EVOlocumab for early reduction of LDL-cholesterol levels in Patients with Acute Coronary Syndromes (EVOPACS)

A randomized, double-blind, placebo-controlled multicenter study

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Declaration of interest

- Others (Honoraria: Amgen, Sanofi)
Background

- LDL-C lowering by means of **high-intensity statins** results in **early** (within 30 days) **clinical benefit** when administered in the **acute phase** of ACS.

![Graph showing comparison of Pravastatin 40 mg and Atorvastatin 80 mg on the outcome of patients with death, MI, or rehospitalization for ACS. The graph shows a significant reduction in events with Atorvastatin compared to Pravastatin.](image)


<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contraindication or history of intolerance, regardless of initial LDL-C values.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

ESC/EAS Dyslipidemia Guidelines
Background

- PCSK9 antibodies result in rapid, profound LDL-C reduction in patient populations without atherosclerotic cardiovascular disease or with stable / stabilized CAD

- LDL-C reduction with PCSK9 antibodies has not been tested in the acute setting of ACS, a clinical setting with highest risk of early event recurrence

- Against a background of pleiotropic effects of statins and non-statin agents (ezetimibe) on inflammatory biomarkers, platelet reactivity, and prevention of contrast-induced acute kidney injury, it remains largely unknown whether PCSK9 antibodies share similar beneficial effects
Background

Timing of patient enrolment after ACS in previous PCSK9-inhibitor trials

ACS → Stabilized CAD

INDEX EVENT

Time after index event (yrs)

1 2 3 4 5 6 7 8

ODYSSEY OUTCOMES
2.6 (1.7-4.4) months
post ACS

FOURIER
3.4 (1-7.4) years
post MI
PCSK9 inhibition with evolocumab, administered in the **early phase of ACS**, is well tolerated and results in greater reduction of LDL-C levels at 8 weeks compared with placebo in patients receiving high-intensity statin treatment.
Study Organisation

Sponsor
Inselspital Bern, Switzerland

Study Chair
Prof. Stephan Windecker

Primary Investigator
Dr. Konstantinos Koskinas

Co-Primary Investigators
Prof. Francois Mach, Prof. Lorenz Räber

Data Management, Monitoring and Statistics
Clinical Trials Unit, Bern

Data and Safety Monitoring Board
Prof. M. Wilhelm, Dr. D. Carballo, Dr. R. Nkoulou

Clinical Event Committee
Dr. S. Stortecky, Dr. R. Piccolo, Dr. A. Franzone, Dr. G. Stefanini, Dr. J. Lanz, Dr. F. D. Lopes

STUDY CENTERS
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Dr. K. Koskinas, Prof. S. Windecker

Geneva University Hospital, Switzerland
Prof. F. Mach

Cardiocentro Lugano, Switzerland
Prof. G. Pedrazzini

Basel University Hospital, Switzerland
Prof. C. Mueller

Fribourg University Hospital, Switzerland
Prof. S. Cook

Zurich University Hospital, Switzerland
Prof. C. Matter

Lausanne University Hospital, Switzerland
Prof. O. Muller

Funding: Investigator-initiated study supported by funds provided by Amgen
Study Endpoints

- **Primary EP**: % Change in LDL-C from baseline to 8 weeks
- **Secondary EP**: Safety and tolerability
- **Exploratory EPs**:
  - hs-CRP and other inflammatory biomarkers
  - Platelet reactivity
  - Contrast-induced acute kidney injury
  - Post-PCI myocardial injury
LDL-C at screening:
- > 1.8 mmol/L on high-intensity statin
- > 2.3 mmol/L on low-/moderate-intensity statin
- > 3.2 mmol/L on no statin

Study Design

Evolocumab SC 420mg + Atorvastatin 40mg QD

Placebo SC + Atorvastatin 40mg QD

Patients with ACS
STEMI <24h
NSTE-ACS <72h

Randomization 1:1

Baseline

Week 4

Week 8

72h (48-96)

Fasting lipids

Inflammation

Troponin
eGFR

Fasting lipids

Inflammation

Platelet function

Troponin
eGFR

Fasting lipids

Inflammation

Platelet function

Primary EP

Exploratory EPs

Trial registration: clinicaltrials.gov; NCT03287609

Week-8 visit: 293 / 308 pts (95.1%)

- Study powered for the primary EP
- Estimated attrition rate: 10%

Flowchart

308 pts randomized

155 evolcumab
- 2 pts died
  - Clinical visit: 135 pts
  - 155 included in efficacy and safety analyses
    - 132 analyzed for primary EP

153 placebo
  - Clinical visit: 146 pts
  - 1 pt withdrew consent
    - Clinical visit: 151 pts
    - 152 included in efficacy and safety analyses
      - 145 analyzed for primary EP
### Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab  n=155</th>
<th>Placebo  n=153</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>60.5 ± 12.0</td>
<td>61.0 ± 10.7</td>
</tr>
<tr>
<td><strong>Male gender, n (%)</strong></td>
<td>128 (83)</td>
<td>123 (80)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, n (%)</strong></td>
<td>23 (15)</td>
<td>24 (16)</td>
</tr>
<tr>
<td><strong>Arterial hypertension, n (%)</strong></td>
<td>79 (51)</td>
<td>85 (56)</td>
</tr>
<tr>
<td><strong>Active smoking, n (%)</strong></td>
<td>64 (41)</td>
<td>46 (30)</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction, n (%)</strong></td>
<td>24 (15)</td>
<td>19 (12)</td>
</tr>
<tr>
<td><strong>Previous PCI, n (%)</strong></td>
<td>25 (16)</td>
<td>23 (15)</td>
</tr>
<tr>
<td><strong>Previous CABG, n (%)</strong></td>
<td>5 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td><strong>Peripheral arterial disease, n (%)</strong></td>
<td>4 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td><strong>History of stroke / TIA, n (%)</strong></td>
<td>7 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Results: Index ACS event

Index ACS event

STEMI
37%

NSTE-ACS
63%

Time between symptoms onset and study enrolment

<table>
<thead>
<tr>
<th>&lt;24h</th>
<th>24-72h</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&lt;24h</th>
<th>24-72h</th>
</tr>
</thead>
<tbody>
<tr>
<td>39%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Treatment of index ACS event

PCI
84%

Medical therapy
9%

CABG
7%
Results: Statin Treatment at Baseline

Statin treatment prior to study enrolment

- No statin: 78.2%
- Low-/moderate-intensity statin**: 11.4%
- High-intensity statin*: 10.4%

Mean LDL-C at baseline
- 3.7 mmol/L
- 2.9 mmol/L
- 2.3 mmol/L

*High-intensity: atorvastatin $\geq 40$mg; rosuvastatin $\geq 20$mg; simvastatin 80mg

**Low-/moderate-intensity: all other statin regimens
Primary endpoint: % Change in LDL-C at 8 wks

-35.4% vs. baseline
-77.1% vs. baseline

Baseline: 3.61 mmol/L (139 mg/dL)
Week 4: 0.79 mmol/L (31 mg/dL)
Week 8: 0.79 mmol/L (31 mg/dL)

* Least-squares means.

Evolocumab group:
- Baseline: 0.79 mmol/L (31 mg/dL)
- Week 4: 0.79 mmol/L (31 mg/dL)
- Week 8: 0.79 mmol/L (31 mg/dL)

Placebo group:
- Baseline: 3.42 mmol/L (132 mg/dL)
- Week 4: 2.00 mmol/L (77 mg/dL)
- Week 8: 2.06 mmol/L (80 mg/dL)

No of pts
Placebo 148
Evolocumab 146
Achievement of LDL-C Treatment Targets

LDL-C target $<1.8$ mmol/L ($<70$ mg/dL)

- **Evolocumab**: 95.7%
- **Placebo**: 37.6%

LDL-C target $<1.4$ mmol/L ($<55$ mg/dL)

- **Evolocumab**: 90.1%
- **Placebo**: 10.7%

ESC/EAS 2019 Dyslipidemia Guidelines
# Primary EP: Key Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab mean ± sd</th>
<th>Placebo mean ± sd</th>
<th>Calculated LDL-C Mean difference (95% CI)</th>
<th>interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>-77.07 ± 15.78 [132]</td>
<td>-35.38 ± 26.61 [145]</td>
<td>-80 - 60 -40 -20</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Statin at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>-63.89 ± 24.83 [26]</td>
<td>-8.05 ± 30.81 [34]</td>
<td></td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>no</td>
<td>-80.30 ± 10.50 [106]</td>
<td>-43.75 ± 18.46 [111]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>-80.52 ± 12.83 [58]</td>
<td>-42.68 ± 21.15 [45]</td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>-74.36 ± 17.36 [74]</td>
<td>-32.09 ± 28.21 [100]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>-78.88 ± 13.90 [89]</td>
<td>-37.05 ± 26.83 [95]</td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>≥65 years</td>
<td>-73.31 ± 18.72 [43]</td>
<td>-32.21 ± 26.17 [50]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>-78.08 ± 15.80 [109]</td>
<td>-35.99 ± 26.41 [116]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>-72.26 ± 15.11 [23]</td>
<td>-32.93 ± 27.72 [29]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Secondary EP: Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>Evolocumab</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event</strong></td>
<td>78 (50.3)</td>
<td>77 (50.7)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Serious adverse event</strong></td>
<td>12 (7.7)</td>
<td>11 (7.2)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Adverse event resulting in IP discontinuation</strong></td>
<td>2 (1.3)</td>
<td>3 (2.0)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Events of special interest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT increase &gt;3x ULN</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Symptomatic overdose</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>General allergic reaction</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Local injection site reaction</td>
<td>5 (3.2)</td>
<td>3 (2.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Neurocognitive event</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>9 (5.8)</td>
<td>4 (2.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (2.6)</td>
<td>3 (2.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (3.9)</td>
<td>3 (2.0)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

ALP: alanine transaminase; IP: investigational product
<table>
<thead>
<tr>
<th>Event</th>
<th>Evolocumab (n=155)</th>
<th>Placebo (n=152)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (2.6)</td>
<td>1 (0.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Myocardial revascularization</td>
<td>33 (21.3)</td>
<td>39 (25.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>TLR</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>Staged procedure</td>
<td>32 (20.6)</td>
<td>38 (25.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Other revascularization</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hospitalization for recurrent ACS</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; HF: heart failure; TLR: target lesion revascularization
Exploratory Endpoints

**hs-CRP**
Baseline to Wk 8

*Change in hs-CRP (mg/L)*
- P=0.20

**Renal function***
Baseline to 72h

*Change in eGFR (ml/min)*
- P=0.37

*Pts who underwent coronary angiography (n=307/308)

**Platelet Reactivity**
*(Multiplate)*
Baseline to Wk 8

*Change in Units*
- ADP: P=0.13
- TRAP: P=0.99

**Post-PCI Myocardial Injury**
Baseline to 72h

*Change in hs-troponin T (ng/L)*
- P=0.35

**Pts who underwent PCI (n=259/308)

CPR: C-reactive protein; PCI: percutaneous coronary intervention
The study was not powered to assess clinical outcomes.
- Larger, longer-term studies should further investigate evolocumab in the acute ACS setting, also assessing potential effects on clinical outcomes.

Although 95% of patients completed the final (week 8) clinical visit, the primary endpoint (change in calculated LDL-C) was available in 90% of patients.
- However, an ancillary analysis of directly measured LDL-C (available in 94% of pts) showed consistent results.

Lipid levels were measured 4 weeks after the first study drug administration; thus, earlier effects of evolocumab could not be assessed.
In patients presenting with ACS and elevated LDL-C levels, in-hospital initiation of evolocumab on top of high-intensity statin therapy for 8 weeks:

- Achieved average LDL-C levels of **0.79 mmol/L** vs. **2.06 mmol/L** with statin alone
- Rendered >90% of patients (vs. 11% of placebo-treated patients) within currently recommended target levels
- Was **safe** and **well tolerated** during the short duration of the study
- Did not result in measurable differences in surrogate outcomes:
  - Inflammatory biomarkers
  - Platelet reactivity
  - Acute kidney injury
  - Myocardial injury
Conclusions

- In this first randomized trial assessing a PCSK9 antibody in the very high-risk acute setting of ACS, evolocumab added to high-intensity statin therapy resulted in substantial reduction in LDL-C levels without raising safety concerns.

- The clinical impact of very early LDL-C lowering with evolocumab initiated in the acute setting of ACS warrants further investigation in a dedicated CV outcomes trial.
Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS)

Konstantinos C. Koskinas, MD, MSc, Stephan Windecker, MD, Giovanni Pedrazzini, MD, Christian Mueller, MD, Stéphane Cook, MD, Christian M. Matter, MD, Olivier Muller, MD, Jonas Häner, MD, Baris Gencer, MD, Carmela Criljenica, MD, Poorya Amini, PhD, Olga Deckarm, MD, Juan F. Iglesias, MD, Lorenz Räber, MD, PhD, Dik Heg, PhD, François Mach, MD

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https://doi.org/10.1016/j.jacc.2019.08.010
BACKUP SLIDES
Results: Adherence to Background Statin Therapy
(atorvastatin 40 / 80mg*)

* Patients who had been taking a statin more potent than atorvastatin 40mg prior to enrolment (i.e. atorvastatin >40, rosvuvastatin >20) received atorvastatin 80mg during the study
Change in LDL-C in relation to pre-enrolment statin treatment

No prior statin

Prior statin (low-/moderate-/high-intensity)

\[ \Delta \text{ between treatment groups: } -36.5\% \]

\[ \Delta \text{ between treatment groups: } -55.8\% \]
Change in LDL-C in relation to pre-enrolment statin treatment

**No statin**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Wk8</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evolocumab</strong></td>
<td>3.81</td>
<td>3.72</td>
<td>-80.3%</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>0.77</td>
<td>0.99</td>
<td>-43.8%</td>
</tr>
</tbody>
</table>

Δ between treatment groups: **-36.5%**

**High-intensity statin**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Wk8</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evolocumab</strong></td>
<td>2.36</td>
<td>2.15</td>
<td>-55.0%</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>0.99</td>
<td>0.99</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

Δ between treatment groups: **-58.3%**