EVOlocumab for early reduction of LDL-cholesterol levels in **P**atients with **A**cute **C**oronary **S**yndromes (***EVOPACS***)

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

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ESC Congress Paris 2019 Together with World Congress of Cardiology

Late-Breaking Science in Acute Coronary Syndromes

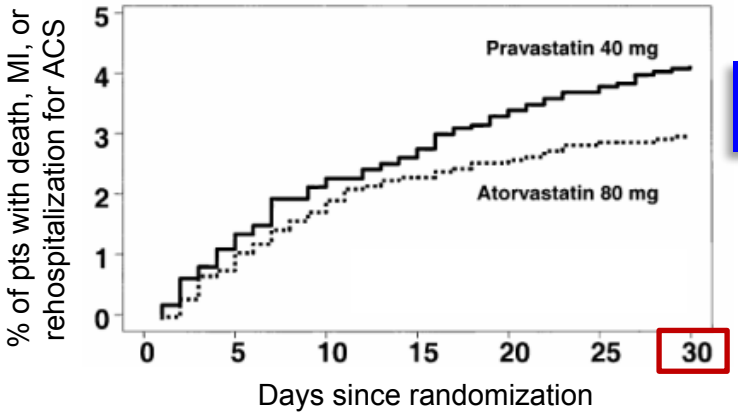
August 31, 2019

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.**



HR 0.72 (CI 0.52-0.99)
P<0.05

Ray KK, et al. *JACC* 2005;46:1405-10
Schwartz GG, et al. *JAMA* 2001;285:1711-8

Recommendations	Class [a]	Level [b]
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values.	I	A

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

Sabatine MS, et al. *NEJM* 2017;376:1713-22
Schwartz GG, et al. *NEJM* 2018;379:2097-107

Background

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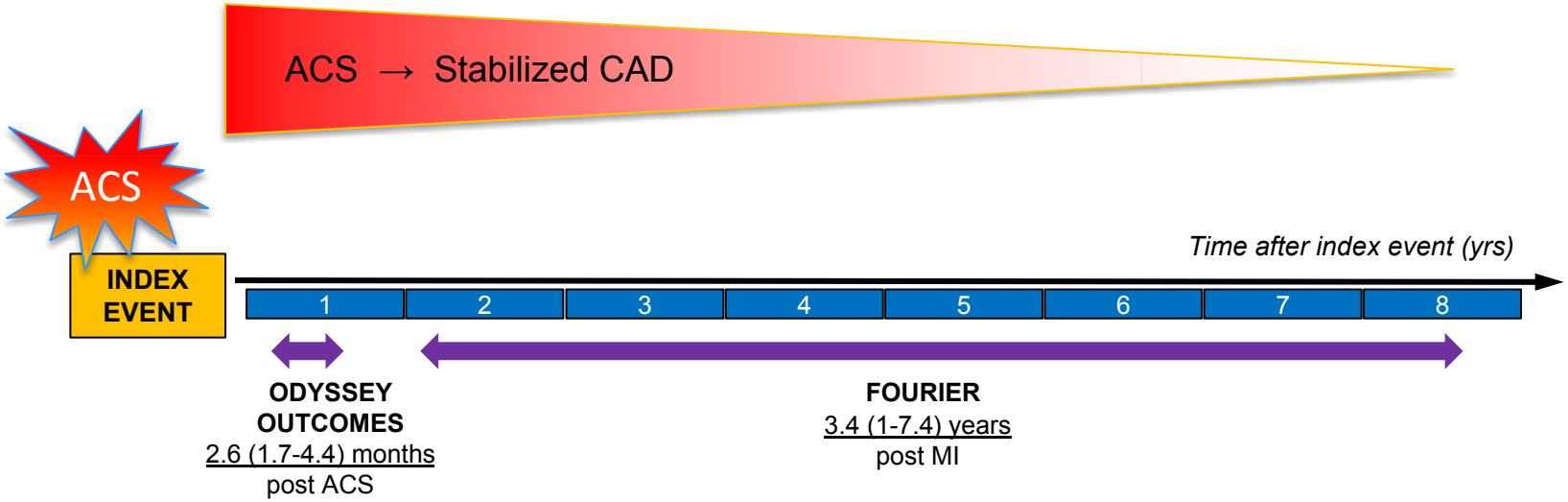
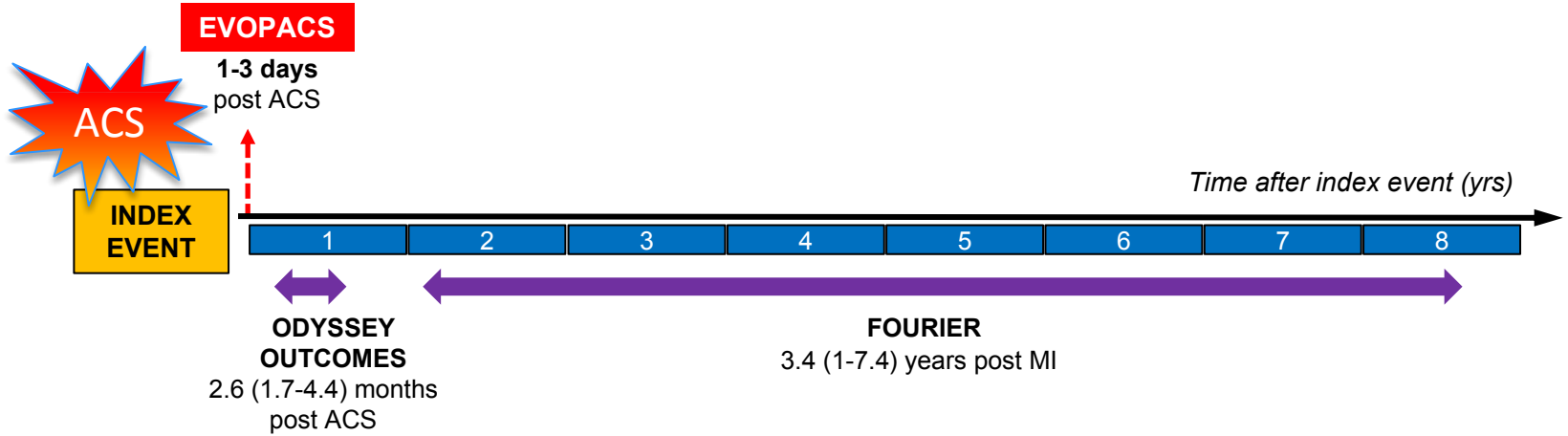
Timing of patient enrolment after ACS in previous PCSK9-inhibitor trials



Koskinas KC, et al. *Clin Cardiol* 2018;41:1513-20

Study Hypothesis

- 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 with high-intensity statin treatment



Study Organisation

EVOPACS

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

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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

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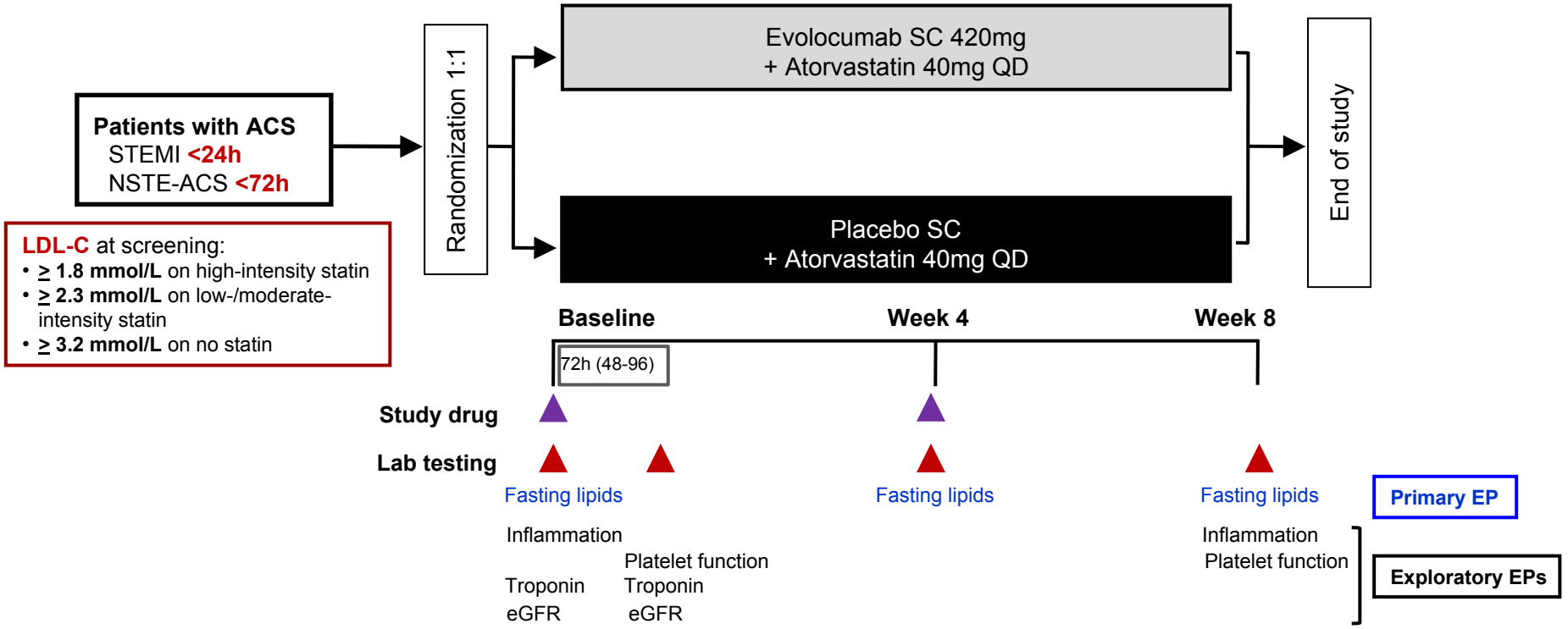
- **Primary EP**: % Change in LDL-C from baseline to 8 weeks
- **Secondary EP**: Safety and tolerability
- **Exploratory EPs**:
  - hs-CRP and other inflammatory biomarkers
  - Platelet reactivity
  - Contrast-induced acute kidney injury
  - Post-PCI myocardial injury

Study Design

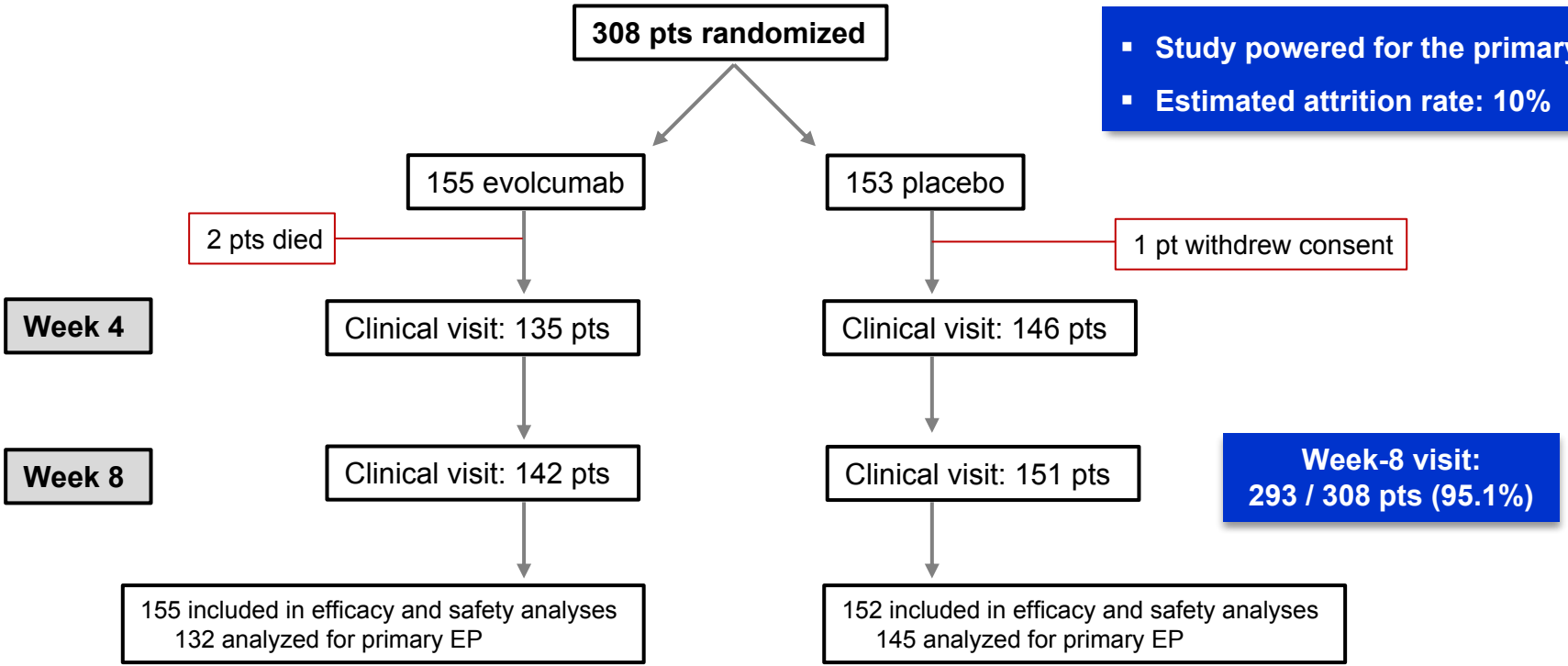
EVOPACS



Trial registration: clinicaltrials.gov; **NCT03287609**

Koskinas KC, et al. *Clin Cardiol* 2018;41:1513-20

Flowchart


308 pts randomized
155 evolcumab
153 placebo
2 pts died
1 pt withdrew consent
Week 4
Clinical visit: 135 pts
Clinical visit: 146 pts
Week 8
Clinical visit: 142 pts
Clinical visit: 151 pts
155 included in efficacy and safety analyses
132 analyzed for primary EP
152 included in efficacy and safety analyses
145 analyzed for primary EP
Study powered for the primary EP
Estimated attrition rate: 10%
Week-8 visit:
293 / 308 pts (95.1%)

Results: Baseline Characteristics

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

Results: Index ACS event

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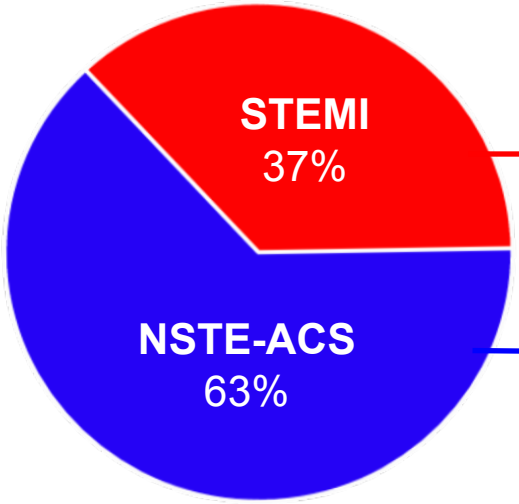
Index ACS event

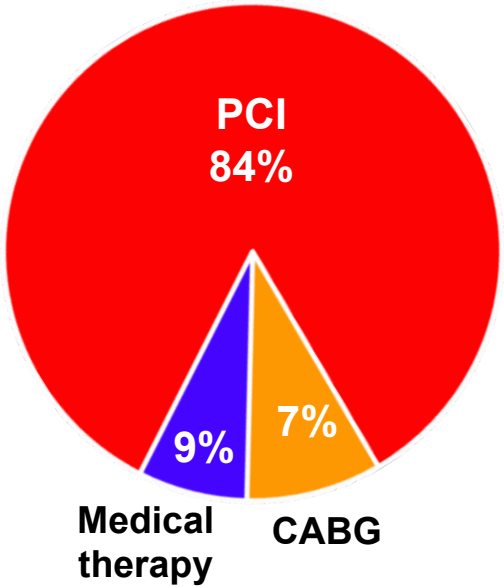


Time between symptoms onset and study enrolment

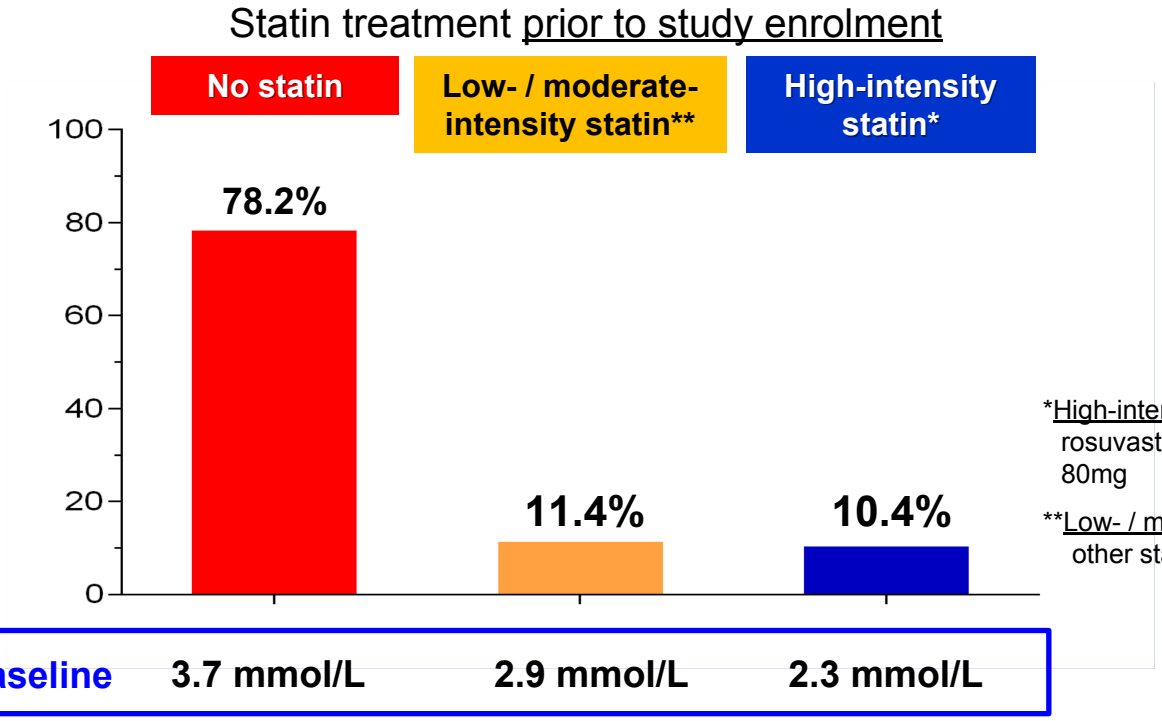
<24h	24-72h
100%	0%

<24h	24-72h
39%	61%

Treatment of index ACS event



Results: Statin Treatment at Baseline

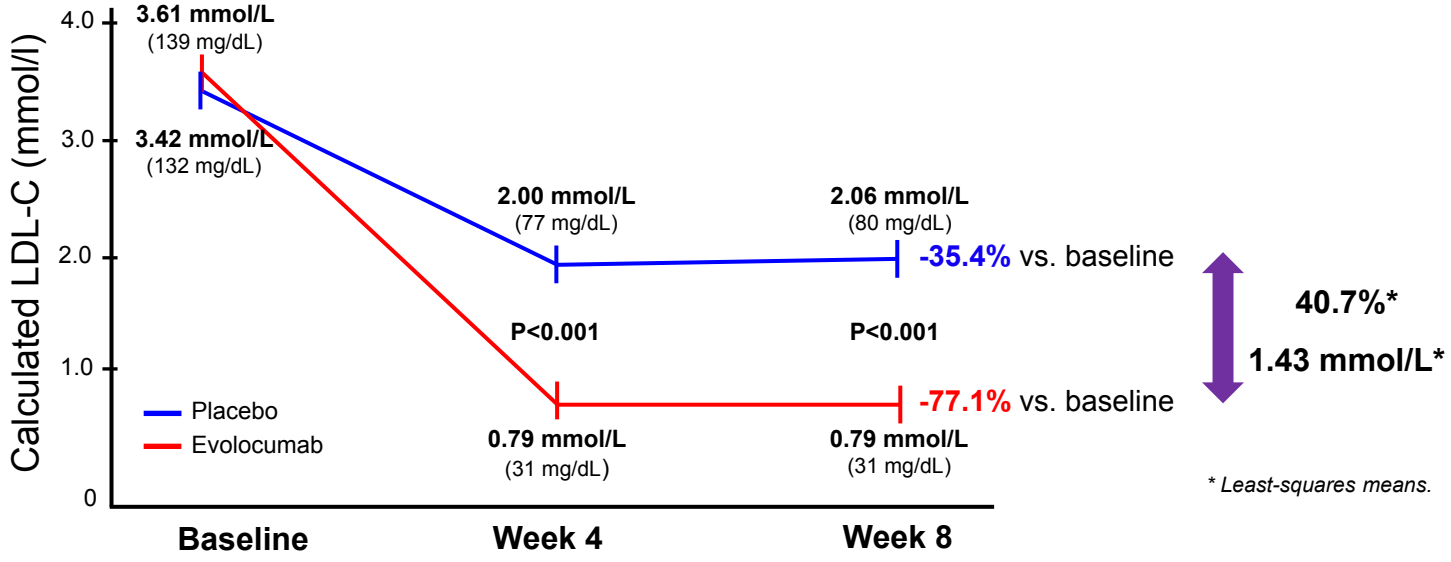


*High-intensity: atorvastatin ≥40mg; rosuvastatin ≥20mg; simvastatin 80mg

**Low- / moderate-intensity: all other statin regimens

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

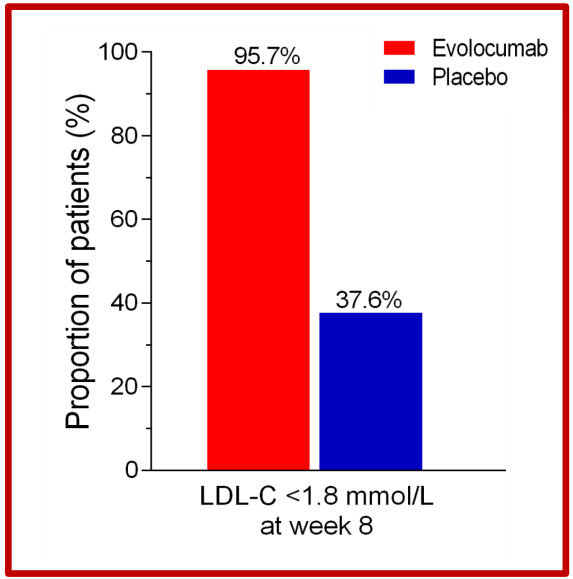
Primary endpoint: % Change in LDL-C at 8 wks



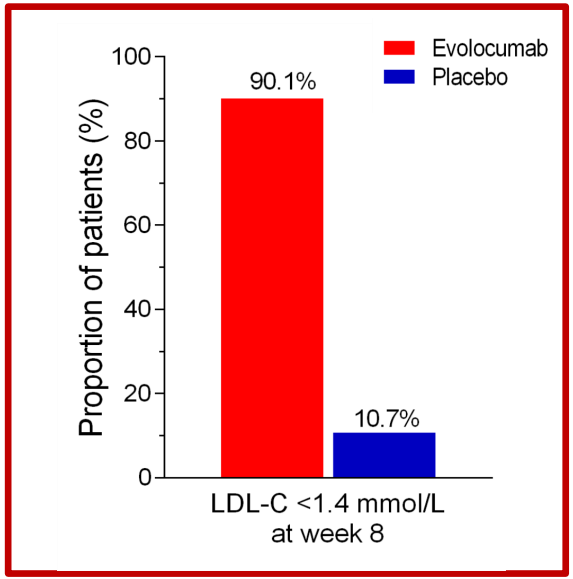
No of pts			
Placebo	148	144	149
Evolocumab	146	136	141

Achievement of LDL-C Treatment Targets

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



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



ESC/EAS 2019 Dyslipidemia Guidelines

Mach F, et al. *Eur Heart J* 2019; In Press

Primary EP: Key Subgroups

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

Secondary EP: Safety

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

ALP: alanine transaminase; IP: investigational product

Adjudicated CV Events

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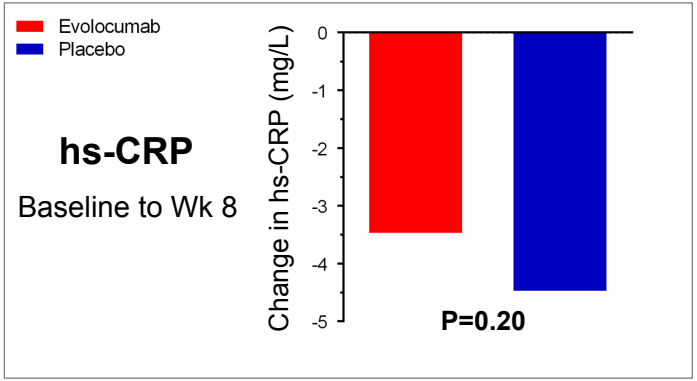
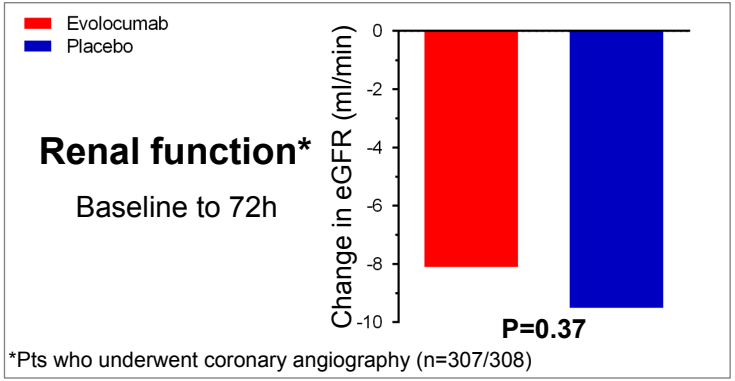
	Evolocumab n=155	Placebo n=152	p-value
All-cause death	2 (1.3)	0 (0.0)	0.50
Cardiovascular death	2 (1.3)	0 (0.0)	0.50
Myocardial infarction	4 (2.6)	1 (0.7)	0.17
Cerebrovascular event	1 (0.6)	0 (0.0)	1.00
Myocardial revascularization	33 (21.3)	39 (25.7)	0.39
TLR	0 (0.0)	1 (0.7)	0.50
Staged procedure	32 (20.6)	38 (25.0)	0.39
Other revascularization	2 (1.3)	0 (0.0)	0.50
Hospitalization for recurrent ACS	0 (0.0)	1 (0.7)	0.50
Hospitalization for HF	0 (0.0)	0 (0.0)	-

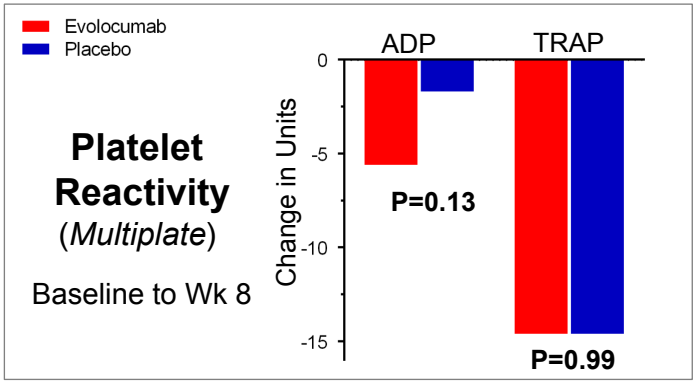
ACS: acute coronary syndrome; HF: heart failure; TLR: target lesion revascularization

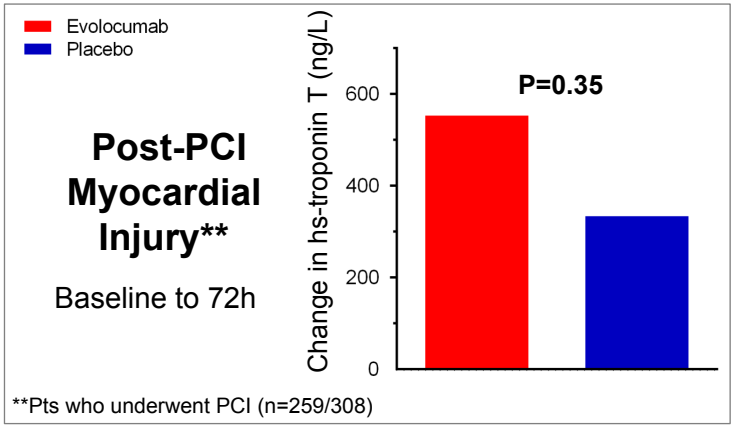
Exploratory Endpoints





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





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

CPR: C-reactive protein; PCI: percutaneous coronary intervention

Limitations

- 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.

Summary

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.

ORIGINAL INVESTIGATIONS

Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS)

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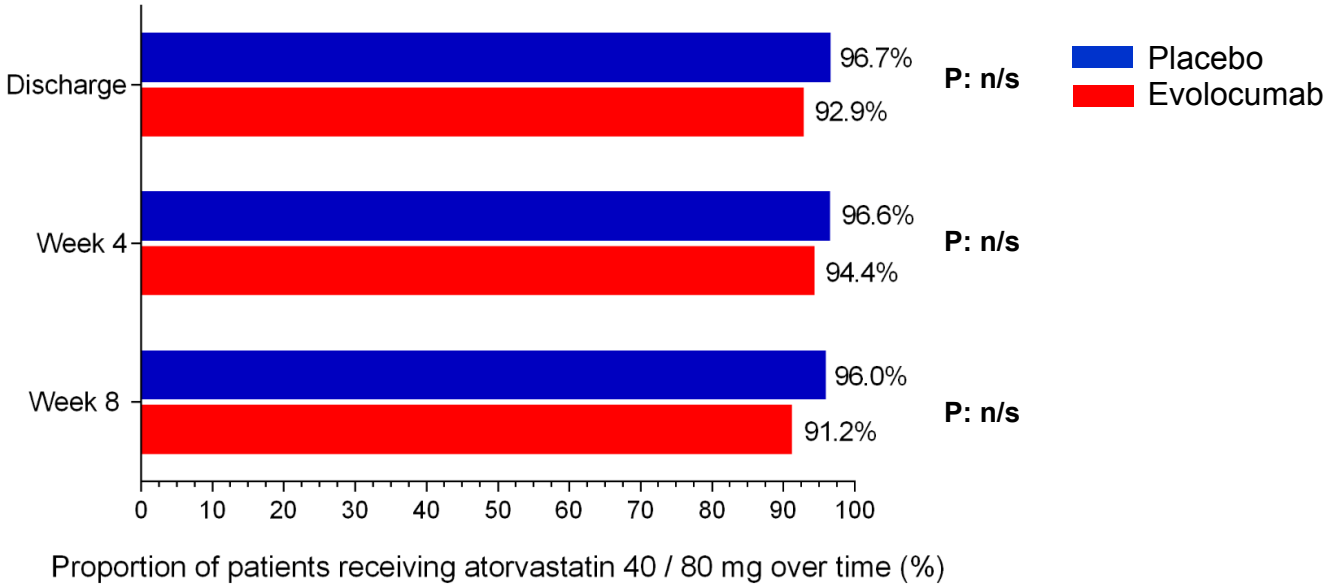
BACKUP SLIDES

Results: Adherence to Background Statin Therapy

(atorvastatin 40 / 80mg*)

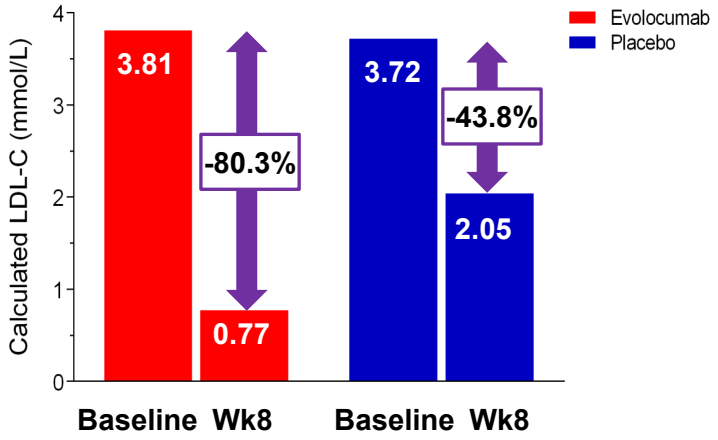


* Patients who had been taking a statin more potent than atorvastatin 40mg prior to enrolment (i.e. atorvastatin >40, rosuvastatin >20) received atorvastatin 80mg during the study

Change in LDL-C in relation to pre-enrolment statin treatment

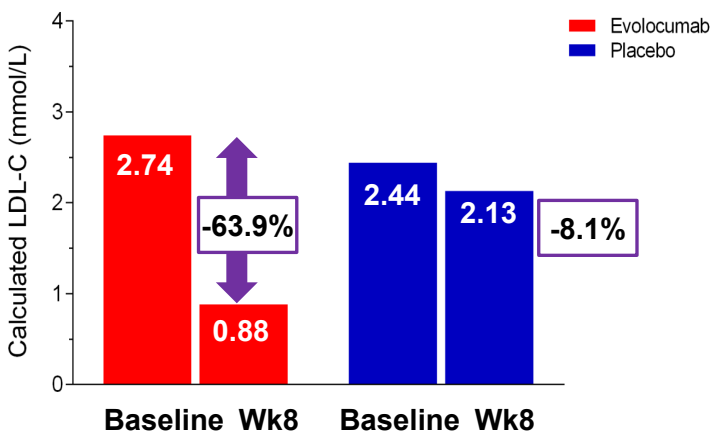
EVOPACS

No prior statin



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

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

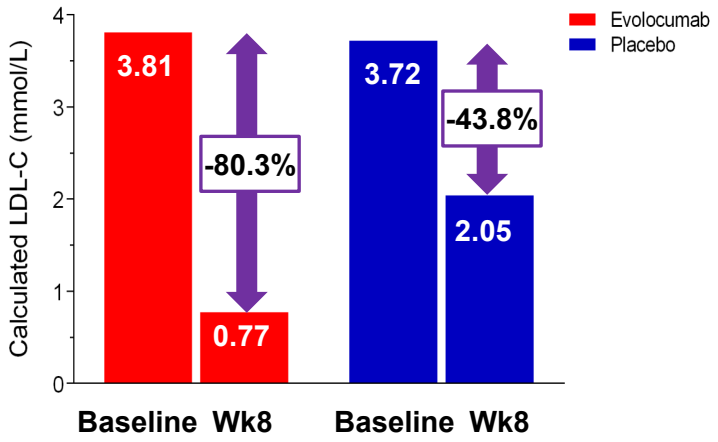


Δ between treatment groups: **-55.8%**

Change in LDL-C in relation to pre-enrolment statin treatment

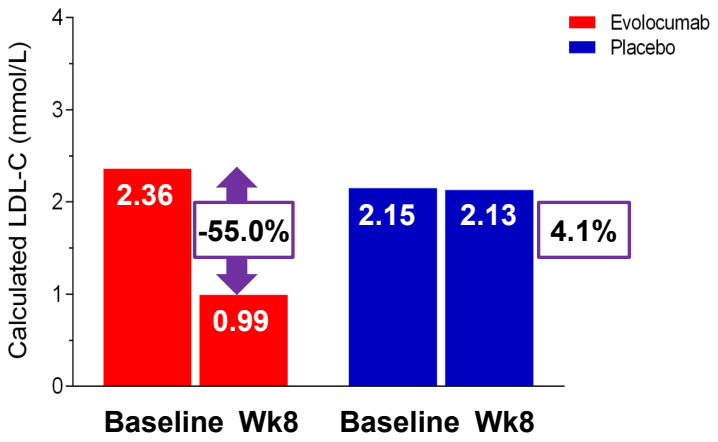
EVOPACS

No statin



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

High-intensity statin



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