LDL-C Lowering Strategies for ACS Patients: How Early is Early?

AMGEN Repatha

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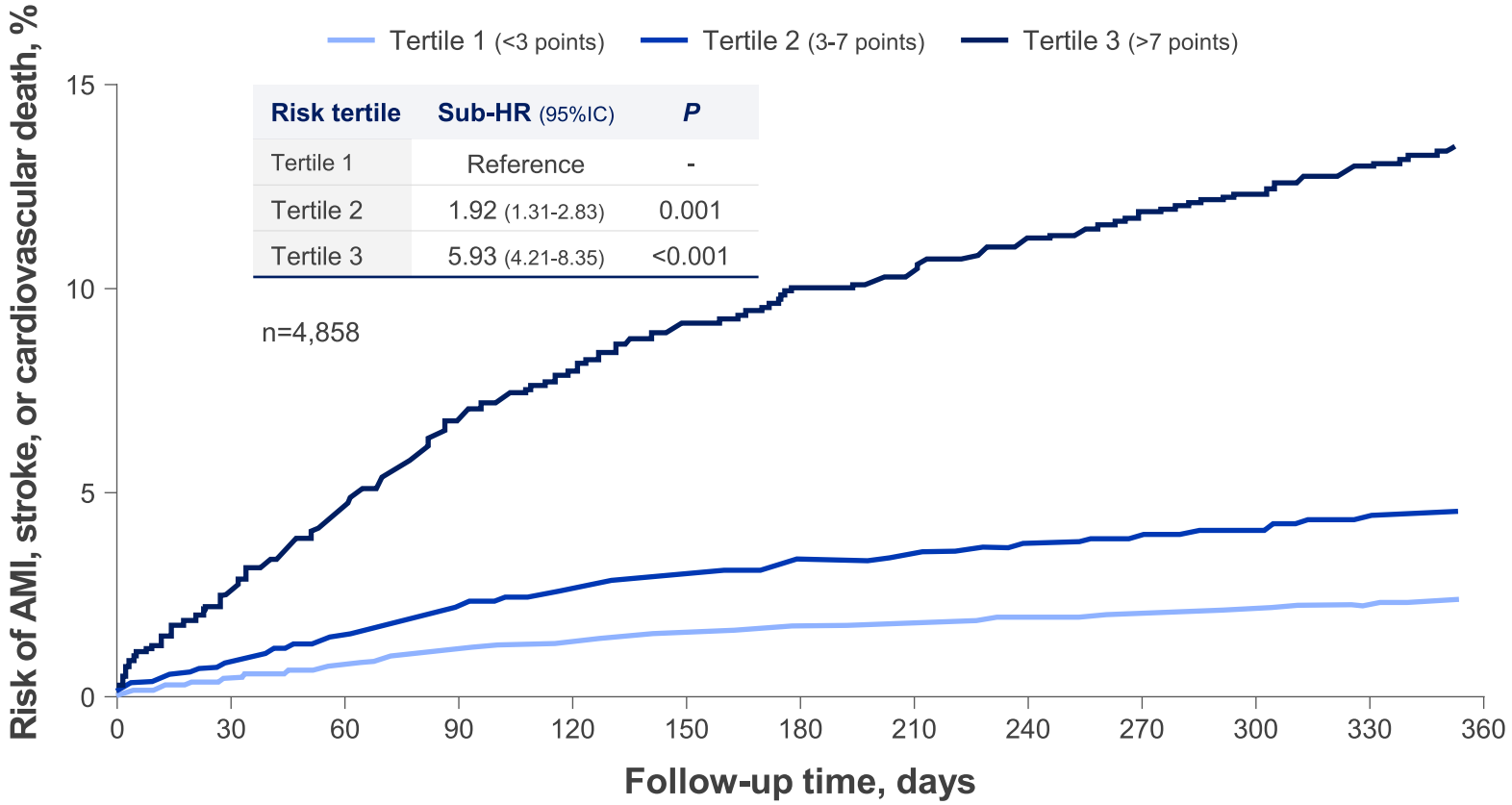
The Risk of a Recurrent Cardiovascular Events Remain High After ACS

- A retrospective study was conducted of 4,858 patients who survived an acute coronary event
- Analyzed the **incidence and predictors of acute myocardial infarction, stroke, or cardiovascular death during the first year (n = 4,858)** vs successive years

Risk factor		Add score
Age (years)	<49.9	-4
	50-59	-2
	61.0-69.9	0
	70.0-79.9	2
	≥80	4
Diabetes mellitus	No	0
	Yes	2
Peripheral artery disease	No	0
	Yes	2.5
Stroke/TIA	No	0
	Yes	3
Previous ischemic heart disease	No	0
	Yes	5.5
History of heart failure	No	0
	Yes	3
NSTEMI	No	0
	Yes	1.5
Multivessel disease	No	0
	Yes	1.5
Not revascularized	No	0
	Yes	2
Serum creatinine	<1.5	0
	1.6-2.4	2
	2.5-2.9	2.5
	3.0-3.4	3
	3.5-5.0	4.5

Cumulative incidence function of AMI, stroke, or CV death during the FIRST YEAR of follow-up stratified by risk tertiles



1. Abu-Assi, et al. Rev Esp Cardiol. 2016;69(1):11–18

Recurrent CV Events Are Greatest in the First Year Post-MI

Patients:

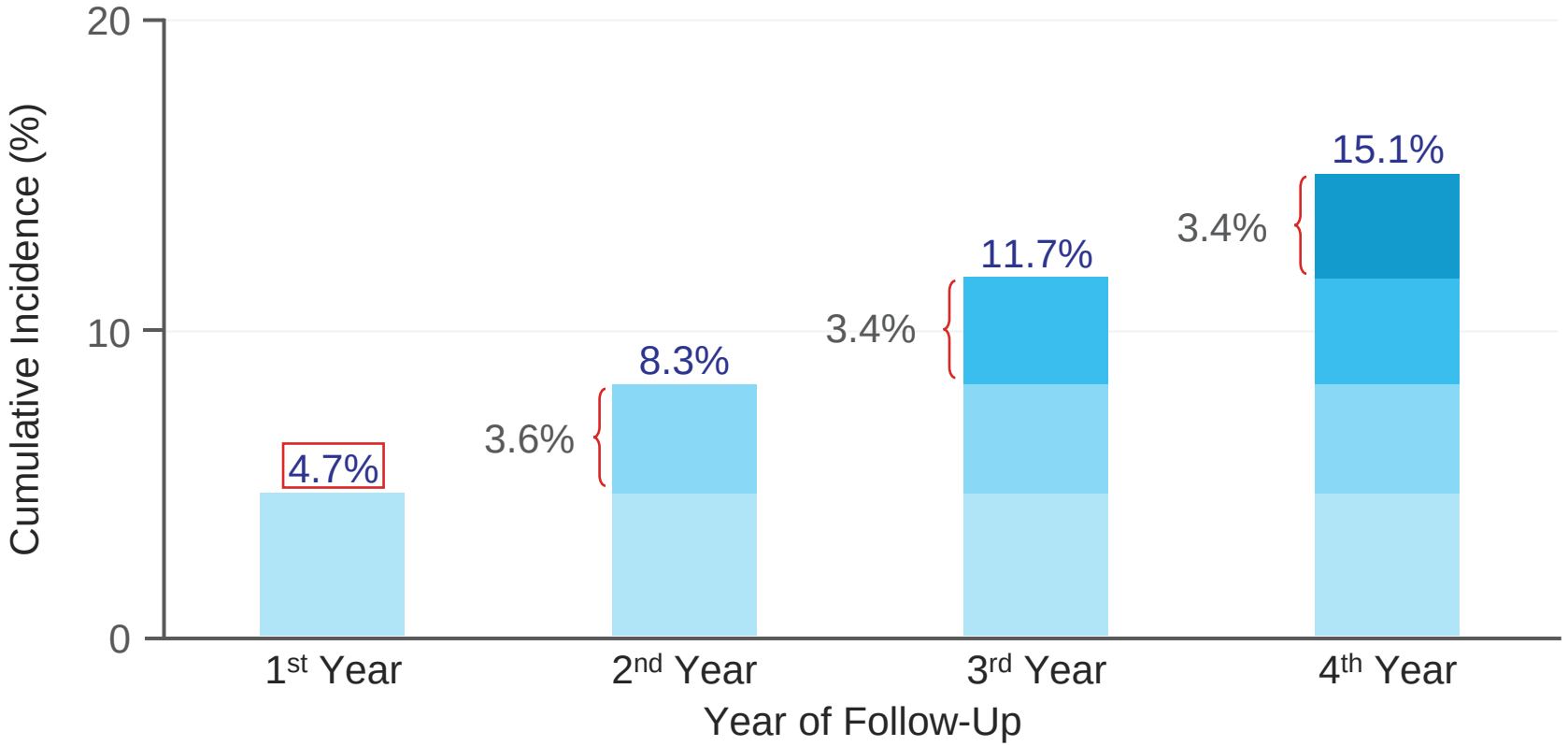
N = 16,770
Patients with established CAD, cerebrovascular disease, PAD, or with >3 atherothrombotic risk factors

International, prospective observational study (REACH registry)

Mean age: 67 years

Follow-up: Initially, 2 years + centers invited to participate in a 2-year extension

Cumulative Incidence Rates of CV Events (CV Death, MI, Stroke) Post-MI



CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral artery disease; REACH, Reduction of Atherothrombosis for Continued Health.

1. Abtan J, et al. Clin Cardiol. 2016;39:670-677.

Re-hospitalization ≤30 Days Occurs in ~1 in 5 Patients Post-MI

Patients:

Patients hospitalized with MI (N=405,531) or UA (N=17,859) (2010 for 1-year mortality)

National cohort of all Medicare Fee-for-Service beneficiaries (1999–2011)

Age: ≥ 65 years

Follow-up: 1 year

Mortality and Re-hospitalization in Patients With MI and UA

	MI (N=405,351)	UA (N=17,859)
	2010–2011	2010–2011
Mortality % (95% CI)		
In-hospital	8.3 (8.18–8.35)	0.8 (0.66–0.93)
30-day	13.7 (13.6–13.8)	2.4 (2.19–2.65)
1-year*	27.22 (27.1–27.3)	8.9 (8.5–9.1)
All-cause, 30-day readmission % (95% CI)	18.7 (18.6–18.8)	13.7 (13.2–14.3)
Mean length of stay, days (SD)	5.4 (5.4)	2.5 (2.4)
Annual inflation-adjusted spending per hospitalization with Medicare mean cost $ (SD)	$14,732 ($15,564)	$4,409 ($5,668)

*2010–2011.

CI, confidence interval; MI, myocardial infarction; SD, standard deviation; UA, unstable angina

1. Krumholz HM, et al. Circulation. 2014;130:966-975.

02

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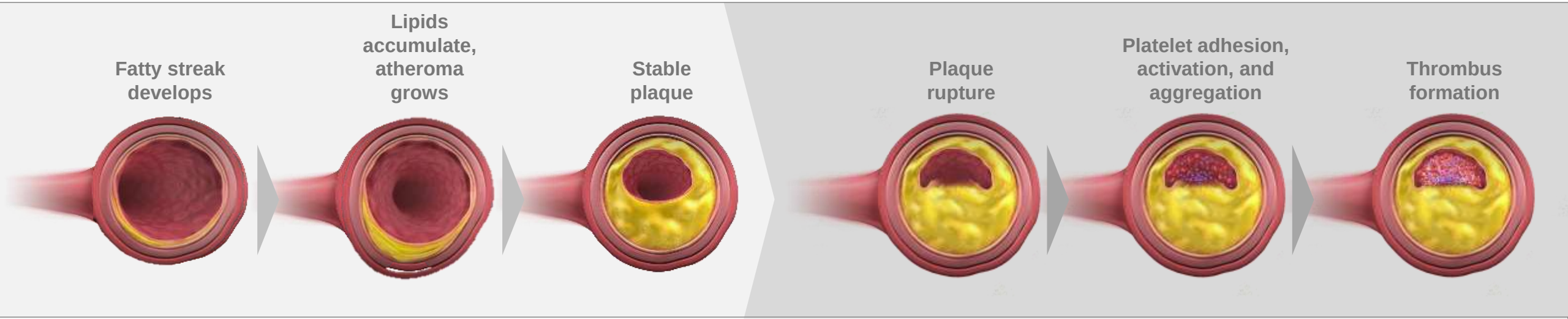
ACS Represents a Constellation of Event Types



The underlying disease mechanism of ACS is atherosclerosis, a systemic, progressive disease that affects multiple vascular beds and can lead to CV events

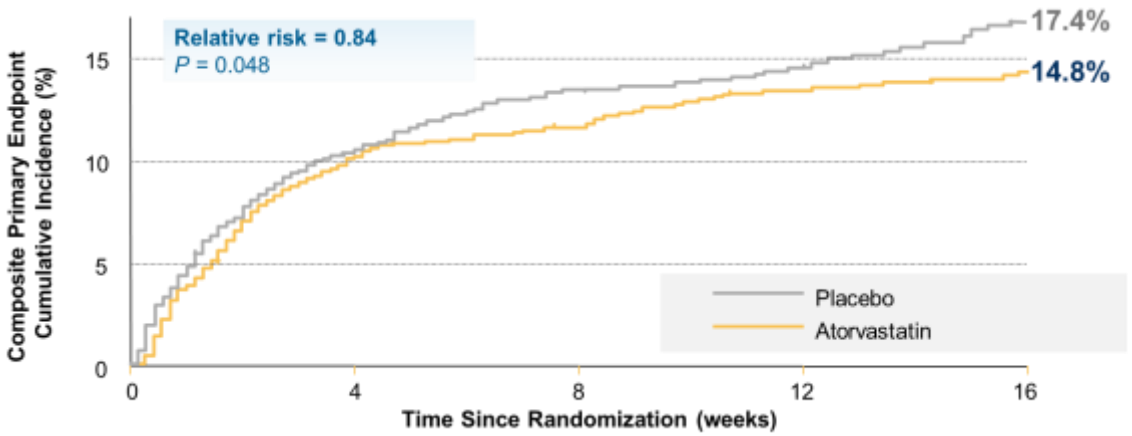
ASCVD = atherosclerotic cardiovascular disease; UA = unstable angina.

Grundy SM, et al. *J Clin Lipidol*. 2014;8:29-60.

Statins in ACS : How Early, How Strong?

MIRACL STUDY

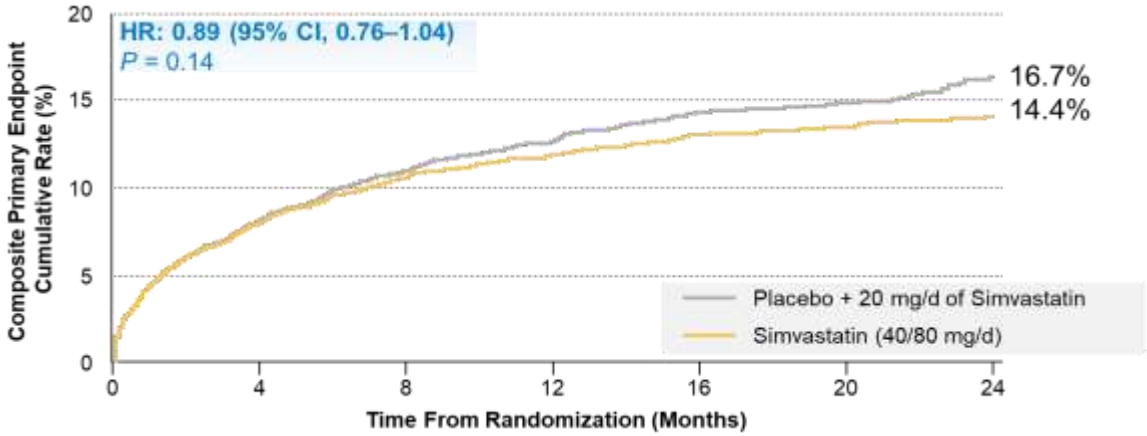
Death, MI, resuscitated cardiac arrest, recurrent myocardial ischemia



Schwartz GG, et al. *JAMA*. 2001;285:1711-1718.

The A to Z Trial: Phase Z

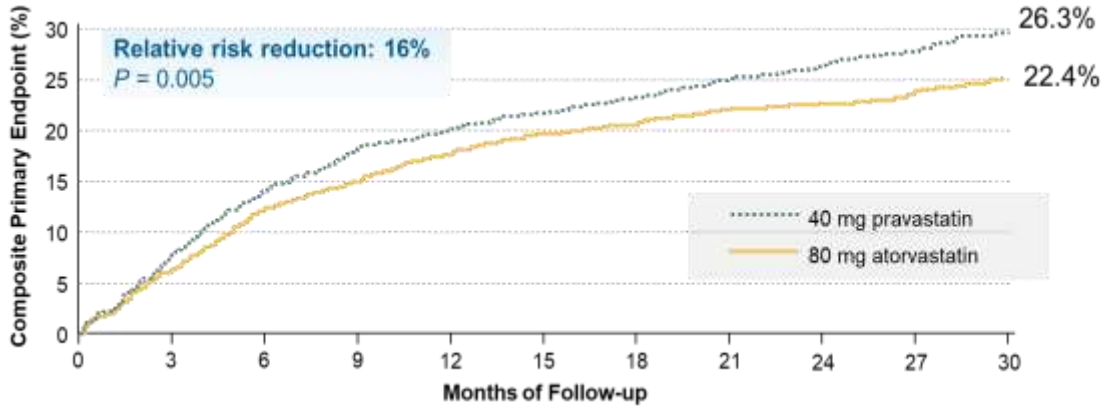
CV death, MI, ACS readmission, stroke



de Lemos JA, et al. JAMA. 2004;292:1307-1316.

PROVE-IT TIMI 22 STUDY

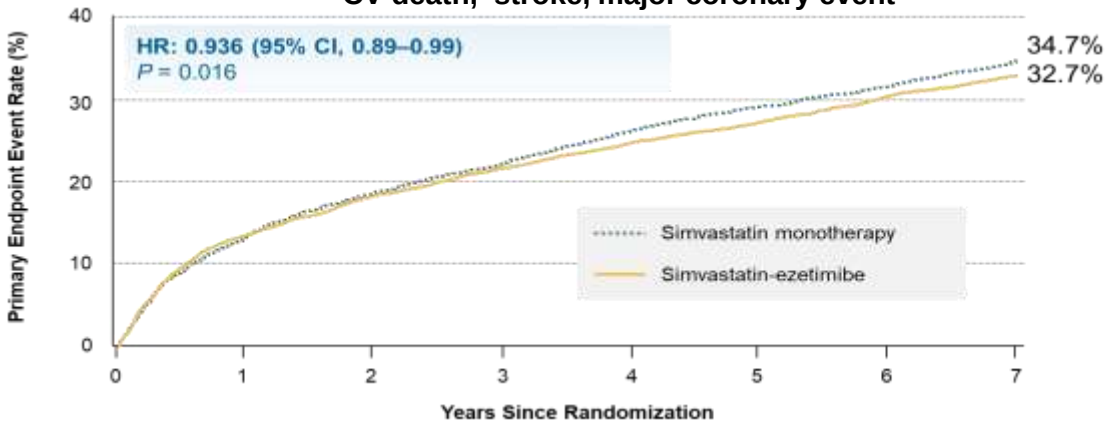
Death From Any Cause or Major CV Event*



*Major CV event defined as MI, documented UA requiring rehospitalization, revascularization with either PCI or CABG (if these procedures were performed at least 30 days after randomization), and stroke.
Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

IMPROVE-IT Study

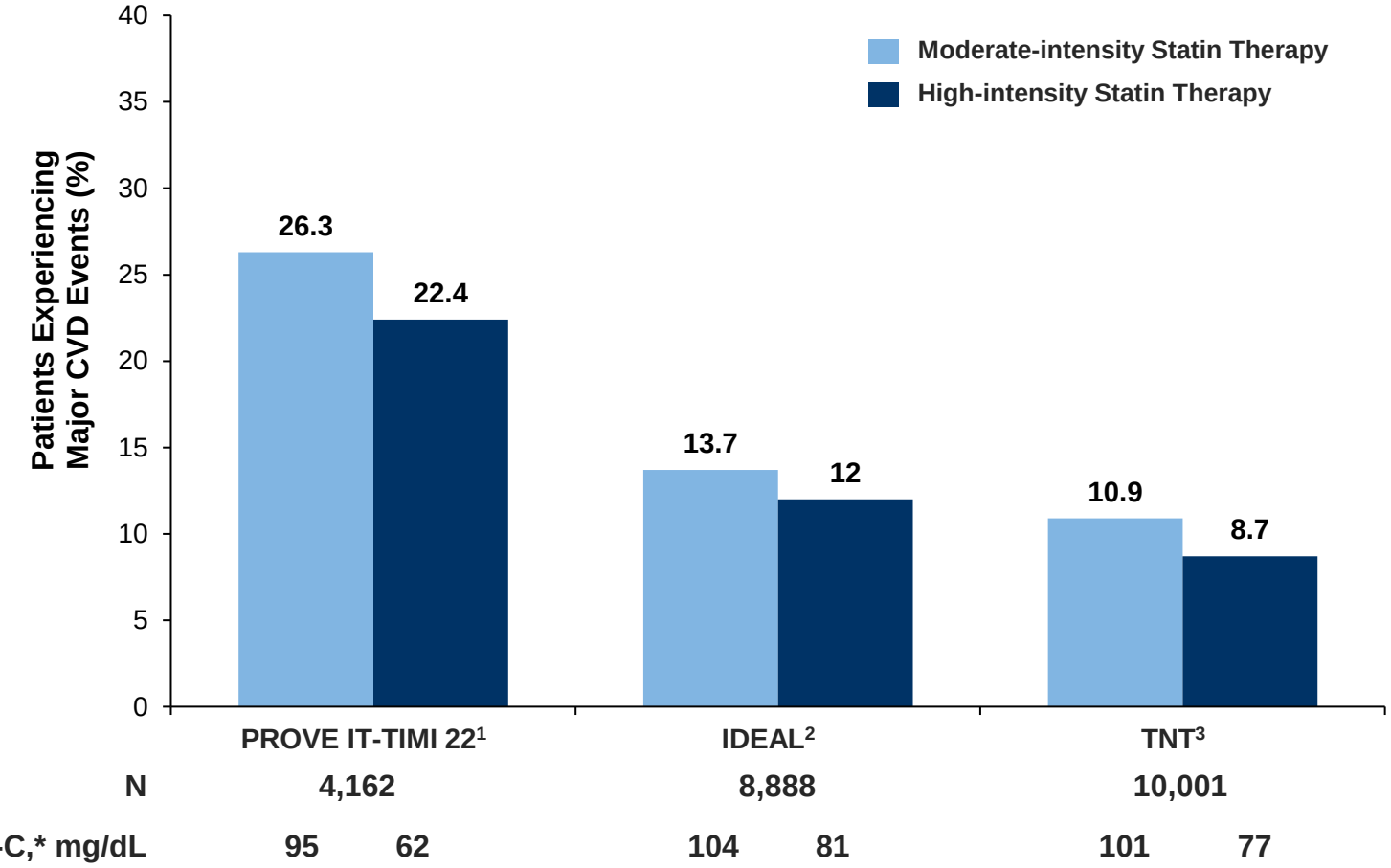
CV death, stroke, major coronary event



Cannon CP, et al. N Engl J Med. 2015;372:2387-2397.

Residual CV Risk Remains Even in Those Receiving Treatment With High-Intensity Statins

Incidence of Major CVD Events and Levels of LDL-C in Patients Receiving Moderate- or High-Intensity Statin Therapy



* Mean or median LDL-C after treatment.
CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

1. Cannon CP, et al. N Engl J Med. 2004;350:1495-1504. **2.** Pederson TR, et al. JAMA. 2005;294:2437-2445. **3.** LaRosa JC, et al. N Engl Med. 2005;352:1425-1435.

2020 ESC Guidelines Recommend PCSK9i As Early As Possible if LDL-C Goal Is Not Achieved in NSTE-ACS

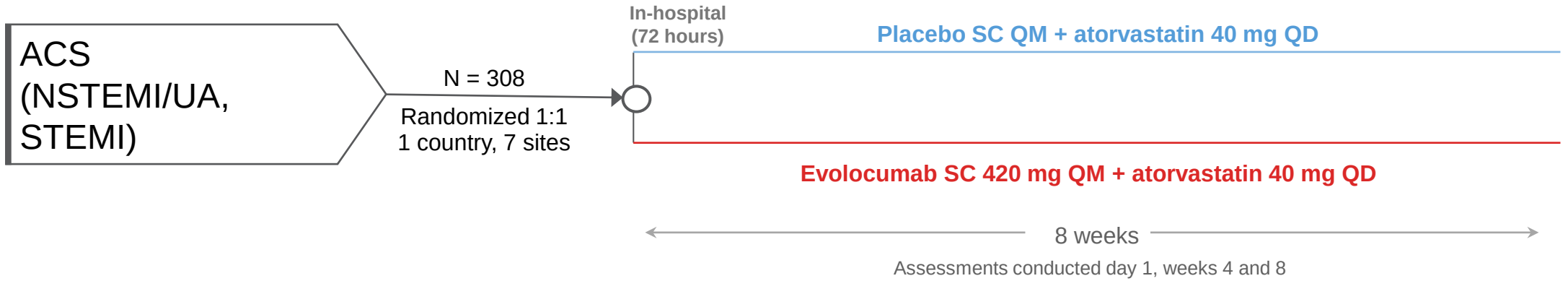
Recommendations	Class*	Level†
Statins are recommendation in all NSTE-ACS patients. The aim is to reduce LDL-C by ≥50% from baseline and/or to achieve LDL-C< <55mg/dL.	I	A
If the LDL-C goal is not achieved after 4-6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B
If the LDL-C goal is not achieved after 4-6 weeks despite maximally tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended.	I	B
If the current NSTE-ACS episode is a recurrence within less than 2 years of a first ACS, while taking maximally tolerated statin-based therapy, an LDL-C goal<40mg/dL may be considered.	IIb	B

*Class of recommendation; †Level of evidence.

1. European Heart Journal (2020) 00, 1-79

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

Study Design



PRIMARY ENDPOINT

- LDL-C change from baseline at week 8

SECONDARY ENDPOINT

- Safety and tolerability (S)AE

INCLUSION CRITERIA

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

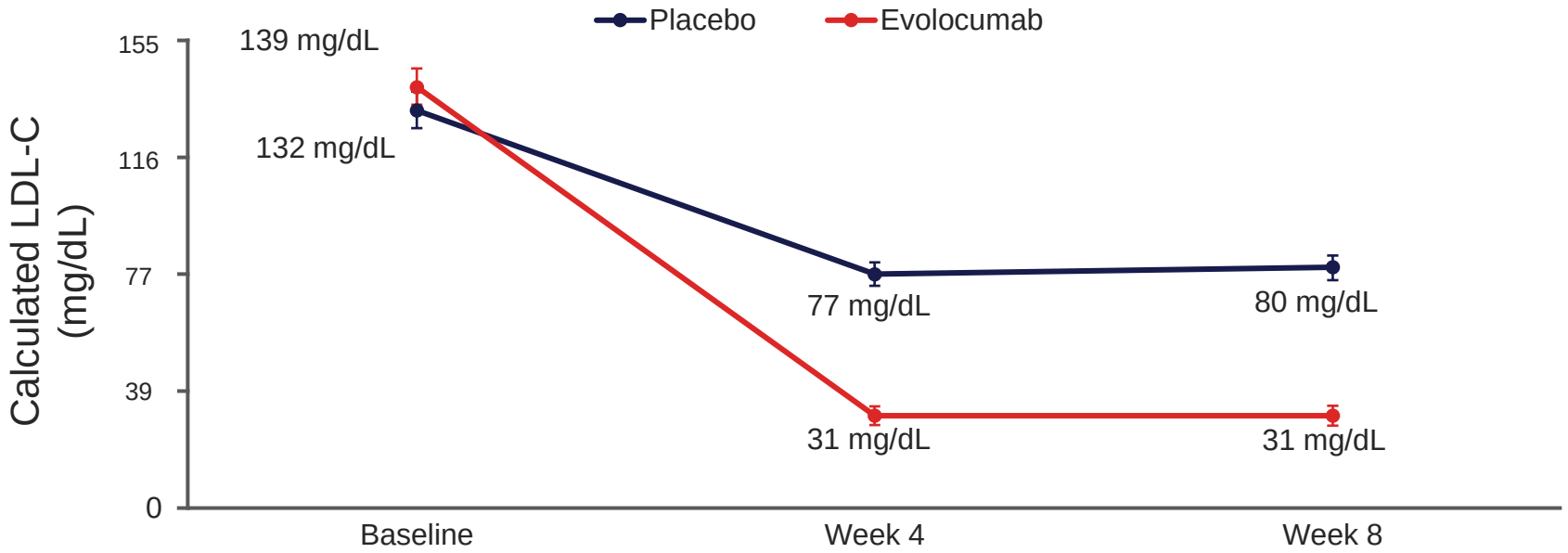
ACS, acute coronary syndrome; SC, subcutaneous; QM, monthly; QD, daily; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST-elevation myocardial infarction; AE, adverse event ; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

1. Koskinas KC, et al. J Am Coll Cardiol. 2019;74:2452-2462.

EVOPACS: Evolocumab Added to Optimized Statin Therapy Achieves Early, Sustained LDL-C Lowering in the Acute Phase of ACS

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

There were no differences observed for any of the exploratory endpoints



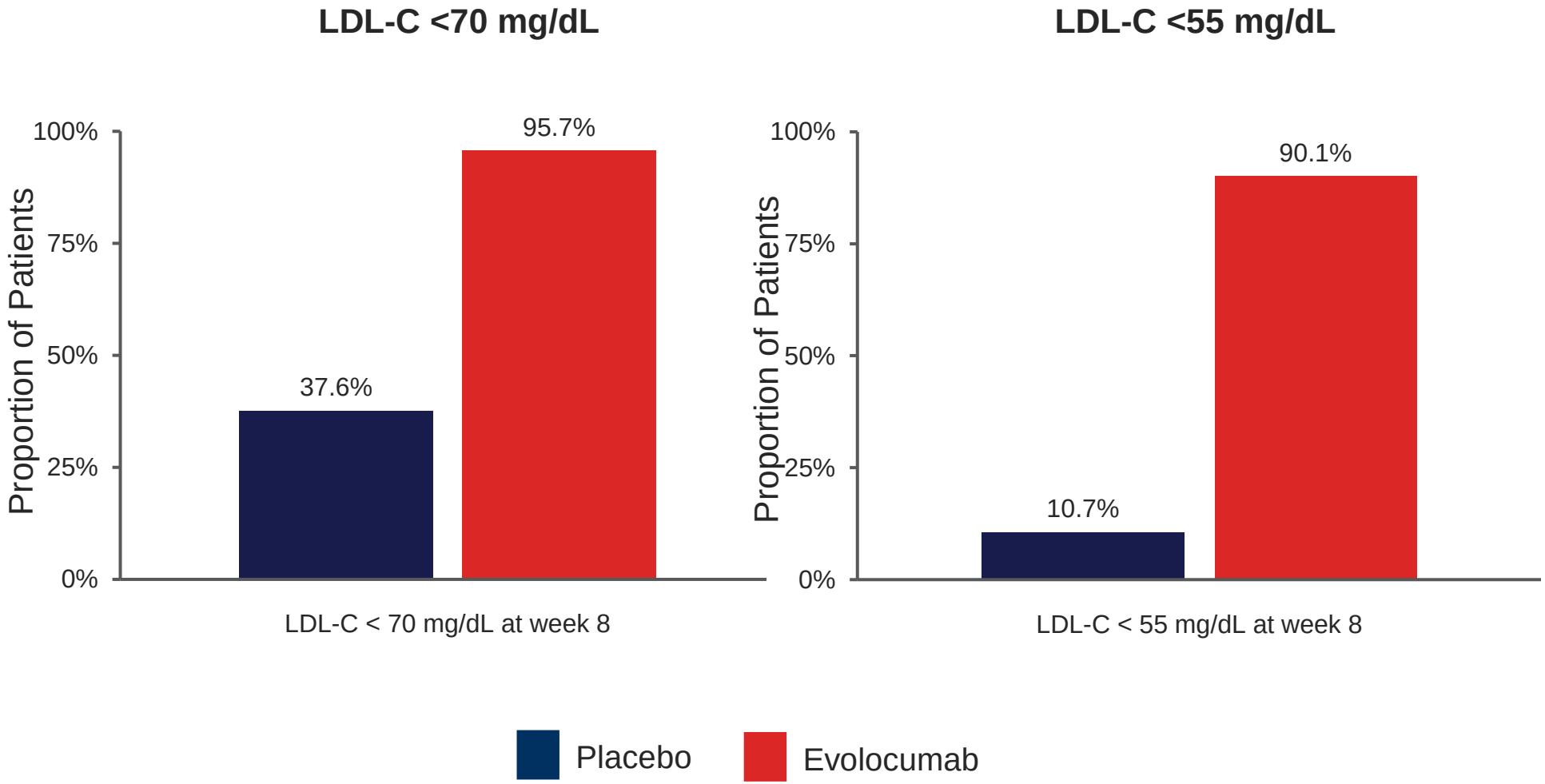
No. of patients			
Placebo	148	144	149
Evolocumab	146	136	141
Percentage difference		38.4%	40.7%
P value		<0.001	<0.001

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

1. Koskinas KC, et al. J Am Coll Cardiol. 2019;74:2452-2462.

EVOPACS: 90% of Patients on Evolocumab Achieved the More Stringent ESC/EAS Target of <55 mg/dL

Compared with placebo, substantially more patients receiving evolocumab were able to achieve LDL-C levels <70 (96% vs 38%) and <55 mg/dL (90% vs 11%)



LDL-C, low-density lipoprotein cholesterol.

1. Koskinas KC, et al. J Am Coll Cardiol. 2019;74:2452-2462.

EVOPACS: No New Safety Findings

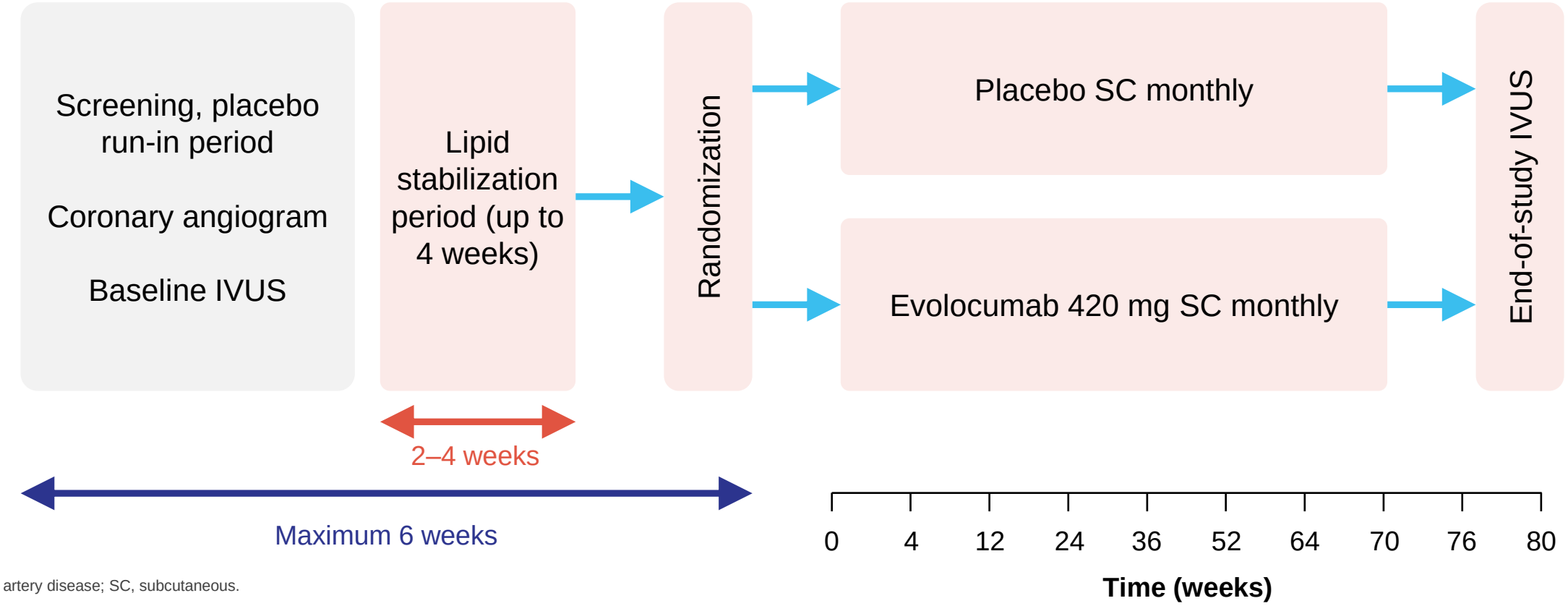
The percentage of patients who experienced AEs, SAEs, and AEs resulting in study drug discontinuation were similar between groups

	Evolocumab (n = 155)	Placebo (n = 152)*	P value
Any AE	78 (50.3)	77 (50.7)	0.72
SAE	12 (7.7)	11 (7.2)	0.84
AE resulting in study drug dis continuation	2 (1.3)	3 (2.0)	0.65

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.
*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.
1. Koskinas KC, et al. J Am Coll Cardiol. 2019;74:2452-2462.

GLAGOV Trial : Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

968 patients with angiographic CAD, stable statin dose, and LDL-C ≥ 80 mg/dL
OR 60–80 mg/dL and with 1 major or 3 minor cardiovascular risk factors



CAD, coronary artery disease; SC, subcutaneous.

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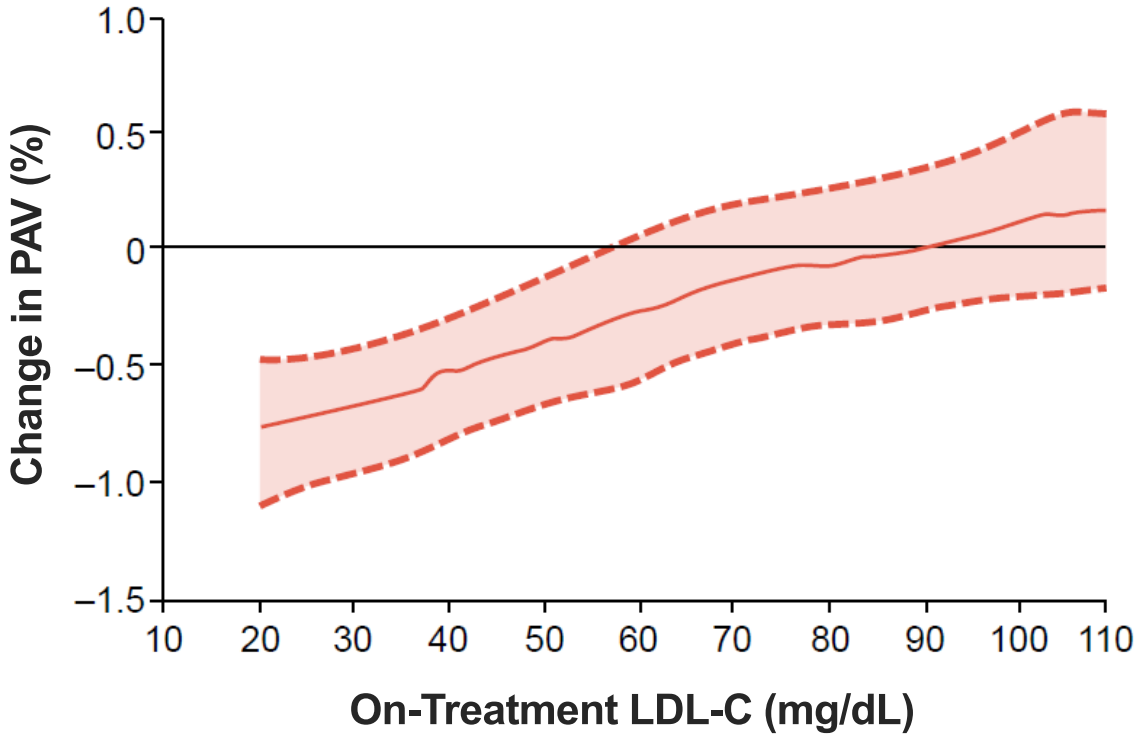
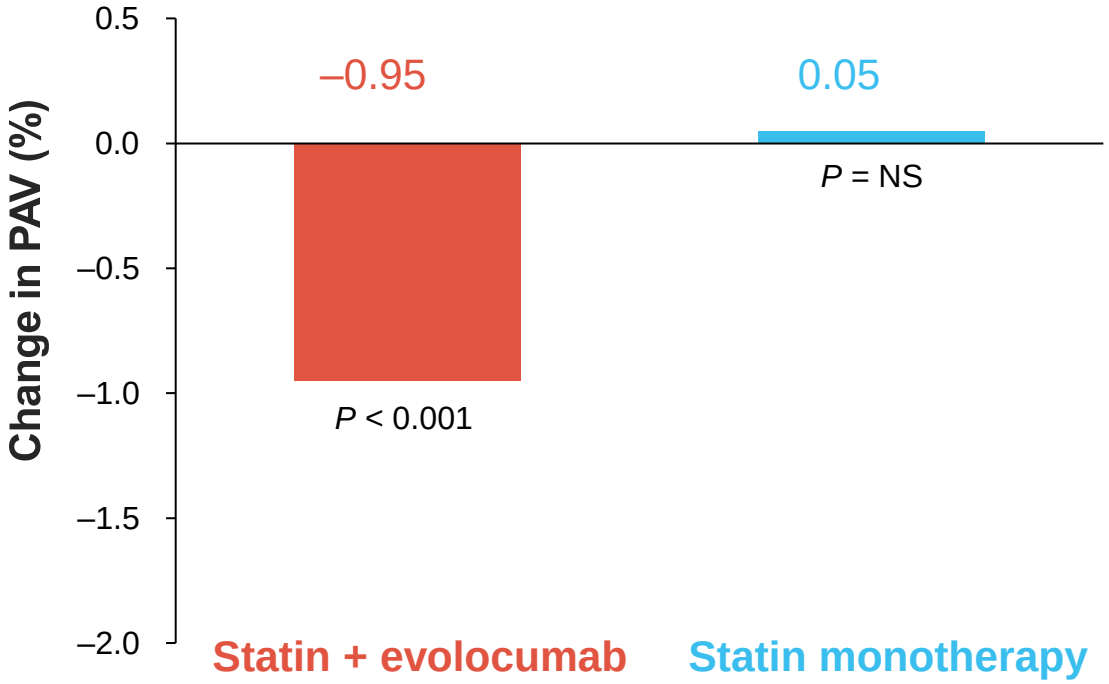
1. Nicholls SJ, et al. *JAMA*. 2016;316:2373-2384.

Evolocumab Demonstrated a Reduction in Atherosclerotic Disease Progression by IVUS as a Non-statin LDL-C Lowering Therapy

GLAGOV Study Primary Endpoint
: Nominal Change in PAV From Baseline to Week 78





* A multicentre, double-blind, placebo-controlled, randomised clinical trial involving 968 patients with angiographic CAD, stable statin dose, and LDL-C ≥ 80 mg/dL OR 60-80 mg/dL with one major or three minor risk factors. Patients were randomly assigned to receive evolocumab (QM 420 mg) or placebo as subcutaneous injection for 76 weeks. Patients underwent clinic visits at weeks 4, 12, 24, 36, 52, 64, 76, and repeat IVUS imaging at week 78.
IVUS, intravascular ultrasound; PAV, percentage atheroma volume; ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; PAV, percent atheroma volume; NS, not significant.

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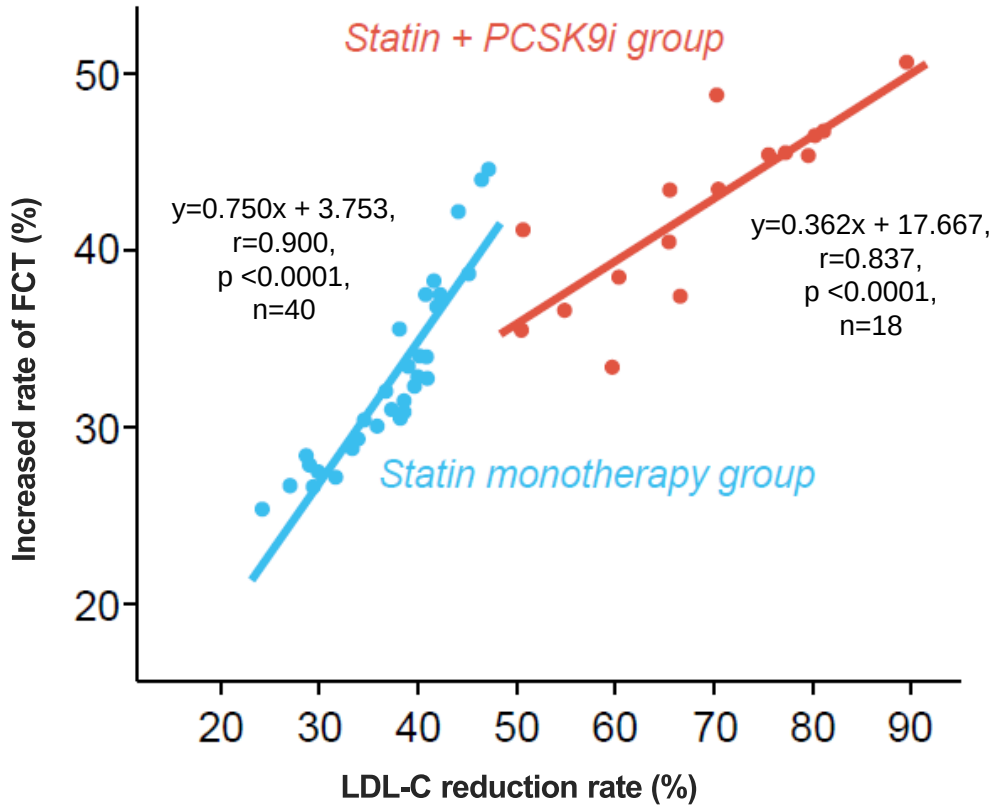
1. Nicholls SJ, et al. *JAMA*. 2016;316:2373-2384.

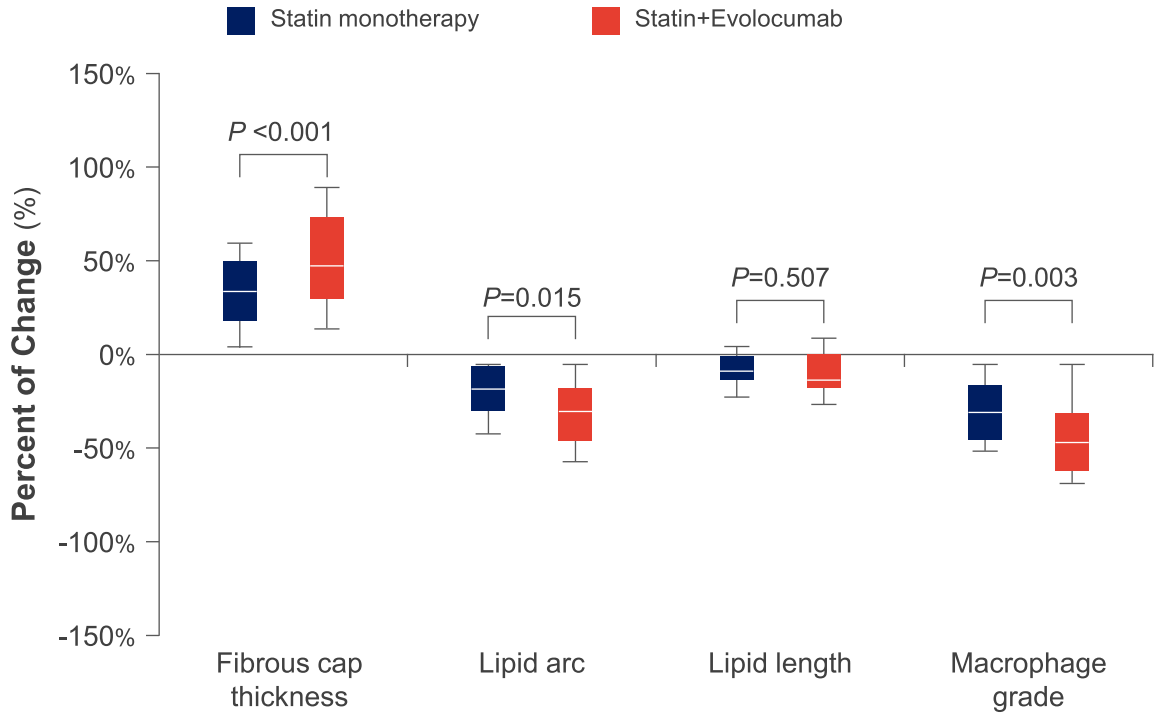
The LDL-C Reduction Rate Significantly Correlated With the Increased Rate of Fibrous Cap Thickness

- To examine the effect of evolocumab on fibrous-cap thickness, and the extent of the atherosclerotic plaque, by serial optical coherence tomography (OCT) analysis in patients with ACS
- Patients received evolocumab (140 mg Q2W) 1 week after the onset of ACS in the statin (rosuvastatin 5mg) + evolocumab group

Correlation Between the Increase Rate of Fibrous Cap Thickness and LDL-C Reduction Rate



Change in OCT measurements baseline vs. 12 weeks



Between Baseline and 12-Week Follow-up

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1. Yano H, et al. J Cardiol. 2019;75:289-295.

A Prespecified Secondary Analysis From the FOURIER Trial - Evolocumab and Clinical Outcomes in Recent MI Patients (≤12 months)

22,320 patients with prior MI were stratified as recent (≤12 months) vs. remote MI (>12 months)

- Primary Endpoint : CV death, MI, stroke, hospitalization for UA, or coronary revascularization
- Key Secondary Endpoint: CV death, MI or stroke

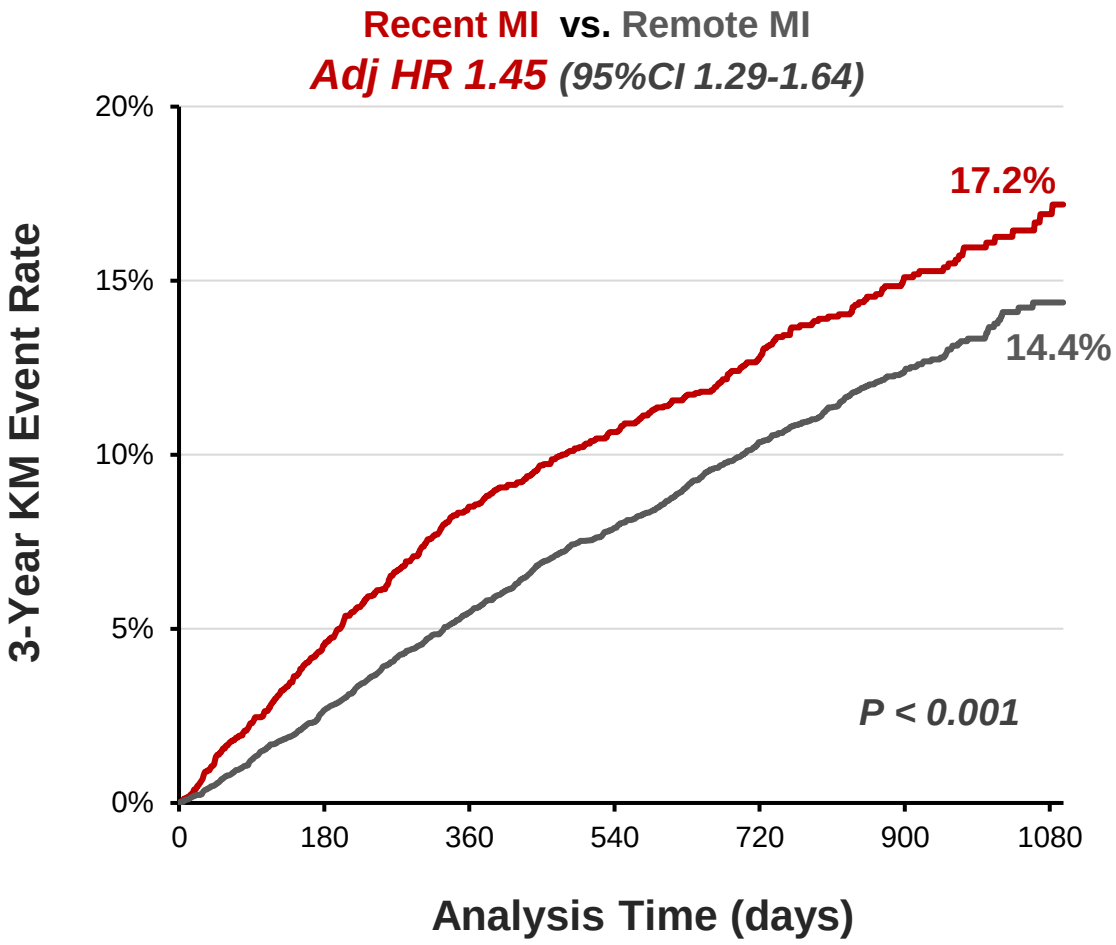
Baseline Characteristics	MI ≤12 months N=5,711	MI >12 months N=16,609	*P*-Value
Median time from MI (month)	**4.8**	59	NA
Mean age (years)	60	63	<0.001
Male, %	78	79	0.14
Hypertension, %	73	81	<0.001
Diabetes mellitus, %	30	37	<0.001
History of stroke, %	5	8	<0.001
History of PAD, %	5	9	<0.001
Prior CABG, %	15	24	<0.001
Mean LDL-C (mg/dL)	**95**	99	<0.001
High intensity statin, %	77	69	<0.001

1. Gencer B, *et al*. JAMA Cardiol . 2020. doi:10.1001/jamacardio.2020.0882.

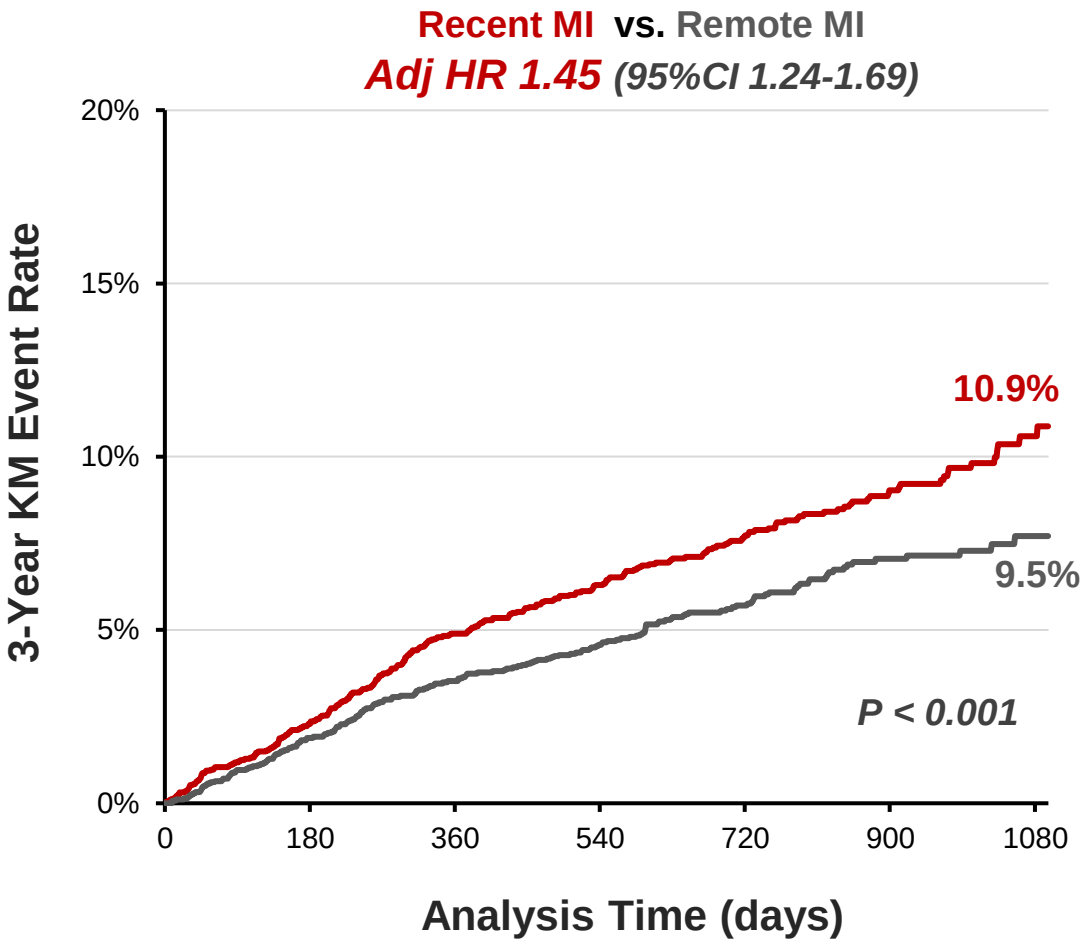
Risk for Both Primary and Key Secondary Endpoints Were Higher in Patients With Recent MI

3-Year Event Rate in Recent vs. Remote MI

Incidence of the Primary Endpoint



Incidence of the Key Secondary Endpoint

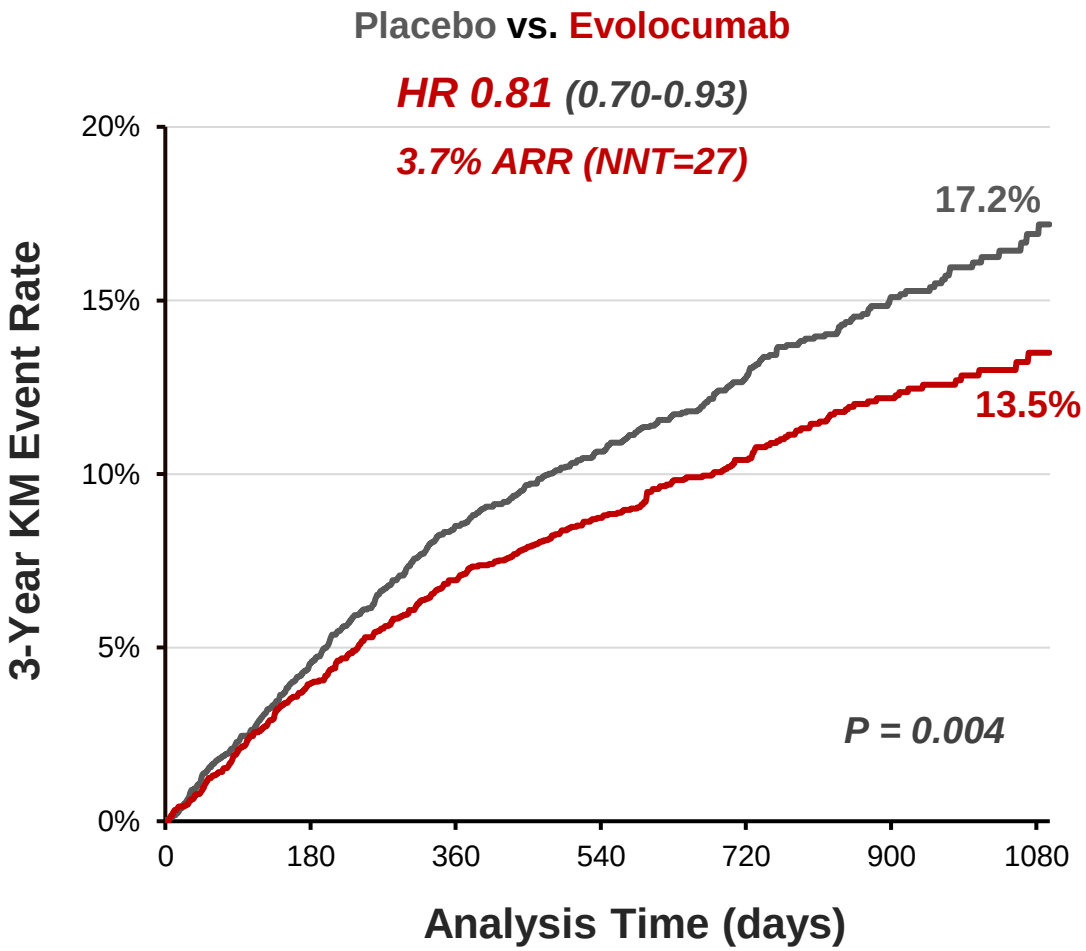


1. Gencer B, *et al*. JAMA Cardiol . 2020. doi:10.1001/jamacardio.2020.0882.

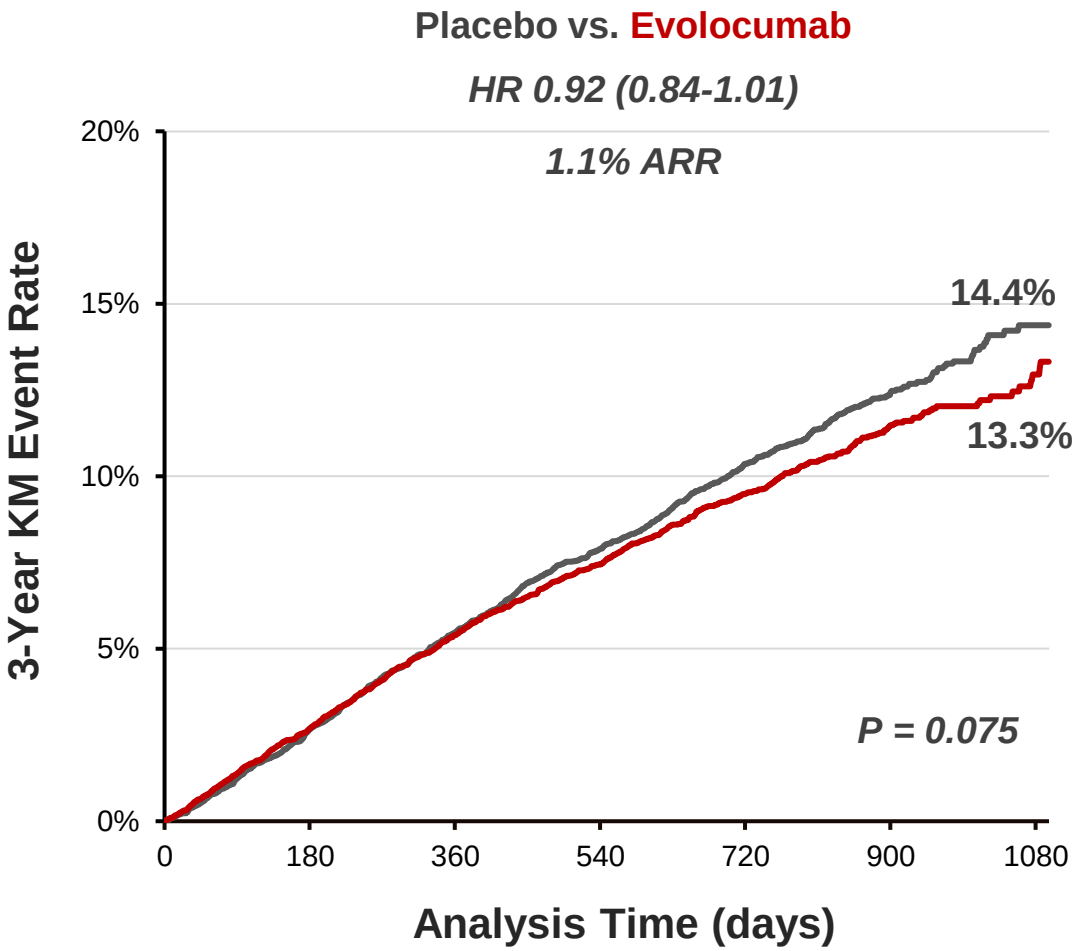
Evolocumab Is More Effective in Patients With Recent MI (≤12 months)

Reduction of the PEP (CV Death, MI, Stroke, UA and Coronary Revascularization) with Evolocumab

Recent MI



Remote MI



1. Gencer B, *et al*. JAMA Cardiol . 2020. doi:10.1001/jamacardio.2020.0882.

Evolocumab Is More Effective in Patients With Recent MI (≤12 months)

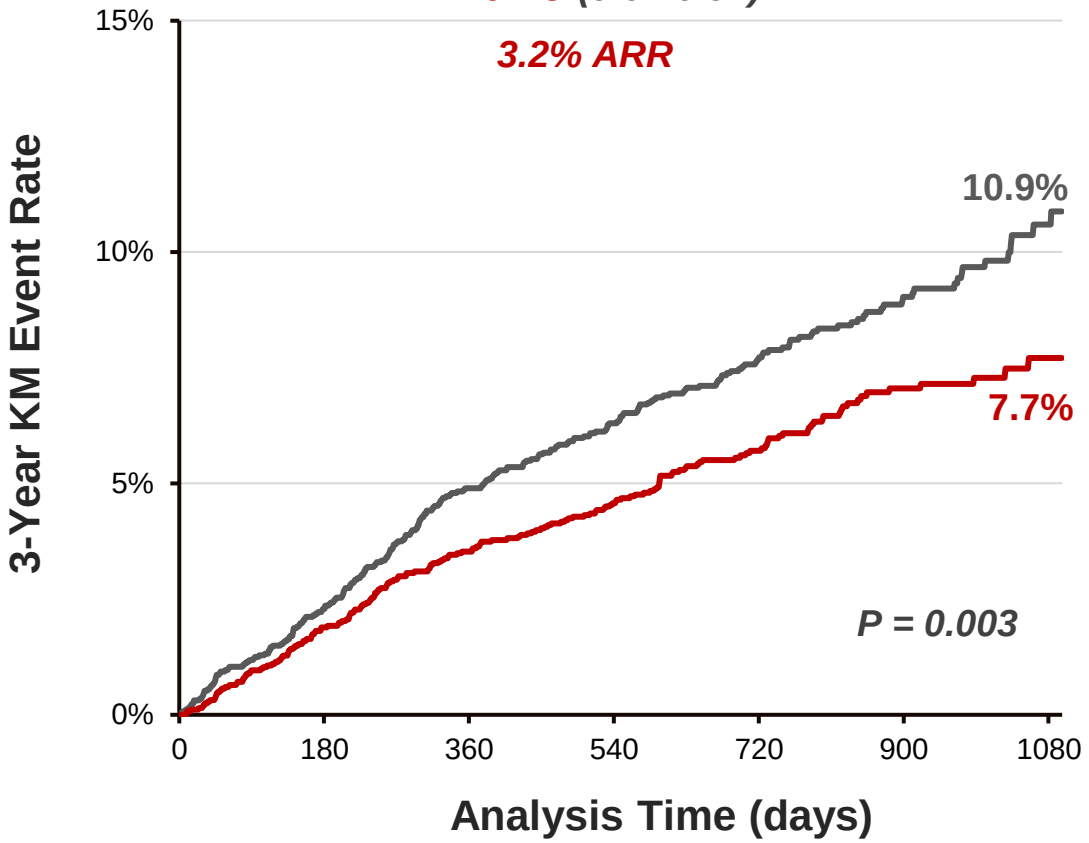
Reduction of the Key SEP (CV death, MI and Stroke) with Evolocumab

Recent MI

Placebo vs. Evolocumab

HR 0.75 (0.62-0.91)

3.2% ARR

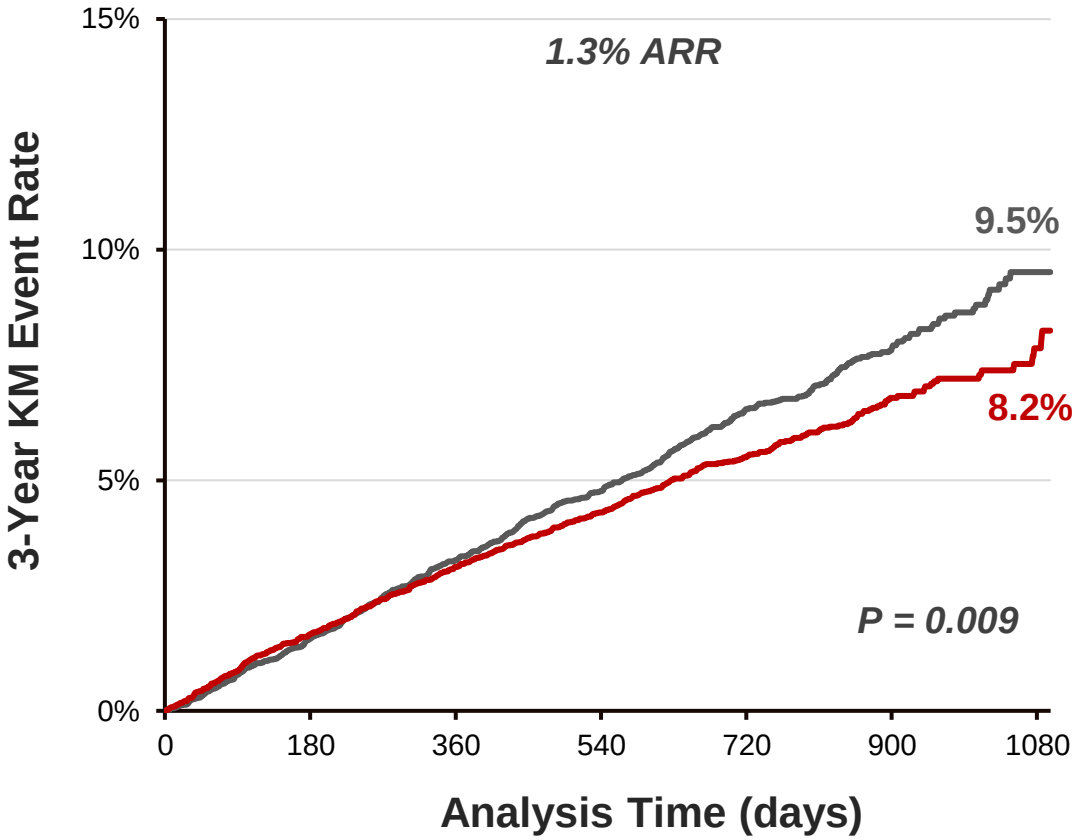


Remote MI

Placebo vs. Evolocumab

HR 0.85 (0.76-0.96)

1.3% ARR



1. Gencer B, *et al*. JAMA Cardiol . 2020. doi:10.1001/jamacardio.2020.0882.

04

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AMGEN Repatha

Repatha®(Evolocumab) Indications

Hypercholesterolemia and mixed dyslipidemia

Repatha is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Atherosclerotic cardiovascular disease

Repatha is indicated in **adults with established atherosclerotic cardiovascular disease** to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: **in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies**

Homozygous familial hypercholesterolemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia in combination with other lipid-lowering therapies.

Dosing

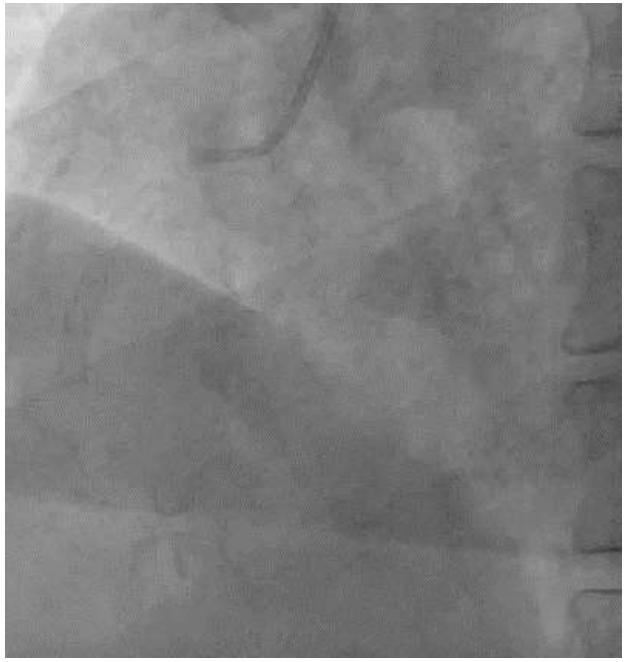
	140mg / 2 weeks	420mg / month
Hypercholesterolemia and mixed dyslipidemia	✓ or	✓
Atherosclerotic cardiovascular disease	✓ or	✓
Homozygous familial hypercholesterolemia		✓

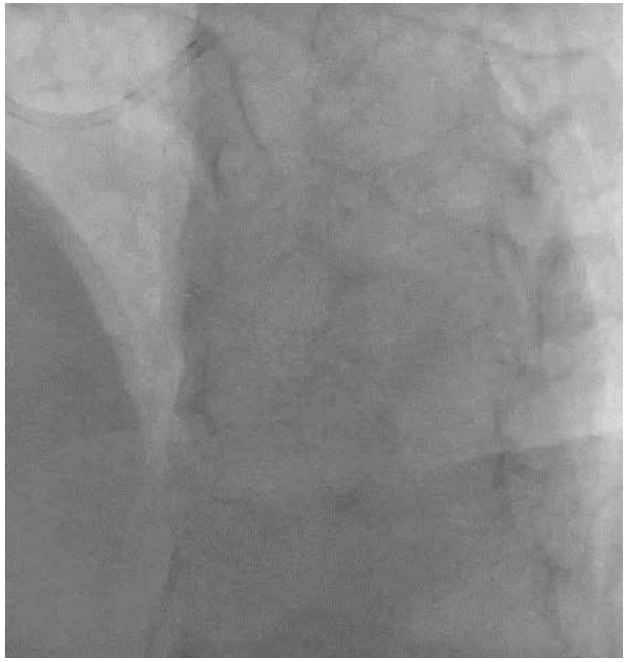
LDL = low density lipoprotein; **LDL-C** = low density lipoprotein-cholesterol.

1. 식품의약품안전처 의약품상세정보 레파타주프리필드펜(에볼로쿠맙)

Case Review : A High-risk ACS Patient

M/57
Unstable angina
Prior MI, 10 years ago
 on rosuvastatin/Ezetimibe 20/10mg
CAG: RCA, LCX ISR, De novo LAD lesion





	LDL level
Previous #1	150 mg/dL
Previous #2	134 mg/dL
At UA presentation	142 mg/dL
After Repatha	20 mg/dL

Take-Home Messages

1. The risk of a recurrent CV events remain high after ACS, and the risk is in the greatest in the 1st year post-ACS.[1,2]

2. Although statin trials proved to reduce cardiovascular events in ACS patients[3-6], there is residual risk even in those receiving treatment with high-intensity statins.[7-9]

3. 2020 ESC guidelines recommend ACS patients to be treated with a PCSK9 inhibitor if LDL-C goal is not achieved after 4-6 weeks despite maximally tolerated statin and ezetimibe therapy.[10]

4. The Earlier, The Better: Evolocumab rapidly lowers LDL-C in ACS patients during hospitalization and proved greater absolute risk reductions in MI patients within 1 year.[11,12]

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