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

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Acute Coronary Syndrome and PCSK9i Use Warranted Further Study

- Acute coronary syndromes (ACS) represents a group of conditions (UA, STEMI, NSTEMI) associated with atherosclerosis[1]
- Patients with ACS are at an increased risk of recurrent ischemic events, especially during the early period following the first event[2]
- It has been established that reduction of LDL-C reduces CV morbidity and mortality in patients with ASCVD[3]
- In the setting of ACS, early, in-hospital initiation of high-intensity statin therapy reduces the occurrence of early events,[4] however, rapid and more potent lowering of LDL-C to levels even below currently recommended targets might be of potential therapeutic benefit in this setting[5-7]
- FOURIER, the evolocumab CV outcomes trial conducted in 27,564 patients with ASCVD, significantly reduced the risk of CV events over a median of 2.2 years, with greater risk reduction in patients closer to their index MI (< 2 years)[8,9]
- The feasibility, safety, and LDL-C lowering efficacy of PCSK9i treatment initiated in the very high-risk, acute phase of ACS are unknown, thus…

…EVOPACS, a randomized, placebo-controlled trial of 308 patients aimed to assess evolocumab administered in-hospital in addition to high-intensity statin therapy, compared with high-intensity statin therapy alone in patients presenting with ACS[10]

UA = unstable angina, STEMI = ST-Elevation Myocardial Infarction; NSTEMI = Non-ST-Elevation Myocardial Infarction; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disese; MI = myocardial infarction; LDL-C = low-density lipoprotein cholesterol; PCSK9i = proprotin-converstase subtillisn/kevin type 9 inhibitor

1. Grundy SM, et al. *J Clin Lipidol.* 2014;8:29-60. 2. Roffi M, et al. *Eur Heart J.* 2016;37:267-315. 3. Baigent C, et al. *Lancet.* 2010;376:1670-1681. 4. Koskinas KC, et al. *Eur Heart J.* 2018;39:1172-1180. 5. Catapano AL, et al. *Eur Heart J.* 2016;37:2999-3058. 6. Grundy SM et al. *J Am Coll Cardiol*. 2019;73:e285-e350. 7. Reiner Z, et al. *Atherosclerosis.* 2016;246:243-250. 8. Sabatine MS, et al. *New Engl J Med*. 2017;376:1713-1722. 9. Sabatine MS, et al. *Circulation*. 2018;138:756-766. 10. Koskinas KC, et al. *JACC*. [published online ahead of print August 31, 2019]. https://doi.org/10.1016/j.jacc.2019.08.010

EVOPACS: Evaluated LDL-C Reduction, Safety, and Additional Exploratory Endpoints

PRIMARY OBJECTIVE

- Evaluate effectiveness of evolocumab vs placebo in LDL-C reduction in acute phase of ACS after 8 weeks

SECONDARY OBJECTIVE

- To assess safety and tolerability of early evolocumab administration in acute phase of ACS

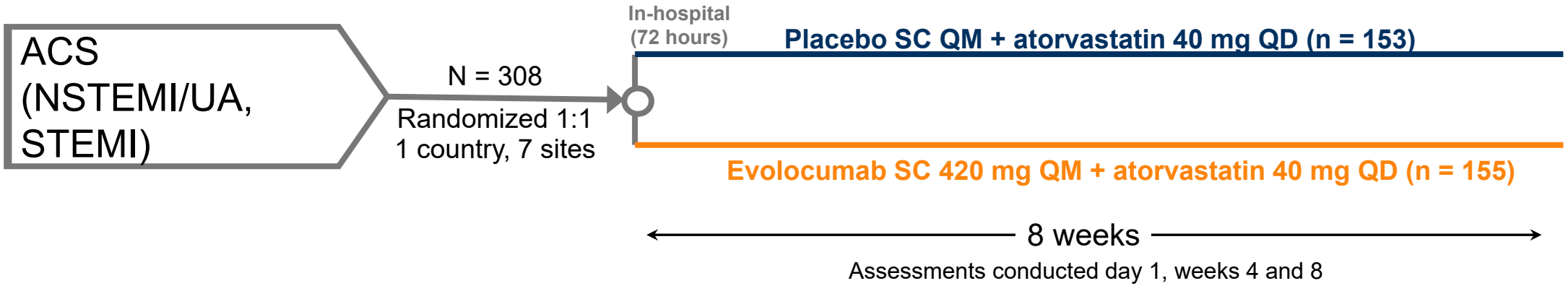
EXPLORATORY OBJECTIVES

- To asses effect of evolocumab vs placebo on
  - hsCRP/other inflammation biomarkers
  - Platelet function
  - Occurrence of contrast-induced acute kidney injury (CI-AKI)
  - Incidence of centrally adjudicated CV events
  - Lipid Core Burden Index (LCBI) (n=~10) via NIRS

LDL-C – low-density lipoprotein cholesterol; ACS = acute coronary syndrome; hsCRP = high-sensitivity C-reactive protein

Koskinas KC, et al. *Clinical Cardiology*. 2018;41:1513-1520.

EVOPACS: Study Design Assessed Evolocumab in ACS Patients Within 24 - 72 Hours



PRIMARY ENDPOINT

- LDL-C change from baseline at week 8

SECONDARY ENDPOINT

- Safety and tolerability

INCLUSION CRITERIA

- ACS (NSTEMI/UA < 72H, STEMI < 24H)
- LDL-C levels
  - ≥ 1.8 mmol/L (70 mg/dl) in patient previously on stable treatment with high-intensity statin OR
  - ≥ 2.3 mmol/L (90 mg/dl) in patients previously on stable treatment with low- or moderate intensity statin OR
  - ≥ 3.2 mmol/L (125 mg/dL) in statin naive patients or patients not on stable statin treatment

ACS = acute coronary syndrome; SC = subcutaneous; QM = monthly; QD = daily; LDL-C = low-density lipoprotein cholesterol; NSTEMI = Non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; UA = unstable angina; AE = adverse eventa

1. Koskinas KC, et al. Clinical Cardiology. 2018;41:1513-1520. 2. Koskinas KC, et al. *JACC*. [published online ahead of print August 31, 2019]. https://doi.org/10.1016/j.jacc.2019.08.010

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Baseline Demographics and CV Risk Factors Were Well Balanced

	Evolocumab (n = 155)	Placebo (n = 153)
Age (years)	60.5±12.0	61.0±10.7
Male gender, n (%)	128 (83)	123 (80)
Body mass index (kg/m²)	26.9±4.0	27.8±3.9
Diabetes mellitus, n (%)	23 (15)	24 (16)
Insulin-treated	1 (1)	6 (4)
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, n (%)	2 (1)	0 (0)
History of TIA, n (%)	5 (3)	0 (0)
History of malignancy, n (%)	13 (8)	10 (7)

In the evolocumab group, 15% of patients had a history of previous MI and 3% of patients had PAD

PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; TIA = trans ischemic attack; MI = myocardial infarction; PAD = peripheral artery disease

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Majority of Patients Enrolled Were Statin-Naïve at Baseline

	Evolocumab (n = 155)	Placebo (n = 153)
Statin treatment[a], n (%)		
No statin	124 (80)	117 (76)
Low- or moderate-intensity statin	13 (8)	22 (14)
High-intensity statin[b]	18 (12)	14 (9)
Ezetimibe treatment, n (%)	6 (4)	9 (6)

[a]Stable (unchanged) in the past ≥4 weeks prior to study enrolment. [b]Atorvastatin ≥40mg, rosuvastatin ≥20mg, or simvastatin 80mg.

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Baseline Index ACS Event Was Numerically Imbalanced Between Groups

	Evolocumab (n = 155)	Placebo (n = 153)
Time of symptom onset <24h, n (%)	100 (65)	90 (59)
Index ACS event, n (%)		
NSTE-ACS	88 (57)	107 (70)
STEMI	67 (43)	46 (30)

There were more STEMI patients in the evolocumab group versus the placebo group (43% vs 30%). Treatment of the index ACS event included PCI (84.1%), medical therapy alone (8.8%), or CABG (7.1%)

ACS = acute coronary syndrome; NSTE-ACS = Non-ST-Elevation-Acute coronary syndrome; STEMI = ST-Elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

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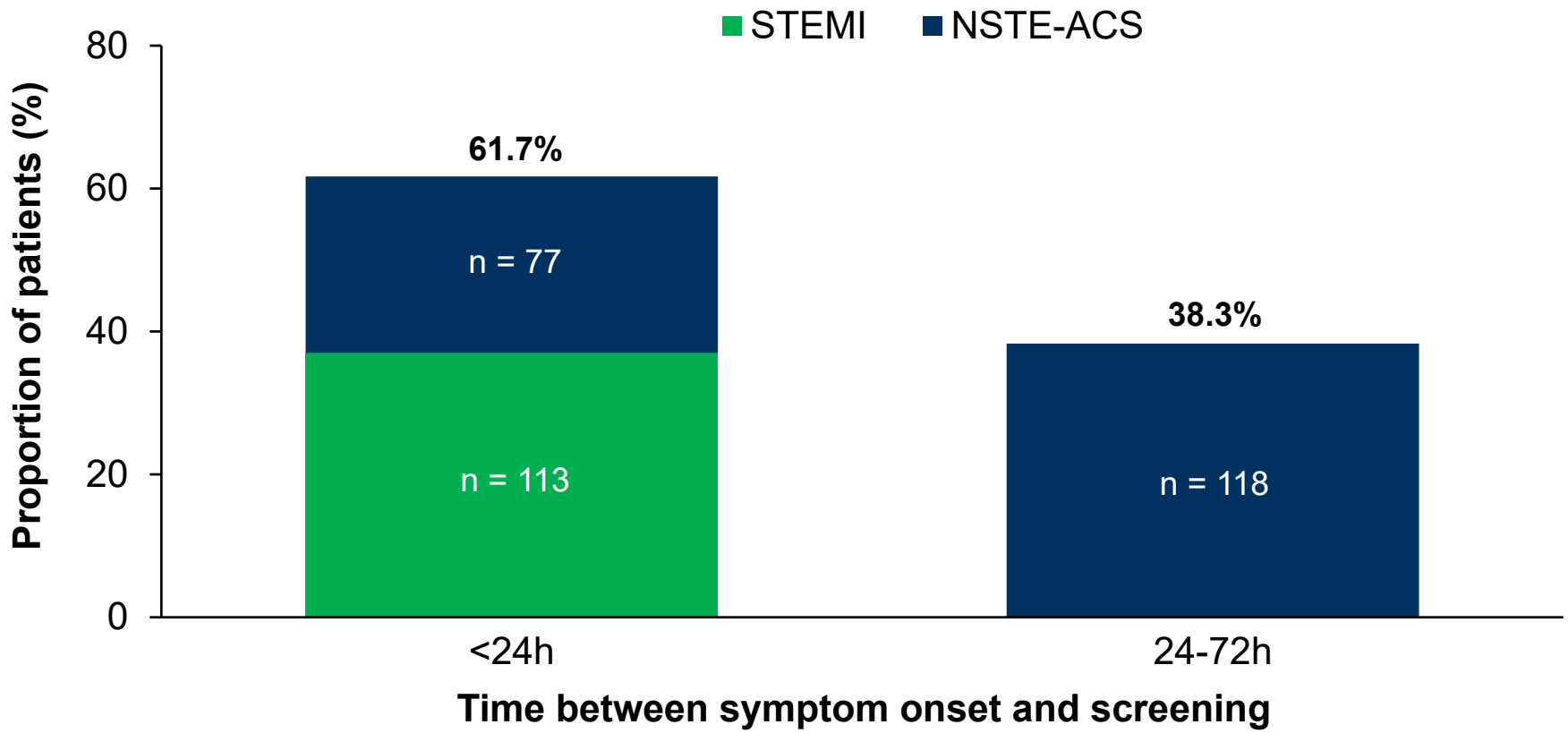
All STEMI Patients Screened <24h; NSTEMI Patients Screened <72h



The majority of enrolled patients (62%) were screened for study participation within <24 hours of patient-reported symptom onset, and all within <72 hours

ACS = acute coronary syndrome; NSTE-ACS = Non-ST-Elevation-Acute coronary syndrome; STEMI = ST-Elevation myocardial infarction

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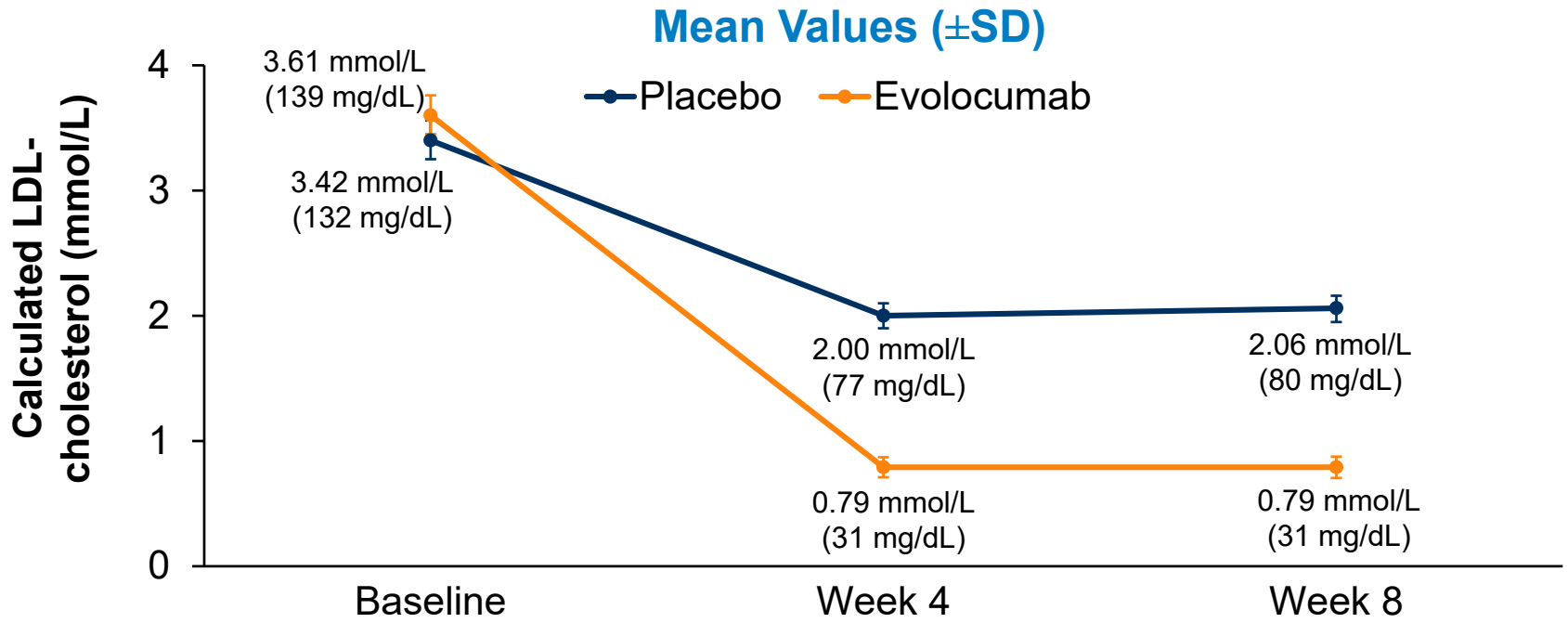
Primary Endpoint: Significant Reduction in LDL-C at 8 Weeks



	Baseline	Week 4	Week 8
No. of patients			
Placebo	148	144	149
Evolocumab	146	136	141
Absolute difference, LS means (mmol/L)		1.34	1.43
Percentage difference		38.4%	40.7%
P-value		<0.001	<0.001

The reduction in LDL-C levels was evident at 4 weeks and maintained at 8 weeks

AE, adverse event; LS = least-squares; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation .

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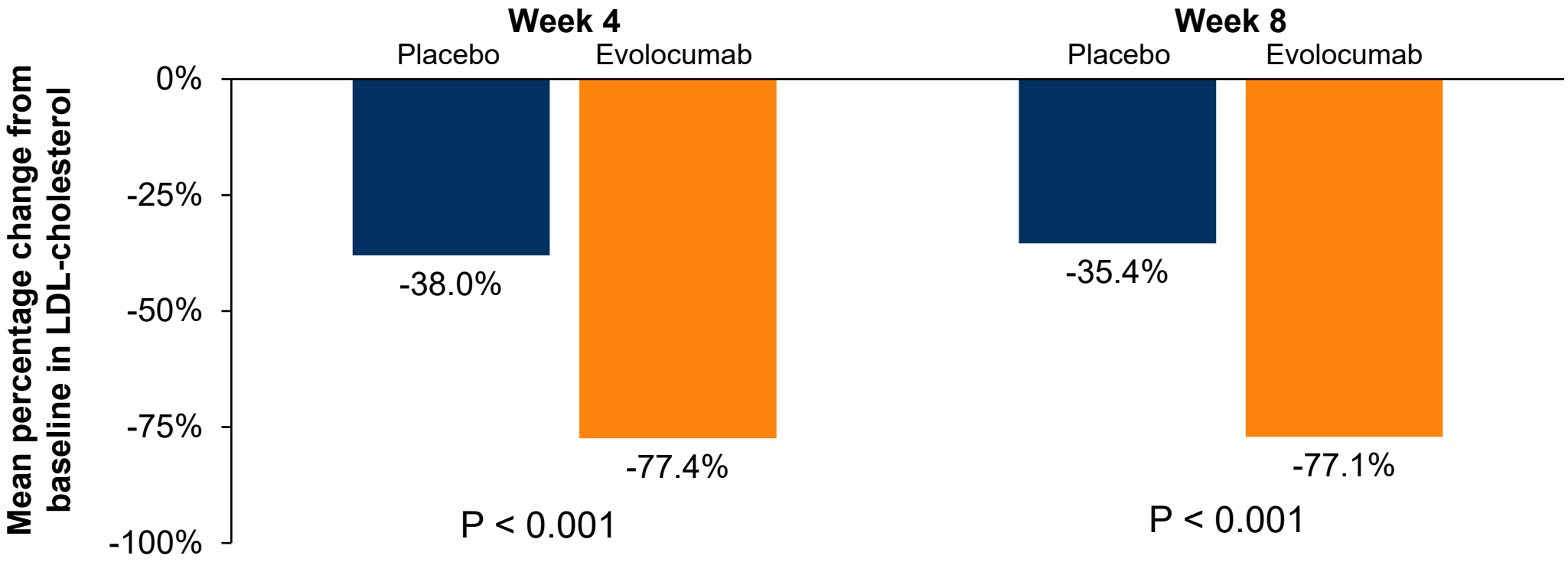
Percent Change in LDL-C at 4 Weeks Was Maintained at Week 8



The percent change in LDL-C from baseline to week 8 was 77% in the evolocumab group and 35% in the placebo group

AE, adverse event; LS = least-squares; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation

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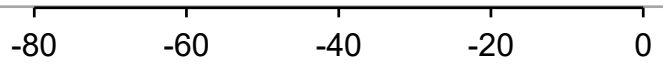
Subgroup Analysis by Statin Treatment at Baseline Demonstrates the Impact of No Prior Statin Therapy on Percent Reduction in LDL-C Between Groups

	Evolocumab (N = 155)		Placebo (N = 152)		Calculated LDL-C Mean Difference (95% CI)	P-value	Interaction P-value
	n	Mean ± SD	n	Mean ± SD			
Overall	132	-77.1 ± 15.8	145	-35.4 ± 26.6	-40.7 (-45.2 to -36.2)	<0.001	
Statin at baseline							<0.001
Yes	26	-63.9 ± 24.8	34	-8.1 ± 30.8	-55.8 (-70.1 to -41.6)	<0.001	
No	106	-80.3 ± 10.5	111	-43.8 ± 18.5	-36.5 (40.5 to -32.5)	<0.001	



Subgroup analyses showed a greater percent reduction in calculated LDL-C with evolocumab vs placebo among patients who had been on statin therapy at baseline

Shown are means ± standard deviations (p-value from mixed models), interaction p-value testing for the interaction effect subgroup x randomized arm from full-factorial mixed model. Stratification for baseline statin treatment was done according to presence or absence of stable (unchanged) statin treatment in the preceding 4 weeks prior to enrollment.

LDL-C = low-density lipoprotein cholesterol

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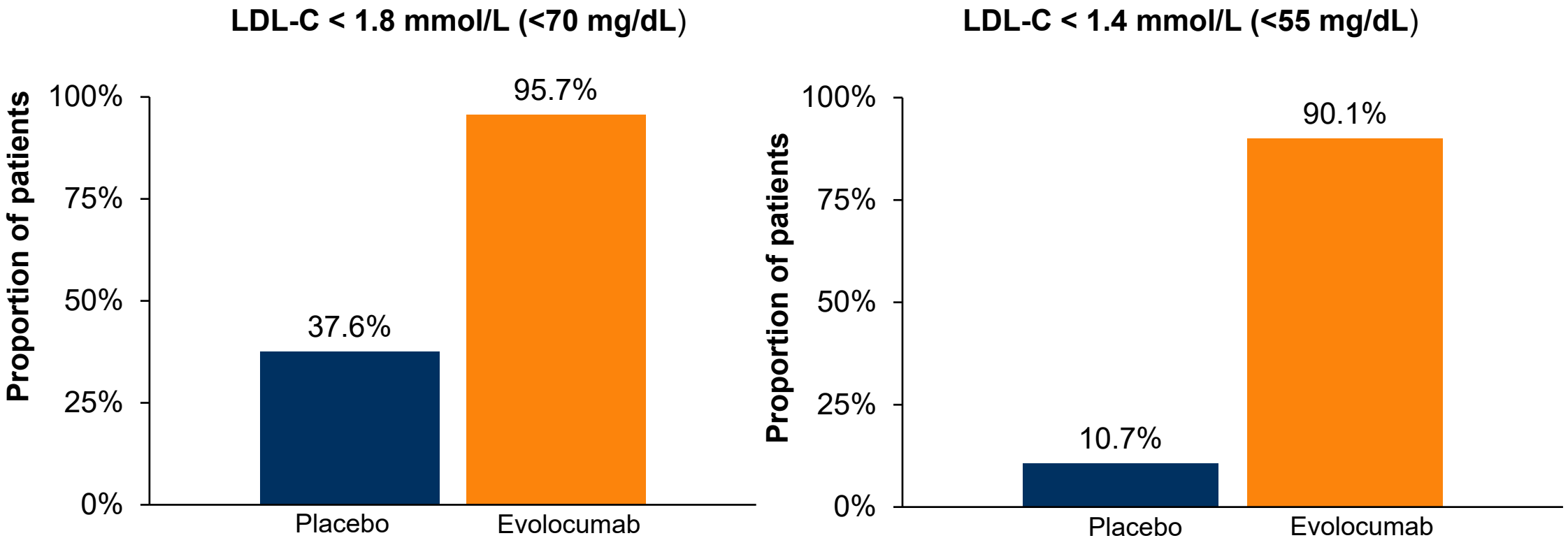
90% of Evolocumab Patients Achieved New ESC/EAS Guideline Goal of LDL-C < 1.4 mmol/L (< 55 mg/dL)



Compared with placebo, substantially more patients receiving evolocumab were able to achieve LDL-C levels < 1.8 (96% vs 38%) and < 1.4 mmol/L (90% vs 11%)

LDL-C = low-density lipoprotein cholesterol

Koskinas KC, et al. ESC 2019, Paris Aug 31-Sept 4.
Koskinas KC, et al. *JACC*. [published online ahead of print August 31, 2019]. https://doi.org/10.1016/j.jacc.2019.08.010
Mach F. et al. *Eur J Heart.* [published online ahead of print August 31, 2019]. https://doi.org/10.1093/eurheartj/ehz455

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Secondary Endpoint: No New Safety Findings

	Evolocumab (n = 155)	Placebo (n = 152)[a]	*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 study drug discontinuation	2 (1.3)	3 (2.0)	0.65

The percentage of patients who experienced AEs, SAEs, and AEs resulting in study discontinuation were similar between groups

Number (proportion) of patients with each event type are reported, not counting multiple events of the same type. Fisher's exact tests in case of zero events in one group.

[a]Excluded is one patient randomly allocated to placebo who withdrew consent early and refused study drug injection and any study intervention.

AE = adverse event; SAE = serious adverse event

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Adverse Events of Special Interest Were Similar Between Groups

	Evolocumab (n = 155)	Placebo (n = 152)[a]	*P*-value
Adverse 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
Musculoskeletal Pain	9 (5.8)	4 (2.6)	0.16
Nasopharyngitis	4 (2.6)	3 (2.0)	0.71
Diarrhea	6 (3.9)	3 (2.0)	0.30
Other	63 (40.6)	64 (42.1)	0.91

Musculoskeletal pain was the most common reported AE, occurring in 9 patients (5.8%) in the evolocumab and 4 patients (2.6%) in the placebo group.

Number (proportion) of patients with each event type are reported, not counting multiple events of the same type. Fisher's exact tests in case of zero events in one group.
[a]Excludes one patient randomly allocated to placebo who withdrew consent early and refused study drug injection and any study intervention.
AE = adverse event; SAE = serious adverse event; ULN = upper limit of normal
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Adjudicated CV Events Did Not Differ Significantly Between Groups

	Evolocumab (n = 155)	Placebo (n = 152)[a]	*P*-value
Positively Adjudicated Adverse Events			
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)[b]	1 (0.7)	0.17
Coronary revascularization	33 (21.3)	39 (25.7)	0.39
Target-lesion revascularization	0 (0.0)	1 (0.7)	0.50
Planned staged procedure	32 (20.6)	38 (25.0)	0.39
Other revascularization	2 (1.3)	0 (0.0)	0.50
Cerebrovascular event (stroke / TIA)	1 (0.6)	0 (0.0)	1.00
Hospitalization for recurrent ACS	0 (0.0)	1 (0.7)	0.50
Hospitalization for heart failure	0 (0.0)	0 (0.0)	

- **The majority of adjudicated CV events were attributed to coronary revascularization procedures**
- **2 CV deaths occurred, both were deemed unrelated to study drug by the independent blinded adjudication committee**
- **5 patients (including the 2 patients who died), experienced recurrent MI**
- **Note, more patients in the evolocumab group had an index event of STEMI, which is associated with worse prognosis**

[a]Excludes one patient randomly allocated to placebo who withdrew consent early and refused study drug injection and any study intervention [b]Including 2 patients who died.

STEMI = ST-elevation myocardial infarction; ACS = acute coronary syndrome; TIA = transient ischemic attack

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No Differences Were Observed For Any Exploratory Endpoints

	Evolocumab (n = 155)	Placebo (n = 152)	Mean difference[a] (95% CI)	P-value
Inflammatory biomarkers (change from baseline to week 8)				
% Change hsCRP	-14.9±255.7	-35.1±.111.7	19.6 (-25.2 to 64.5)	0.39
hs-CRP level <2 mg/L at week 8 (%)	0.688	0.693	-0.7 (-11.4 to 9.9)	0.89
Change in interleukin-1β (pg/ml)	0.05±0.90	-0.01±0.89	0.06 (-0.14 to 0.27)	0.53
Change in interleukin 6 (pg/ml)	9.95±14.62	9.34.±.15.23	0.59 (-2.87 to 4.05)	0.74

[a]Evolocumab minus placebo.

ADP = adenosine diphosphate; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reacting protein; TRAP = thrombin receptor activating peptide

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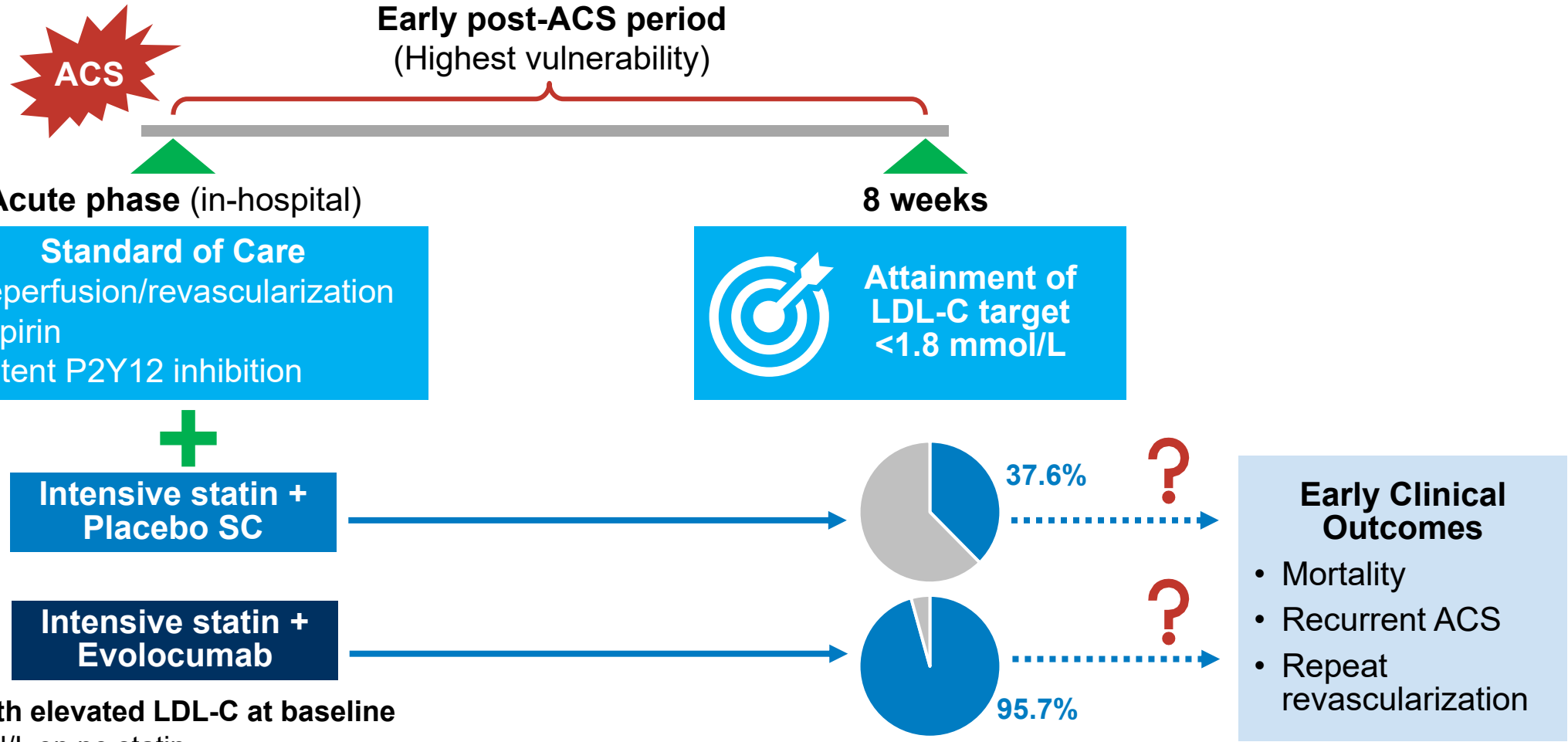
ACS Phase and New Treatment Paradigms to Consider



Patients with elevated LDL-C at baseline

- ≥3.2 mmol/L on no statin
- ≥2.3 mmol/L on low/moderate intensity statin
- ≥1.8 mmol/L on high-intensity statin

LDL-C = low-density lipoprotein cholesterol; ACS = acute coronary syndrome

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Summary

- The EVOPACS study demonstrated that evolocumab, in addition to high-intensity statin therapy, resulted in significantly greater reduction in LDL-C levels after 8 weeks, compared with high-intensity statin therapy alone
- Evolocumab was well tolerated, with no new safety findings
- Treatment with evolocumab in the ACS setting enabled:
  - > 95% of patients to achieve LDL-C targets < 1.8 mmol/L (<70 mg/dL), compared with 38% of patients receiving statin therapy alone
  - > 90% of patients to achieve LDL-C targets < 1.4 mmol/L (<55 mg/dL), compared with 11% of patients receiving statin therapy alone, which aligns with the LDL-C goal in 2019 ESC/EAS Dyslipidemia Guidelines

LDL-C = low-density lipoprotein cholesterol

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Mach F, et al. *Eur J Heart*. [published online ahead of print August 31, 2019]. https://doi.org/10.1093/eurheartj/ehz455

Back Up

Inclusion Criteria

- Male or female ≥ 18 years of age
- Hospitalized for a recent ACS (unstable angina or NSTEMI within < 72 hours, STEMI within <24 hours prior to screening)
- **LDL-C levels** defined as follows:
  - LDL-C ≥70 mg/dL (**≥1.8 mmol/L)** or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L) in patients who have been receiving stable treatment with **high-intensity statin** within ≥ 4 weeks prior to enrollment (i.e. continuous treatment that has not changed with regard to statin intensity over the past 4 weeks)
  - LDL-C ≥90 mg/dL (**≥2.3 mmol/L**) or non-HDL-C ≥120 mg/dL (≥3.1 mmol/L) in patients who have been receiving stable treatment with **low- or moderate-intensity statin** within ≥ 4 weeks prior to enrollment
  - LDL-C ≥125 mg/dL (**≥3.2 mmol/L**) or non-HDL-C ≥155 mg/dL (≥4.0 mmol/L) in patients who are **statin-naïve** or have not been on a stable (unchanged) statin regimen for at least 4 weeks prior to enrollment
- Ability to understand the requirements of the study and to provide informed consent

ACS = acute coronary syndrome; UA = unstable angina; STEMI = ST-Elevation Myocardial Infarction; NSTEMI = Non-ST-Elevation Myocardial Infarction

Koskinas KC, et al. *Clinical Cardiology*. 2018;41:1513-1520.

Exclusion Criteria (1/2)

- **Unstable clinical status** (hemodynamic or electrical instability)
- Uncontrolled cardiac **arrhythmia**
- **Severe renal dysfunction**, defined by estimated glomerular filtration rate <30 ml/min/1.73m^2
- **Active liver disease or hepatic dysfunction**, either reported in patient medical record or defined by asparate aminotransferase (AST) or alanine aminotransferase (ALT) levels > 3x the upper limit of normal
- Reported **intolerance to atorvastatin** (any dose) OR **statin intolerance** defined by pre-defined criteria *(inability to tolerate at least 2 different statins (one statin at the lowest starting average daily dose and the other statin at any dose); intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities; symptom or biomarker changes resolution upon dose decrease or discontinuation; symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions)*
- Known **allergy** to contrast medium, heparin, aspirin, ticagrelor or prasugrel
- Known **sensitivity** to any substances to be administered

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Exclusion Criteria (2/2)

- Patients who previously received **evolocumab** or other **PCSK9 inhibitor**
- Patient who received **cholesterol ester transfer protein inhibitors** in the past 12 months
- Treatment with systemic **steroids** or systemic **cyclosporine** in the past 3 months
- Known active infection or **major hematologic, metabolic, or endocrine dysfunction** in the judgment of the Investigator
- Patients who will not be available for **study-required procedures** in the judgment of the Investigator
- Current enrollment in another investigational device or drug study
- Active **malignancy** requiring treatment
- Pregnant women. For female of childbearing potential (age <50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy, pregnancy will be excluded by a pregnancy test prior to inclusion in the study

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Exloratory Endpoints (1 / 2)

- Nominal change in calculated **LDL-C** from baseline to 8 weeks
- Percent of patients reaching LDL-C level <70 mg/dL (<1.8 mmol/L) at 8 weeks
- Change on other **lipid parameters** (total cholesterol, HDL-C, triglycerides, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, etc.) at 8 weeks
- Percent change in **hs-CRP** from baseline to 8 weeks
- Percent of patients reaching a dual target of LDL-C (<70 mg/dL) and hs-CRP (<2 mg/dL) at 8 weeks
- Change in other **inflammatory biomarkers** (IL-1b, IL-6) from baseline to 8 weeks
- Change in biomarkers of **myocardial injury** (high-sensitivity troponin T) from baseline to 72 hours
- **Platelet function** assessed by impedance aggregometry (Multiplate Analyzer®) in whole blood stimulated with ADP and TRAP test at 72 hours and 8 weeks

LDL-C = low-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; ADP = adenosine di-phosphate; TRAP = tumor necrosis factor receptor; HDL-C = High-density lipoprotein cholesterol; ApoA = apolipoprotein A; ApoB = apolipoprotein B

Koskinas KC, et al. *Clinical Cardiology*. 2018;41:1513-1520.

Exloratory Endpoints (2 / 2)

- Incidence of **contrast-induced acute kidney injury (CI-AKI)** at 72 hours in the subset of patients undergoing diagnostic coronary angiography (with or without PCI) at baseline

- Incidence of centrally **adjudicated events**:
  - Death by any cause
  - Cardiovascular death
  - Myocardial infarction (re-infarction)
  - Hospitalization for recurrent ACS
  - Hospitalization for heart failure
  - Coronary revascularization
    - Performed at site of index PCI (target-lesion revascularization)
    - Performed for other stenosis present at the time of index PCI (staged PCI)
    - Other, clinically indicated coronary revascularization
  - Stroke
  - Transient ischemic attack (TIA)

ACS = acute coronary syndrome

Koskinas KC, et al. *Clinical Cardiology*. 2018;41:1513-1520.

Background Statin Treatment During the Study

- All patients received high-intensity statin therapy (**atorvastatin 40mg**), starting on Day 1 and up to Week 8
- If patients had been on previous statin other than atorvastatin 40mg prior to screening, it was and replaced by atorvastatin 40mg
- If patients had been on a more potent statin regimen prior to enrolment (i.e., atorvastatin > 40mg or rosuvastatin > 20mg QD), the background therapy was *atorvastatin **80mg*** throughout the study period
- Between randomization and end of study (Week 8), changes in background statin therapy were not allowed
- In the event of adverse events deemed to represent **statin intolerance** (e.g. muscle-related symptoms with or without CK elevation), reduction of the dose of atorvastatin or statin discontinuation were allowed, according to clinical judgement

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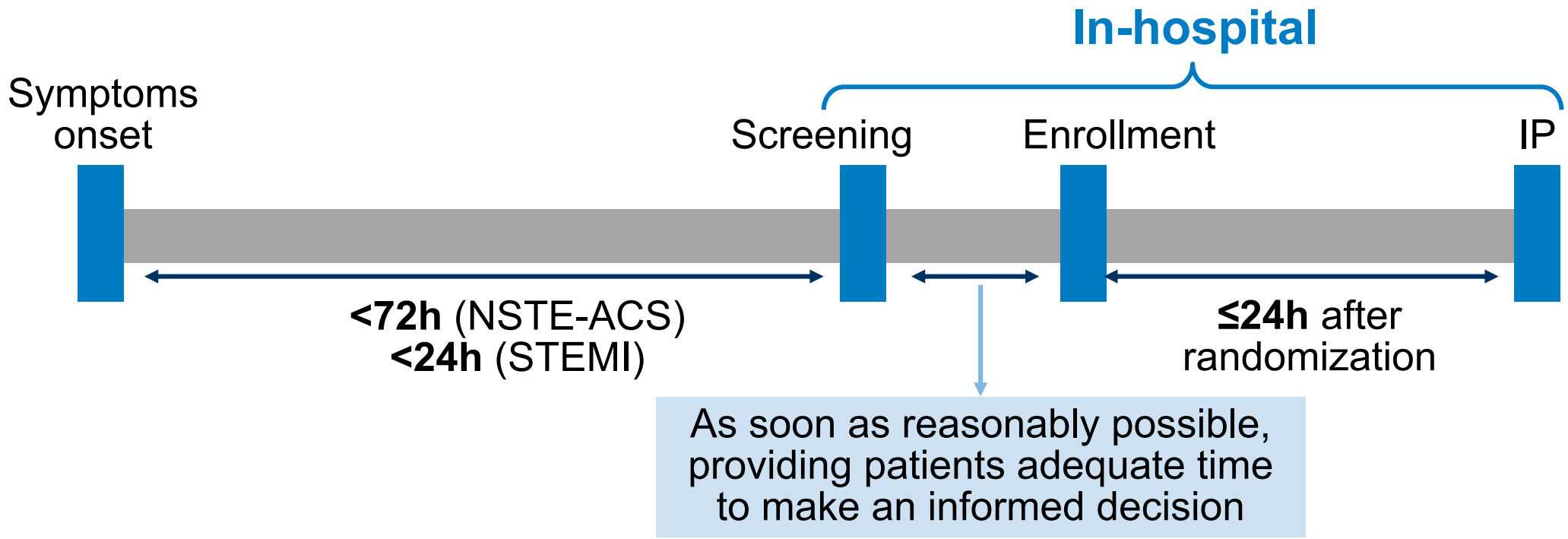
Koskinas KC, et al. *Clinical Cardiology*. 2018;41:1513-1520.

Protocol-Defined Time Windows for Enrollment and Administration

Protocol-defined time windows for enrollment and administration of the IP at baseline in relation to the time of onset of symptoms in patients presenting with ACS



ACS = acute coronary syndromes; IP = investigational product; STEMI = ST-Elevation Myocardial Infarction; NSTEMI = Non-ST-Elevation Myocardial Infarction

Koskinas KC, et al. *Clinical Cardiology*. 2018;41:1513-1520.

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EVOPACS: Summary of Study Protocol

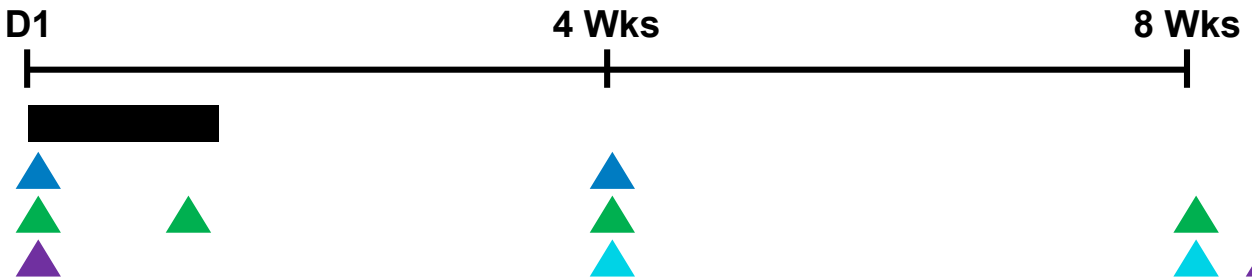
Patients with ACS (n = 308)

- ACS (NSTEMI / UA < 72 hours, STEMI <24 hours)
- **LDL-C levels** defined as follows:
  - ≥1.8 mmol/L (70 mg/dL) in patients previously on stable treatment with **high-intensity statin**, OR
  - ≥2.8 mmol/L (90 mg/dL) in patients previously on stable treatment with **low- or moderate-intensity statin**, OR
  - ≥3.2 mmol/L (125 mg/dL) in **statin-naïve** patients or patients not on stable statin treatment

Randomization 1:1

- Evolocumab SC 420 mg + Atorvastatin 40mg QD
- Placebo SC+ Atorvastatin 40mg QD

End of Study



- In-hospital (≥72h)
- IP administration
- Lab testing
- Clinical follow-up
- NIRS (imaging sub-study)

ACS = acute coronary syndrome; UA = unstable angina; STEMI = ST-Elevation Myocardial Infarction; NSTEMI = Non-ST-Elevation Myocardial Infarction; QD = daily; SC = subcutaneous; IP = investigational product

Koskinas KC, et al. *Clinical Cardiology*. 2018;41:1513-1520
Koskinas KC, et al. *JACC*. [published online ahead of print August 31, 2019]. https://doi.org/10.1016/j.jacc.2019.08.010

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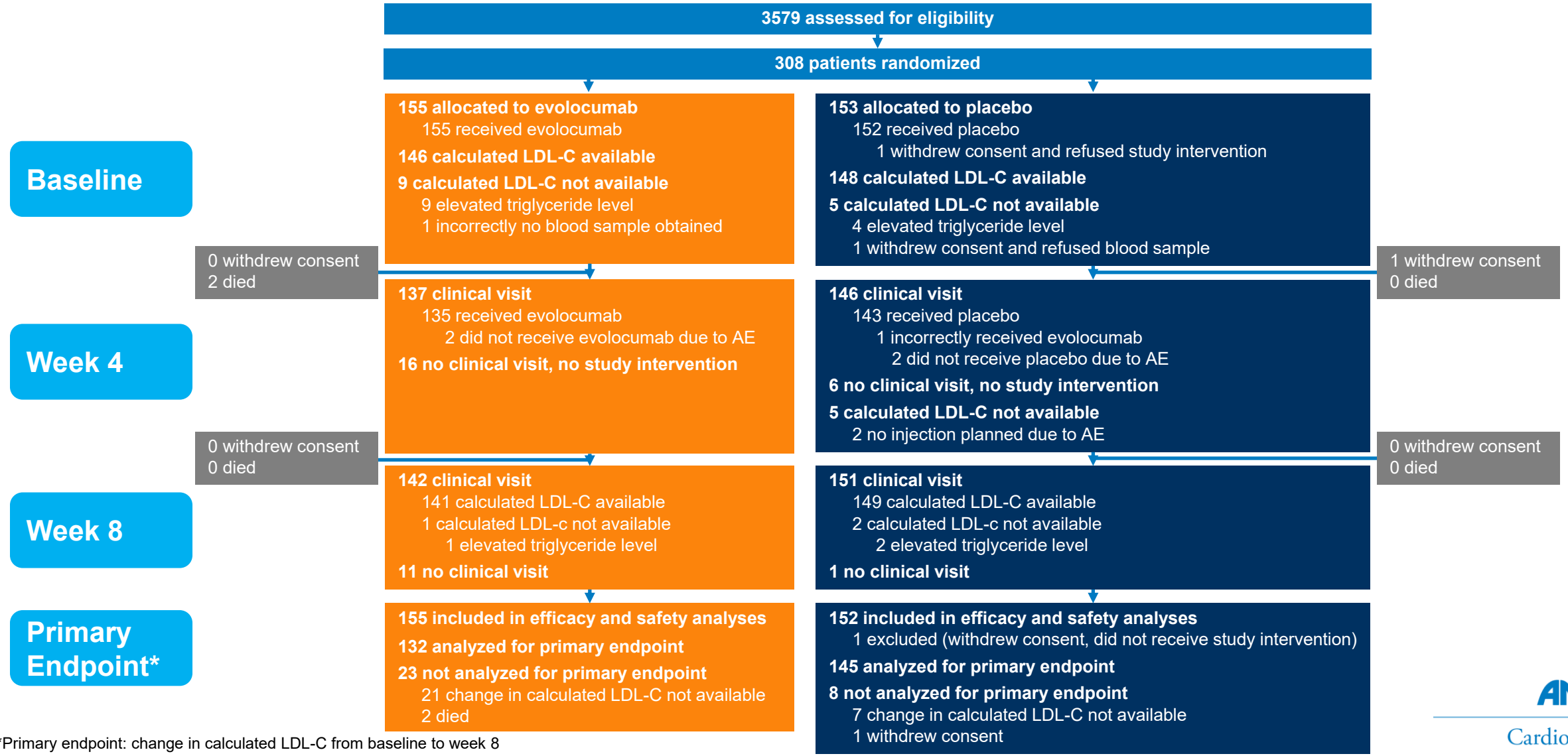
Study Flowchart



*Primary endpoint: change in calculated LDL-C from baseline to week 8

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LDL-C Efficacy Outcomes

Intention-to-Treat Analysis

	Evolocumab	Placebo	Mean difference (95% CI)[a]	P-value
Calculated LDL-C				
Baseline	3.61±1.00 [146]	3.42±0.94 [148]	0.14 (-0.05 to 0.32)	
Week 8	0.79±0.46 [141]	2.06±0.63 [149]	-1.27 (-1.40 to -1.14)	<0.001
Absolute change from baseline (mg/dL)	-2.83±1.02 [132]	-1.35±1.04 [145]	-1.43 (-1.63 to -1.22)	<0.001
% Change from baseline (primary endpoint)	-77.1%±15.8% [132]	-35.4%±26.6% [145]	-40.7% (-45.2% to -36.2%)	<0.001
Calculated LDL-C <1.8 mmol/L at week 8, %	95.7% [141]	37.6% [149]	57.8% (66.2% to 49.4%)	<0.001

The percent change in LDL-C from baseline to week 8 in the evolocumab group was 77%.
The mean difference of LDL-C reduction between treatment groups was 41%.

Data expressed as means or least-squares means ± standard deviations or n (%). P-value of the randomized arm, using mixed models correcting for a random effect of study site and a fixed effect of stable statin treatment before randomization.

[a]Evolocumab minus placebo.

Koskinas KC, et al. *JACC*. [published online ahead of print August 31, 2019]. https://doi.org/10.1016/j.jacc.2019.08.010

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Lipid Efficacy Outcomes

Intention-to-Treat Analysis

	Evolocumab	Placebo	Mean difference (95% CI)[a]	P-value
Other lipids, % change from baseline to week 8				
Cholesterol	-51.8%±14.6% [140]	-24.4%±19.3% [150]	-26.5% (-29.9% to -23.1%)	<0.001
Apolipoprotein B	-63.6%±14.9% [137]	-28.8%±23.4% [149]	-34.2% (-38.2% to -30.2%)	<0.001
Non-HDL-C	-67.3%±15.4% [140]	-31.7%±23.7% [150]	-34.6% (-38.5% to -30.6%)	<0.001
Triglycerides	-16.4%±40.4% [140]	4.5%±98.4% [150]	-20.0% (-37.4% to -2.6%)	0.024
HDL-C	9.5%±17.9% [140]	4.9%±19.7% [150]	4.8% (0.5 to 9.1%)	0.03
Apolipoprotein A1	5.6%±15.5% [137]	3.5%±14.7% [148]	2.2% (-1.2% to 5.7%)	0.21

Evolocumab compared with placebo significantly reduced total cholesterol by 26.5%, ApoB by 34.2%, non-HDL by 34.6% and raised HDL-C by 4.8%

Data expressed as means or least-squares means ± standard deviations or n (%). P-value of the randomized arm, using mixed models correcting for a random effect of study site and a fixed effect of stable statin treatment before randomization.

[a]Evolocumab minus placebo.

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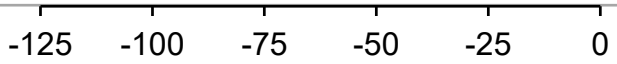
Percent Change in LDL-C from Baseline to 8 Weeks By Baseline Subgroup

	Evolocumab (N = 155)		Placebo (N = 152)				Interaction
	n	Mean ± SD	n	Mean ± SD	Calculated LDL-C Mean Difference (95% CI)	P-value	P-value
Overall	132	-77.1 ± 15.8	145	-35.4 ± 26.6	-40.7 (-45.2 to -36.2)	<0.001	
Statin at baseline							<0.001
Yes	26	-63.9 ± 24.8	34	-8.1 ± 30.8	-55.8 (-70.1 to -41.6)	<0.001	
No	106	-80.3 ± 10.5	111	-43.8 ± 18.5	-36.5 (40.5 to -32.5)	<0.001	
Study center							0.50
#1	45	-75.1 ± 17.9	48	-38.9 ± 23.8	-35.0 (-42.2 to -27.9)	<0.001	
#2	6	-73.0 ± 17.0	8	-44.1 ± 9.5	-33.4 (-42.9 to -24.0)	<0.001	
#3	5	-79.2 ± 3.9	7	-26.2 ± 44.3	-42.9 (-71.4 to -14.4)	0.003	
#4	41	-79.2 ± 12.3	46	-35.9 ± 26.5	-42.8 (-50.7 to -35.0)	<0.001	
#5	4	-66.3 ± 31.8	2	-3.3 ± 36.1	-59.2 (-104.8 to -13.7)	0.011	
#6	24	-79.0 ± 16.1	25	-29.0 ± 27.5	-47.6 (-59.0 to -36.2)	<0.001	
#7	7	-79.1 ± 12.7	9	-37.8 ± 29.2	-43.7 (-58.6 to -28.8)	<0.001	
Clinical Presentation							0.42
STEMI	58	-80.5 ± 12.8	45	-42.7 ± 21.2	-37.8 (-44.4 to -31.3)	<0.001	
NSTE-ACS	74	-74.36 ± 17.4	100	-32.1 ± 28.2	-42.3 (-49.5 to -35.0)	<0.001	
Age							0.90
<65 years	89	-78.9 ± 13.9	95	-37.1 ± 26.8	-41.8 (-48.0 to -35.6)	<0.001	
≥65 years	43	-73.1 ± 18.7	50	-32.2 ± 26.2	-41.1 (-50.4 to -31.8)	<0.001	
Gender							0.69
Male	109	-78.1 ± 15.8	116	-36.0 ± 26.4	-42.1 (-47.8 to -36.4)	<0.001	
Female	23	-72.3 ± 15.1	29	-32.9 ± 27.7	-39.3 (-51.7 to -27.0)	<0.001	
LDL-C at baseline							0.01
≥ median	70	-80.9 ± 10.6	69	-46.3 ± 16.2	-34.6 (-39.1 to -30.1)	<0.001	
< median	62	-72.8 ± 19.3	76	-25.5 ± 30.2	-47.3 (-55.9 to -38.7)	<0.001	



Shown are means ± standard deviations (p-value from mixed models), interaction p-value testing for the interaction effect subgroup x randomised arm from full-factorial mixed model. Stratification for baseline statin treatment was done according to presence or absence of stable (unchanged) statin treatment in the preceding 4 weeks prior to enrolment.

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Pre-specified Sensitivity Analysis of the Primary Endpoint

	All patients	Evolocumab	Placebo	Mean difference (95% CI)†	p value
Calculated LDL-C					
% Change from baseline to week 8	-55.30 (-58.77 to -51.83)	-74.16 (-77.65 to -70.66)	-36.06 (-40.37 to -31.76)	-37.15 (-42.13 to -32.18)	<0.001

Consistent with the primary endpoint results, the percent change in LDL-C from baseline to week 8 using a pre-specified sensitivity analysis in the evolocumab group was 55%. The mean difference of LDL-C reduction between treatment groups was 37%.

*According to the protocol, a sensitivity analysis for the primary endpoint using multiple imputation to impute the primary endpoint was pre-specified if calculated LDL-C at 8 weeks was missing in more than 5% of the patients. Calculated LDL-C was not available at week 8 in 18 patients (5.8% of all 308 randomised patients).

P-value of the randomised arm, using mixed models correcting for a random effect of the site and a fixed effect of stable statin treatment 4 weeks before randomisation. Computations based on combining the results from 20 multiple imputed data sets using Rubin's rule. Imputations based on predictive mean matching to five nearest neighbours, using the following baseline variables: corneal arcus, xanthomas, thyroid dysfunction, eGFR, AST, ALT, ALP, ADP, TRAP, age, gender, BMI, systolic BP, diastolic BP; family history of CAD, peripheral arterial disease, diabetes mellitus, insulin-treated diabetes mellitus, arterial hypertension, hypercholesterolemia, smoking history, active smoker, history of MI, PCI, CABG, CAD, HF, stroke, TIA, malignancy, no vs medium vs high intensity statins in the 4 weeks before randomisation; and follow-up variables: clinical visit week 4, clinical visit week 8, adverse event leading to study drug discontinuation; lipid measurements imputed for baseline, week 4 and week 8 (if missing).

†Evolocumab minus placebo.

CI = confidence intervals

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Exploratory Analysis of the Primary Endpoint

	All patients	Evolocumab	Placebo	Mean difference (95% CI)†	p value
Calculated or directly measured LDL-C					
Baseline (mmol/L)	3.53 ± 0.98 [306]	3.61 ± 0.99 [154]	3.44 ± 0.96 [152]	0.12 (-0.06 to 0.30)	0.2
Week 8 (mmol/L)	1.53 ± 0.78 [291]	0.95 ± 0.44 [141]	2.07 ± 0.62 [150]	-1.11 (-1.23 to -0.99)	<0.001
Absolute change from baseline (mmol/L)	-1.99 ± 1.21 [290]	-2.66 ± 1.00 [140]	-1.37 ± 1.05 [150]	-1.24 (-1.44 to -1.04)	<0.001
% Change from baseline	-53.08 ± 28.29 [290]	-71.89 ± 15.35 [140]	-35.52 ± 26.25 [150]	-35.32 (-39.61 to -31.02)	<0.001
LDL-C < 1.8 mmol/L at Week 8	66.0% [291]	95.7% [141]	38.0% [150]	57.9 (49.4 to 66.5)	<0.001

Consistent with the primary endpoint results, mean calculated LDL-C levels at baseline were 3.51±0.97 mmol/L

Exploratory analysis of the primary endpoint using calculated LDL-C, or directly measured LDL-C in cases of calculated LDL-C <40 mg/dL or TG > 400 mg/dL

LDL-C = low-density lipoprotein cholesterol

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Narratives for Two Deaths that Occurred During the EVOPACS Study

Patient	Randomised arm	Description	Blinded assessment of relationship of death with study drug
Patient # 1	Evolocumab	A 75-year-old male patient with known coronary artery disease (history of myocardial infarction and PCI) presented with NSTE-ACS. Symptoms had reportedly began 2 days before. Cardiovascular risk factors included active smoking, diabetes mellitus, arterial hypertension, and hypercholesterolemia (LDL cholesterol 2.8 mmol/l at baseline under atorvastatin 20mg). Baseline medical treatment included aspirin, amlodipin, lisinopril, and atorvastatin. The patient was enrolled in the study and received the baseline study drug on the same day of admission in the hospital. Coronary angiography showed complex three- vessel coronary artery disease (chronic occlusion of the right coronary artery, significant stenoses in the proximal left anterior descending artery and first marginal branch). The patient was scheduled for coronary artery bypass surgery after 7 days, and remained in-hospital. On the day of the scheduled surgery (day 7 after study enrolment), the patient reported retrosternal pain. ECG showed ST elevation in anterior and inferior leads. The patient underwent urgent coronary angiography, which showed acute occlusion of the proximal left anterior descending artery, occlusion of the right circumflex artery, and a critical lesion in the first marginal branch. The patient developed cardiogenic shock and, during attempted recanalization of the left anterior descending artery, developed rhythm disorders and cardiac arrest. Despite resuscitation (30 minutes compression) and attempted extracorporeal membrane oxygenation (ECMO), the patient died with electromechanical dissociation. The CEC adjudicated the death as cardiovascular.	• Local Investigator: No/Unlikely • DSMB: No/Unlikely

CEC = Clinical Events Committee; DSMB = Data and Safety Monitoring Board; ECG = electrocardiogram; PCI = percutaneous coronary intervention; NSTEMI = non-ST-Elevation Myocardial Infarction

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Narratives for Two Deaths that Occurred During the EVOPACS Study

Patient	Randomised arm	Description	Blinded assessment of relationship of death with study drug
Patient #2	Evolocumab	A 76-year-old patient with a history of atrial fibrillation presented with NSTE-ACS. CV risk factors included arterial hypertension, obesity (BMI 32.6), and hypercholesterolemia (LDL-C 3.86 mmol/L under no lipid-lowering therapy). The patient was enrolled in the study and received the baseline study drug on the same day of hospital admission, on the same day and following the coronary angiography. Angiography showed complex three-vessel disease, and aortic valve stenosis was found in echocardiography with preserved left ventricular function (LVEF 58%). The patient was transferred to another hospital for cardiac surgery. The patient remained in-hospital, and surgery (quadruple coronary bypass grafting and concomitant aortic valve replacement) was performed at 11 days after study enrolment. Surgery was complicated by intraoperative rupture of the calcific aortic root and the right coronary ostium requiring composite graft implantation (Bentall procedure) with re-implantation of the right coronary artery using a short saphenous venous graft. Postoperatively the patient remained hemodynamically unstable requiring hemodynamic support with a veno-arterial extracorporeal membrane oxygenation device (ECMO) and underwent two repeat surgical revisions for pericardial tamponade. Right ventricular failure was the leading presentation. Coronary angiography six days after surgery (17 days after study enrolment) revealed an occluded venous graft to the right coronary artery; however, no repeat revascularization was attempted. Progressive cardiogenic shock with multi-organ failure (ischemic hepatic failure, acute kidney failure requiring hemodialysis) evolved and six days later, replacement of the veno-arterial ECMO by a percutaneous right ventricular assist device was attempted. This immediately resulted in acute left ventricular decompensation refractory to further medical treatment. The patient died 14 days after surgery (25 days after study enrolment). The CEC adjudicated the death as cardiovascular.	• Local Investigator: No/Unlikely • DSMB: No/Unlikely

CEC = Clinical Events Committee; CV = cardiovascular; DSMB = Data and Safety Monitoring Board; ECG = electrocardiogram; PCI = percutaneous coronary intervention; NSTEMI = non-ST-Elevation Myocardial Infarction

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