genetic Variants Affecting LDL-C

9 polymorphisms from 6 different genes affecting LDL-C levels in 312,321 subjects

CHD risk reduction per 1 mmol/L (38.7 mg/dL) lower LDL-C:
54.5% (95% CI: 48.8-59.5%)

Ference BA et al. JACC 2012;60:2631–9
Effect of Lifelong Lower LDL-C & SBP

- 102,773 individuals
- LDL-C genetic score: 46 snps
- SBP genetic score: 33 snps
- 14,368 Major Vascular Events

**OR_{MVE}: 0.139 (0.114-0.170)**
per 1.0 mmol/l lower LDL-C & 10 mmHg lower SBP

**OR_{MVE}: 0.542 (0.509-0.577)**
per 0.31 mmol/l lower LDL-C & 3.1 mmHg lower SBP
Conclusions

1. PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy

2. The achieved benefit further validates the LDL-C hypothesis, now down to 20-25 mg/dL

3. We should strive to achieve very low levels of LDL-C early in individuals to maximize cardiovascular benefit

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