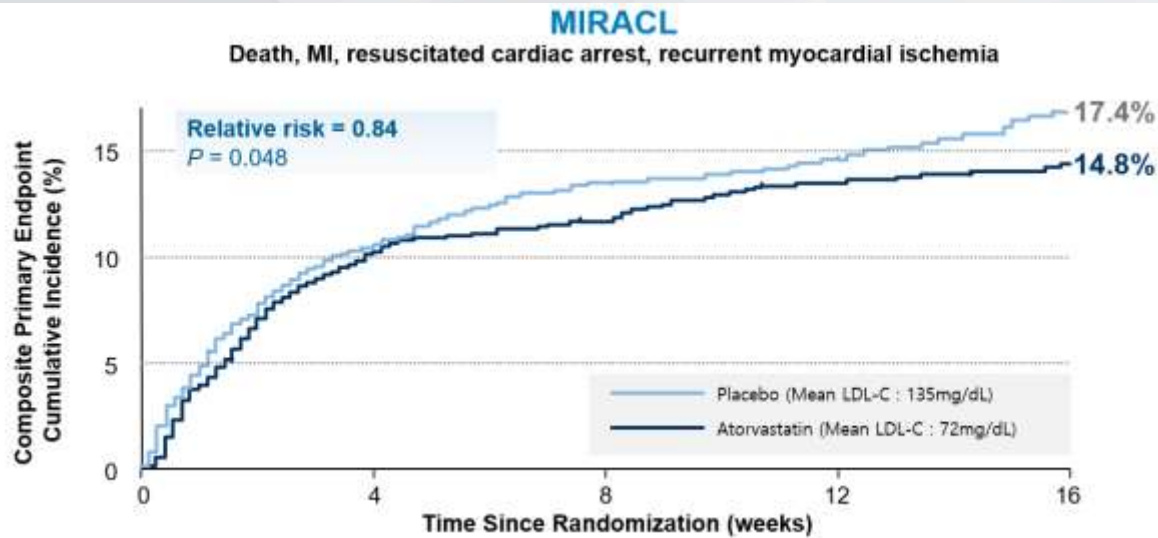


Recent Update in Lipid Management for ACS Patients

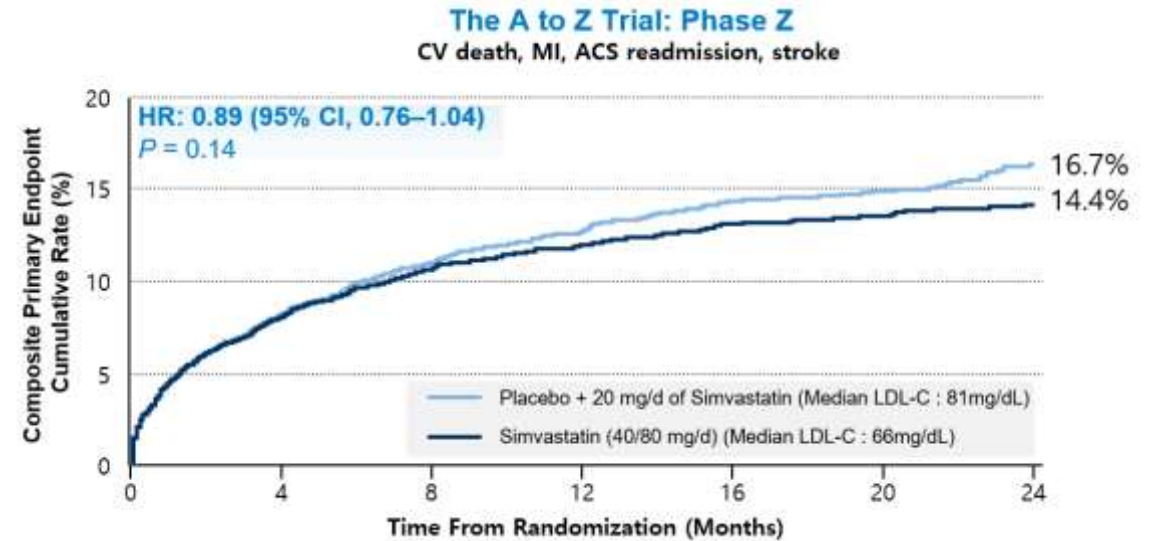
Hyun-Jong Lee, MD, PhD

Sejong general hospital, Bucheon, South Korea

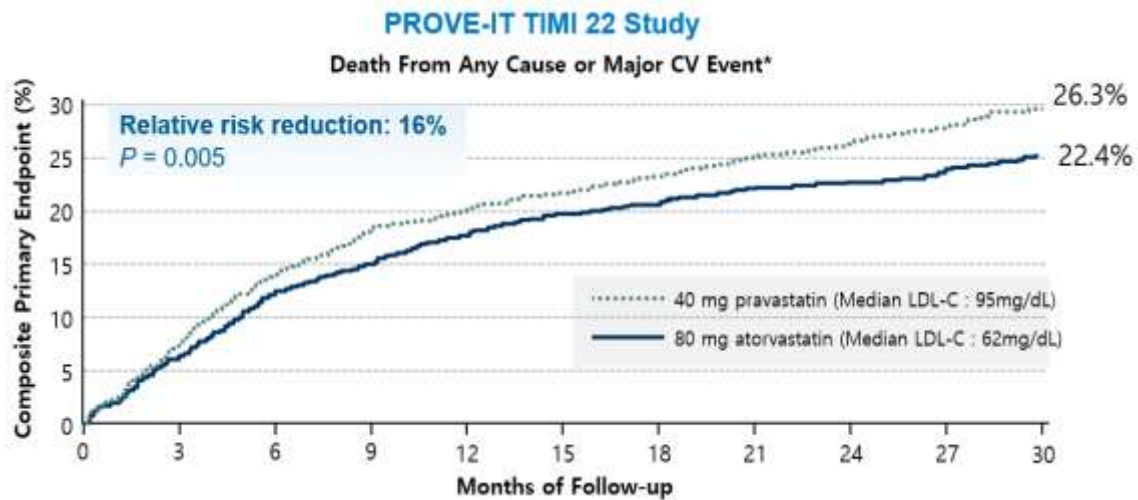
Lower LDL-C is better in ACS Patients



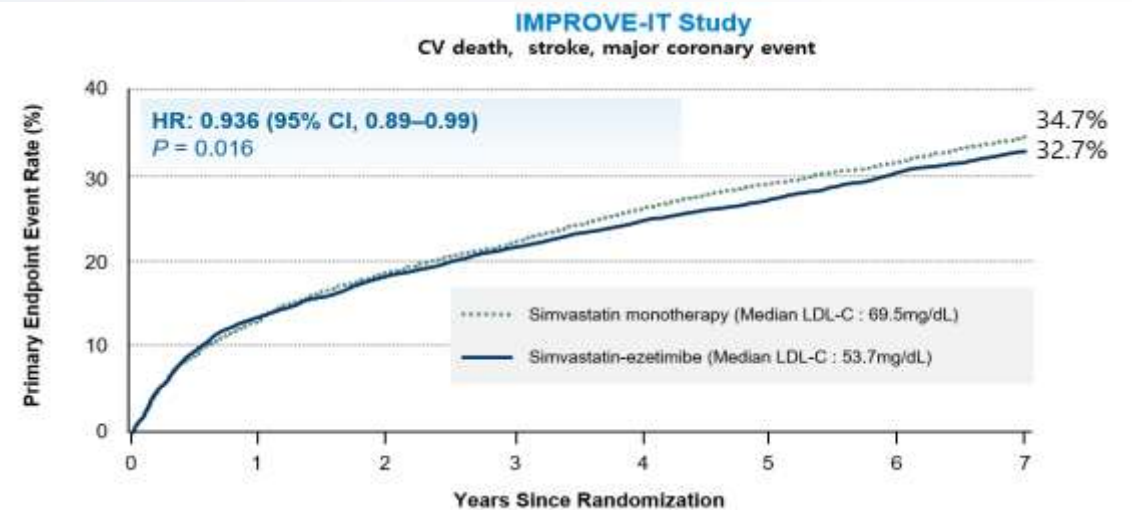
Schwartz GG, et al. *JAMA*. 2001;285:1711-1718



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



Cannon CP, et al. *N Engl J Med*. 2004;350:1495-1504.

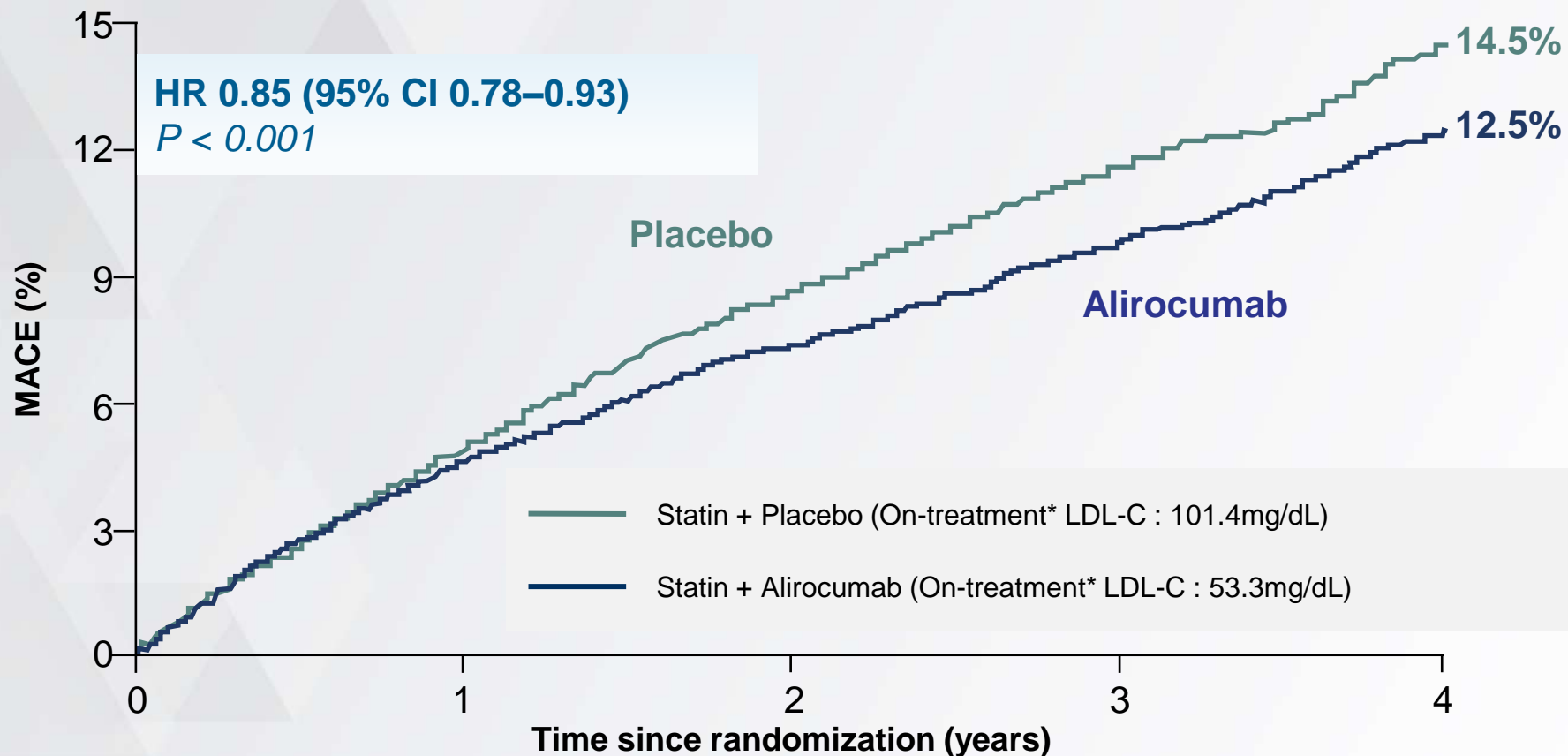


Cannon CP, et al. *N Engl J Med*. 2015;372:2387-2397

Alirocumab Demonstrated an RRR of 15% in MACE Among Patients with Prior ACS

ODYSSEY Outcomes Study

MACE:* CHD death, nonfatal MI, ischemic stroke, or UA requiring hospitalization



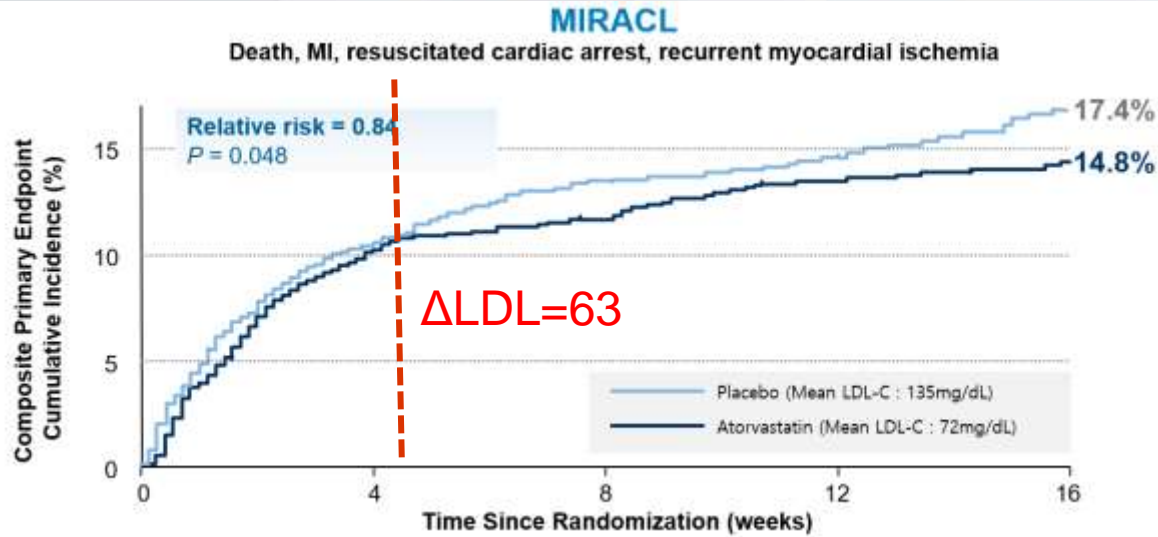
Number at risk:

	0	1	2	3	4
Placebo	9,462	8,805	8,201	3,471	629
Alirocumab	9,462	8,846	8,345	3,574	653

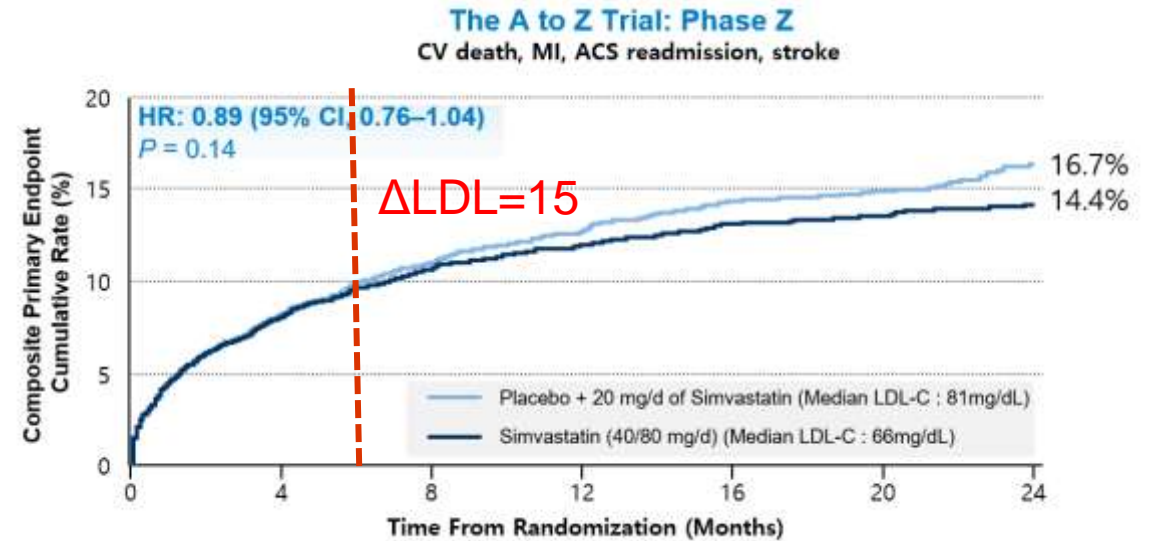
* Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

Schwartz GC, et al. *N Engl J Med.* 2018;379:2097-107.

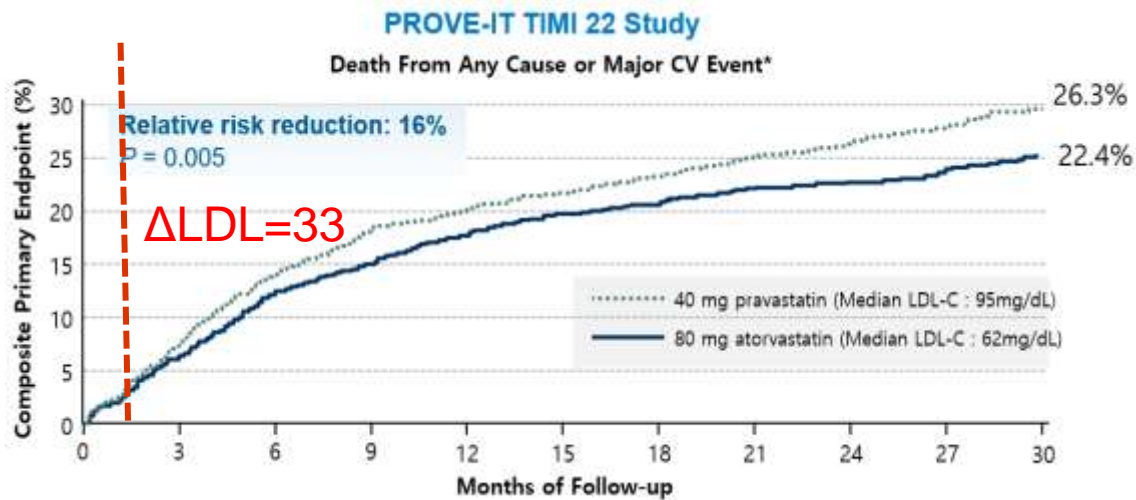
Potent LDL-C lowering showed early benefit



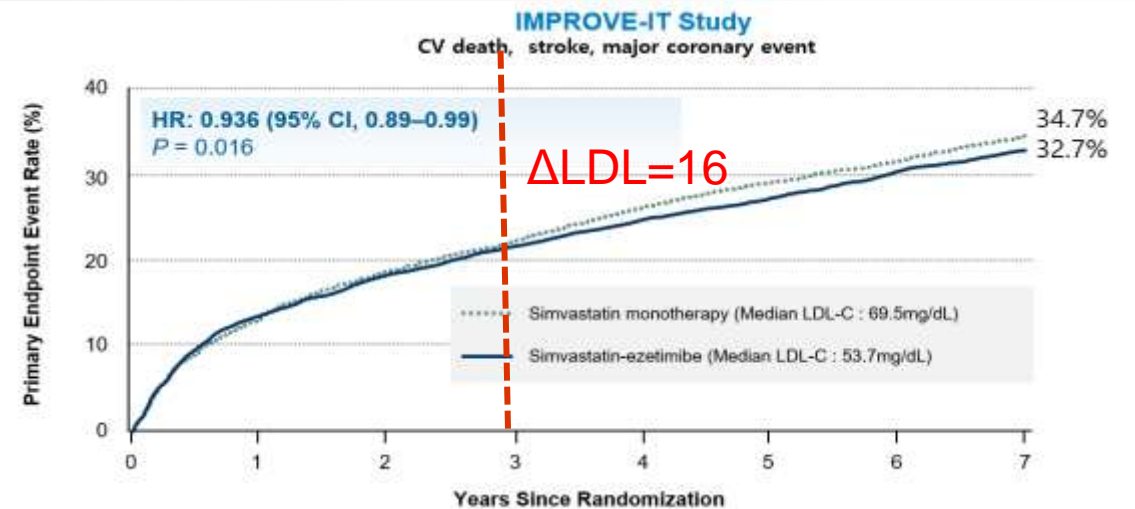
Schwartz GG, et al. *JAMA*. 2001;285:1711-1718



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



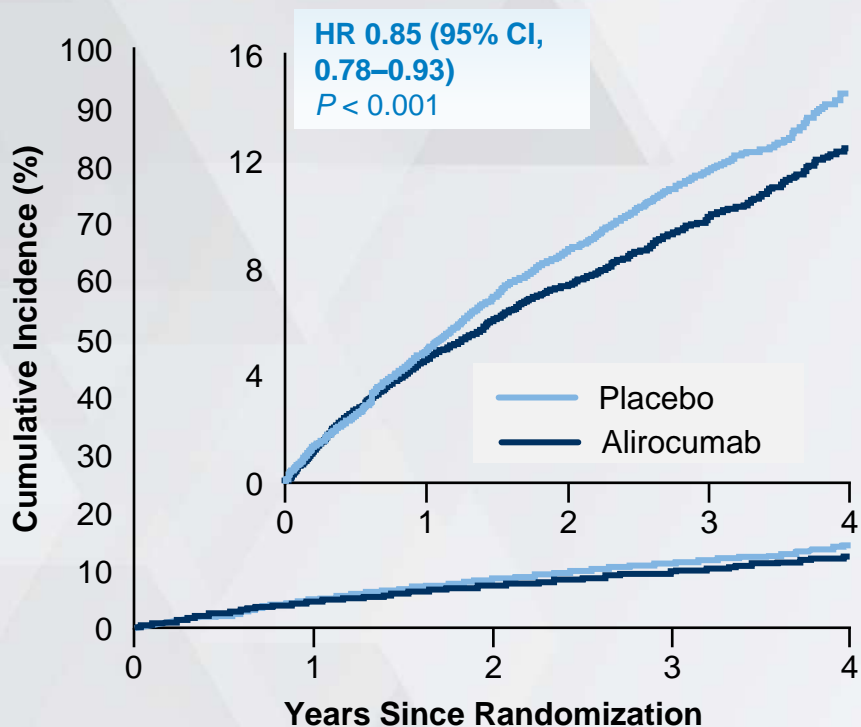
Cannon CP, et al. *N Engl J Med*. 2004;350:1495-1504.



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

PCSK9 Inhibition After 1 Month But Within 1 Year After an ACS

ODYSSEY Primary Composite Endpoints



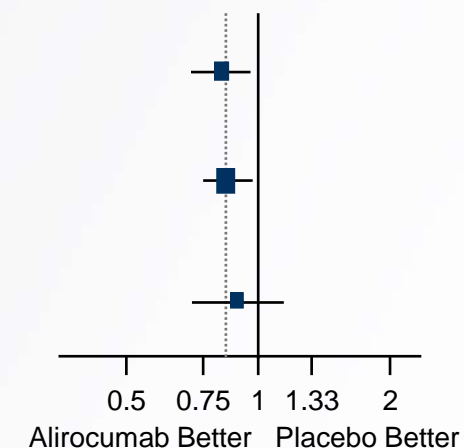
No. at Risk

	0	1	2	3	4
Placebo	9,462	8,805	8,201	3,471	629
Alirocumab	9,462	8,846	8,345	3,574	653

Primary Endpoints in Prespecified Subgroups

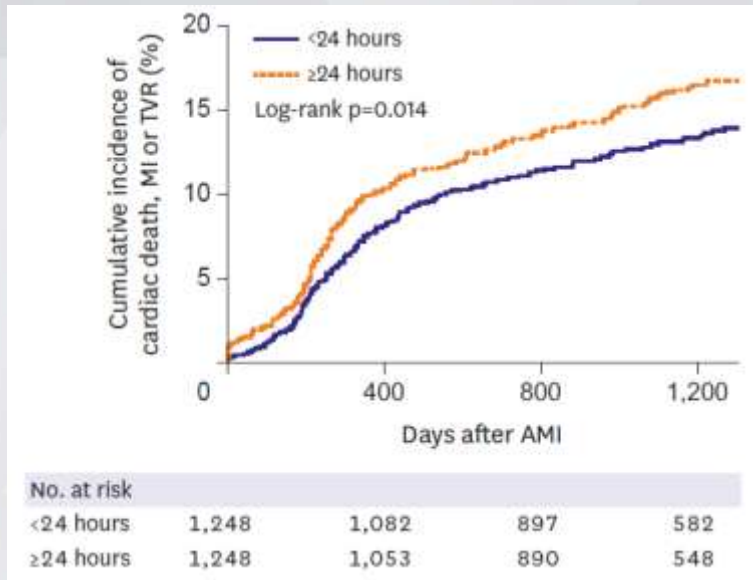
Index to randomization

Index to randomization	No. of Patients	Placebo (%)	Alirocumab (%)	HR (95% CI)
< 2 months	6,187	10.3	12.3	0.83 (0.71–0.96)
2 – < 6 months	9,518	9.6	11.1	0.85 (0.75–0.96)
≥ 6 months	3,228	8.0	8.7	0.90 (0.71–1.14)

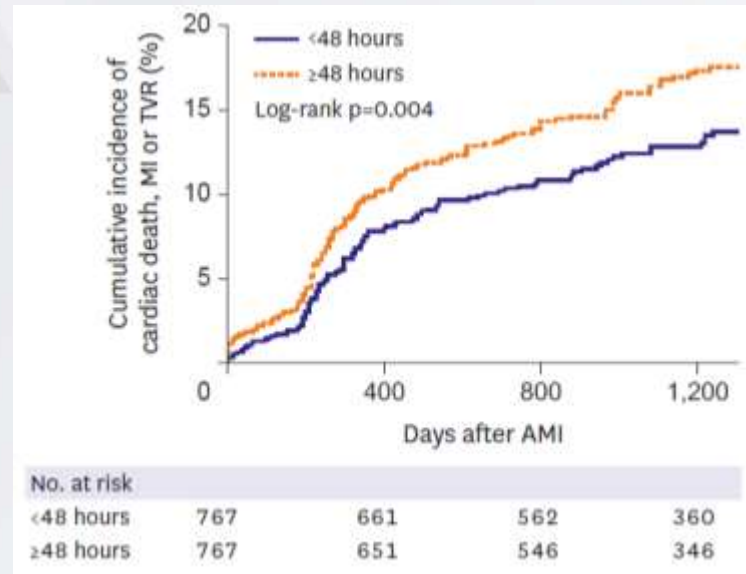


An Early Initiation of Statin Therapy Is an Important Factor in Patient Outcomes in the Case of AMI

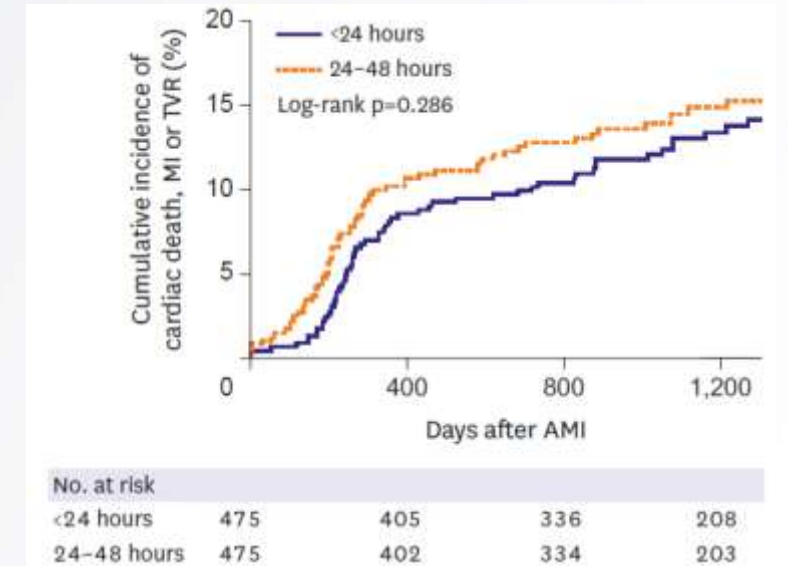
Kaplan-Meier curves for cumulative incidence of cardiac death, myocardial infarction or TVR in patients who received statin



<24 hours vs. ≥24 hours after admission



<48 hours vs. ≥48 hours after admission



<24 hours vs. 24–48 hours after admission

Early statin therapy within 48 hours after admission in statin-naïve patients with AMI reduced long-term clinical outcomes compared with statin initiation later

2019 ESC/EAS Guidelines: Recommendations For very high-risk patients with ACS

Recommendations	Class*	Level†
In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.	I	A
Lipid levels should be re-evaluated 4-6 weeks after ACS to determine whether a reduction of ≥ 50% from baseline and goal levels of LDL-C <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.	IIa	C
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 maximal tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contraindicated, ezetimibe should be considered.	IIa	C
For patients who present with an ACS and whose LDL-C levels are not at goal, despite already taking a maximally tolerated statin dose and ezetimibe, the addition of a PCSK9 inhibitor early after the event (during hospitalization for the ACS event if possible) should be considered	IIa	C

2020 NSTE-ACS ESC Guidelines

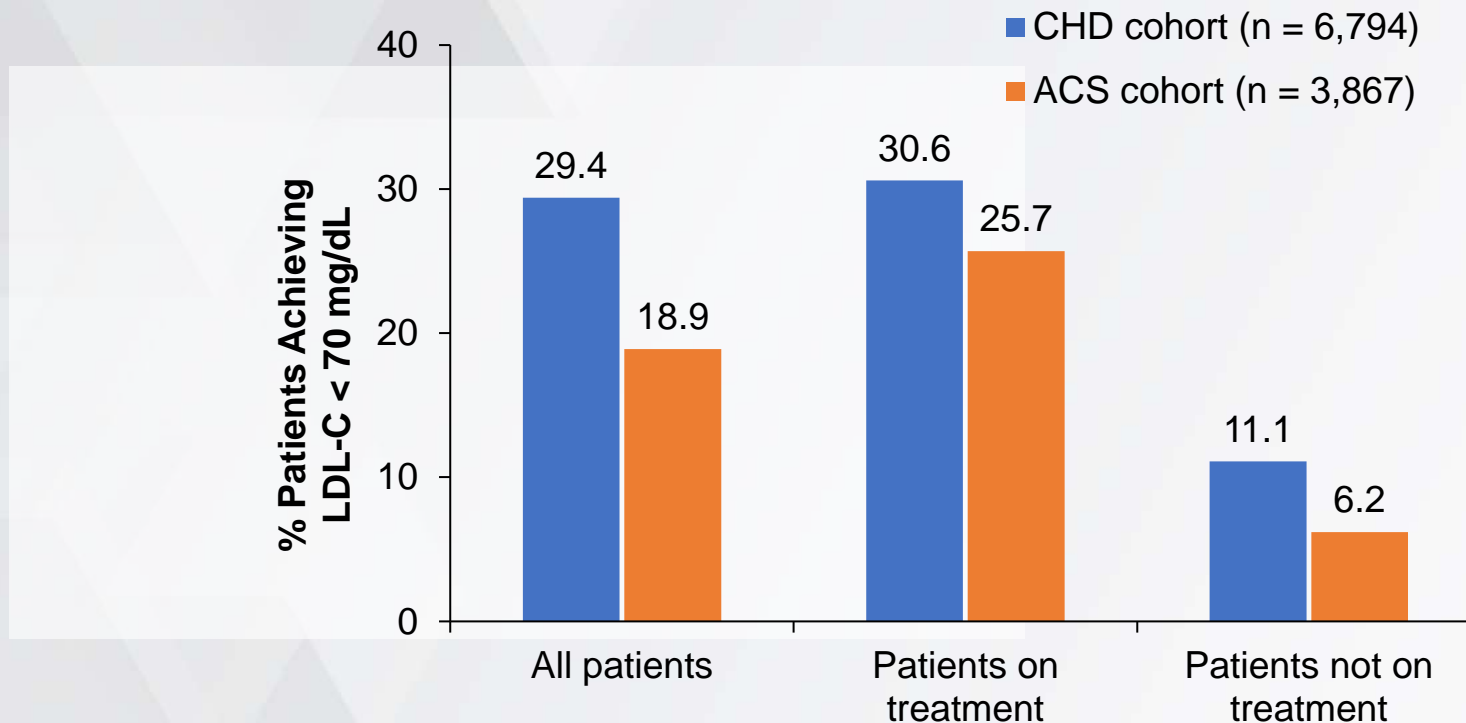
Recommendations	Class*	Level†
Statins are recommendation in all NSTE-ACS patients. The aim is to reduce LDL-C by $\geq 50\%$ from baseline and/or to achieve LDL-C $< 55\text{mg/dL}$.	I	A
If the LDL-C goal is not achieved after 4-6 weeks with the maximally tolerated statin dose, combination with ezetimibe 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 $< 40\text{mg/dL}$ may be considered.	IIb	B

*Class of recommendation; †Level of evidence.

1. European Heart Journal (2020) 00, 1-79 doi:10.1093/eurheartj/ehaa575

Real world data in patients with ACS

CHD and ACS Patients Achieving Target LDL-C in Multinational, Prospective, Observational DYSIS II Study, 2012–2013



Only 1/3 of high-risk CHD patients and 1/4 of ACS patients receiving treatment achieved LDL-C < 70 mg/dL

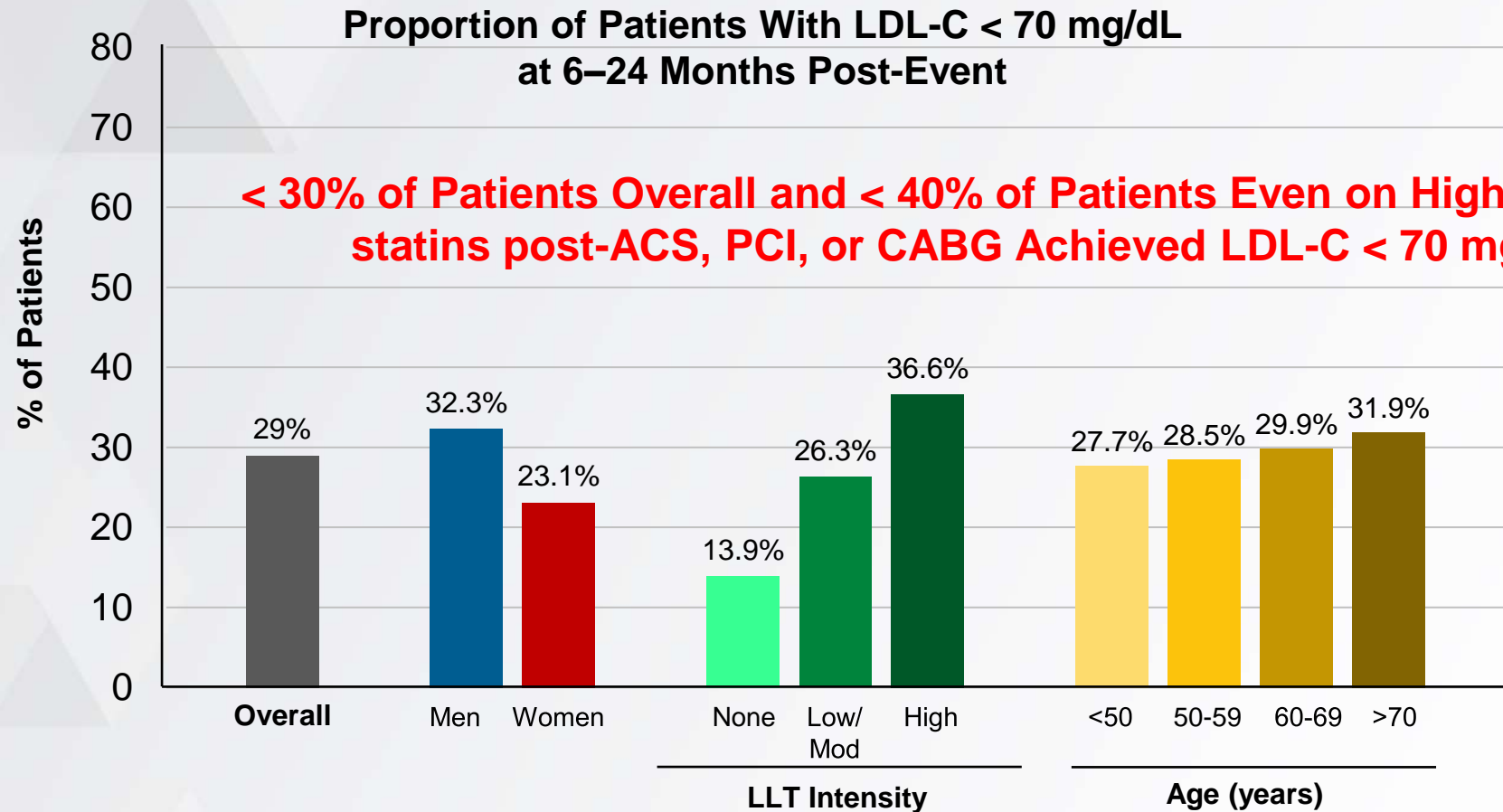
Real world registry data in patients with ACS

Cross-sectional Survey Across 27 European Countries ESC-EORP EUROASPIRE V

Patients:
N = 7,824
Patient with history of
ACS, PCI, or CABG

Age: > 18 – < 80 years

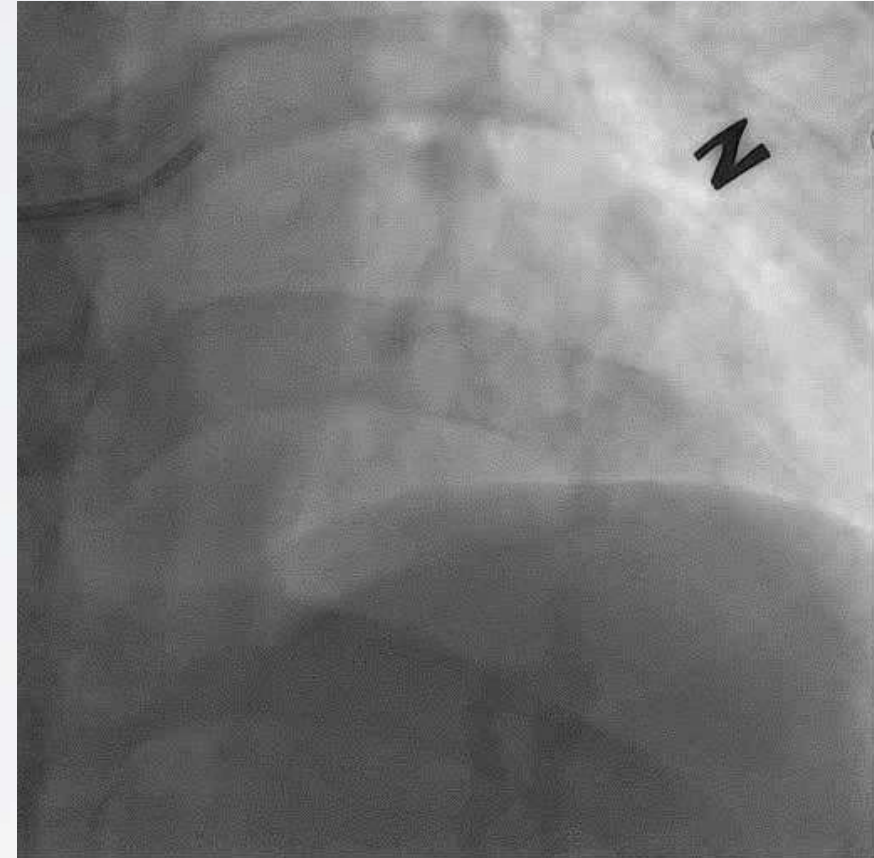
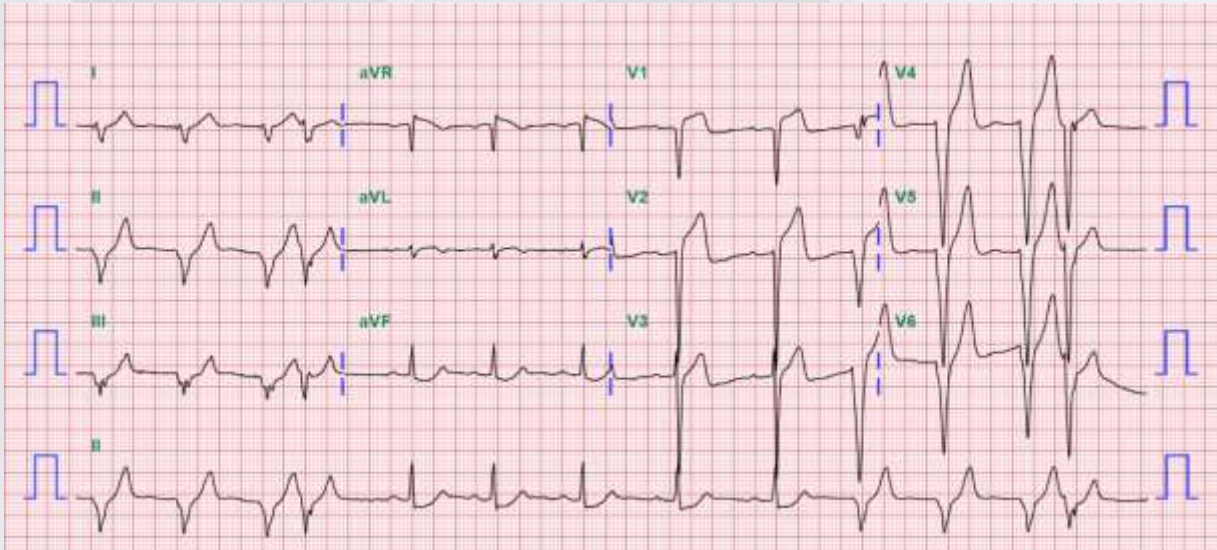
Follow up: 6–24
months post-event



EVO-STEMI Case-7; 43-year old man,

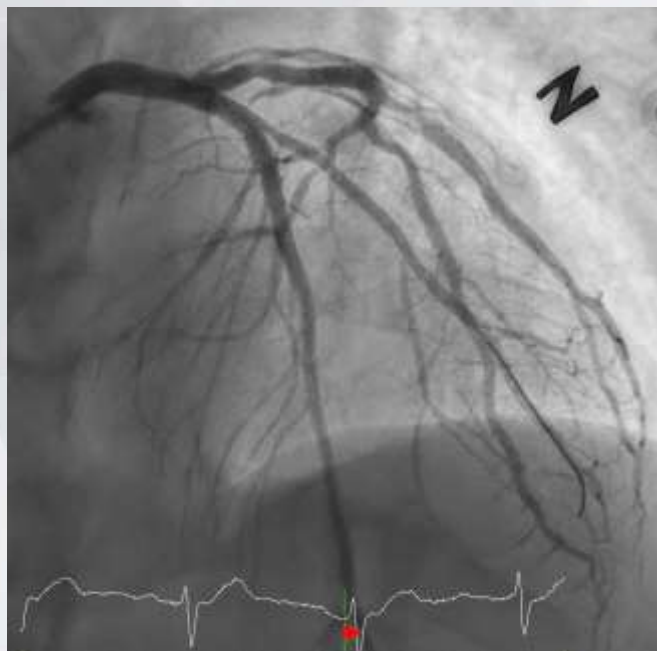
Ongoing squeezing chest pain for 1 hour

HTN, current smoker

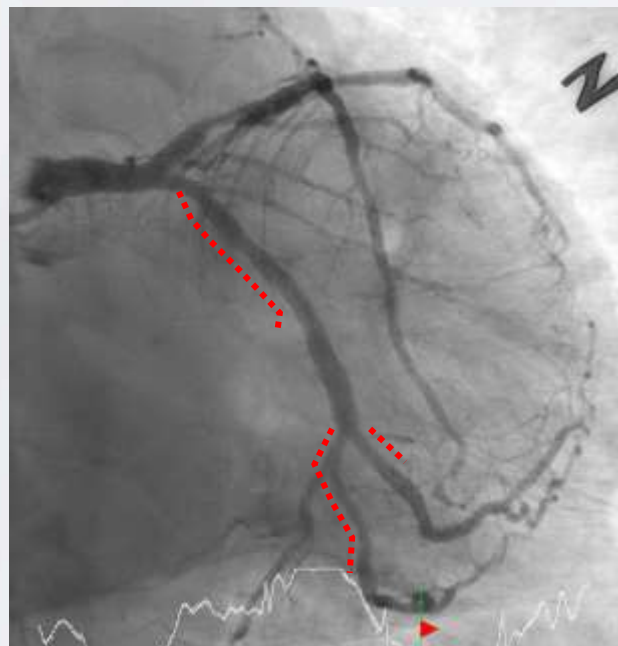


Anterior STEMI with TIMI 3 flow

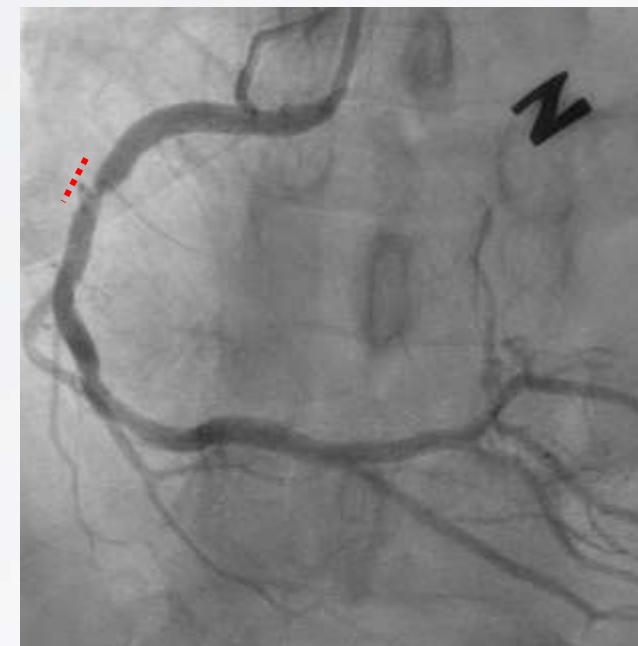
How to reduce LDL-c and residual ischemic risk early and potently?



Successful pPCI



Residual mild to moderate stenosis at LCx and RCA



Total Cholesterol	241
Triglyceride	248
HDL-Cholesterol	54
LDL-Cholesterol	164
Lipoprotein (a)	< 7.0


Many Patients Require Statins Plus Additional Lipid-Lowering Therapy to Achieve Their LDL-C Goal

- In patients who are very high risk and remain at high risk despite maximally tolerated statin treatment, combination with ezetimibe is recommended (Class I*)
- If the LDL-C goal is still not achieved, the **addition of a PCSK9 inhibitor is recommended**, either to a statin alone or a statin plus ezetimibe

Total Cholesterol	241
Triglyceride	248
HDL-Cholesterol	54
LDL-Cholesterol	164

Guideline-provided estimates of the LDL-C-lowering benefit of recommended lipid-lowering regimens

Treatment	Average LDL-C reduction	
Moderate-intensity statin	~ 30%	114
High-intensity statin	~ 50%	82
High-intensity statin + ezetimibe	~ 65%	57
PCSK9 inhibitor	~ 60%	66
PCSK9 inhibitor + high-intensity statin	~ 75%	41
PCSK9 inhibitor + high-intensity statin + ezetimibe	~ 85%	25

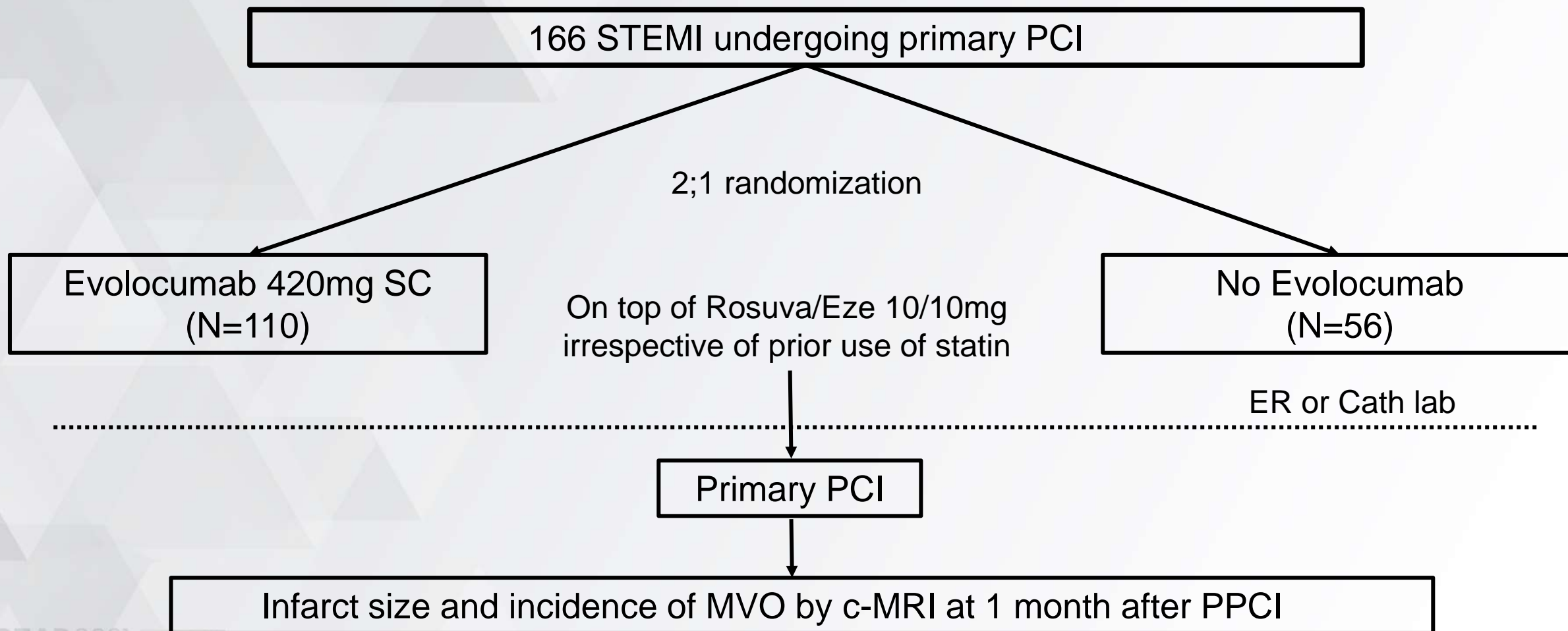


*Class I recommendations, the highest level recommendations in the guidelines, are based on evidence and/or general agreement that a given treatment is beneficial, useful, and effective.

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

1. Mach F, et al. *Eur Heart J*. 2019. doi:10.1093/eurheartj/ehz455. [Epub ahead of print.].

The effect of EVOlocumab and combination lipid-lowering agent on infarct size in patients with ST-segment Elevation Myocardial Infarction undergoing primary PCI (EVO-STEMI); KCT0005323



Preemptive use of PCSK9 inhibitor

Evolocumab 420mg (pre-pPCI) + Rosuvastatin 10mg, ezetimibe 10mg

Total Cholesterol	241	→	Total Cholesterol	95	(60%↓)
Triglyceride	248		Triglyceride	144	(42%↓)
HDL-Cholesterol	54		HDL-Cholesterol	63	(15%↑)
LDL-Cholesterol	164		LDL-Cholesterol	18	(89%↓)
Lipoprotein (a)	< 7.0		Lipoprotein (a)	< 7.0	

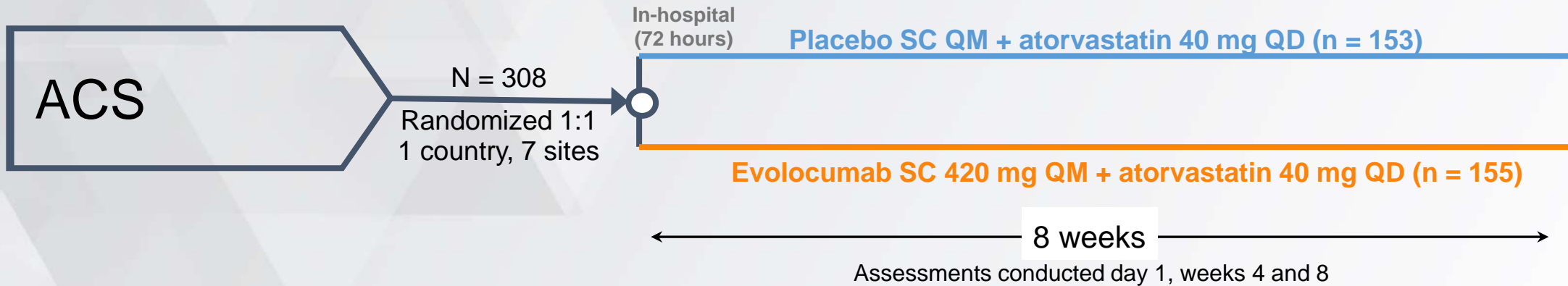
1 month

No myalgia

No increase of GOT/GPT and CPK

It seems to be best approach to achieve LDL goal earliest and safe in ACS

EVOPACS: Evolocumab in ACS Patients Within 24 - 72 Hrs



PRIMARY ENDPOINT

- LDL-C change from baseline at week 8

INCLUSION CRITERIA

- ACS (NSTEMI/UA < 72H, STEMI < 24H)

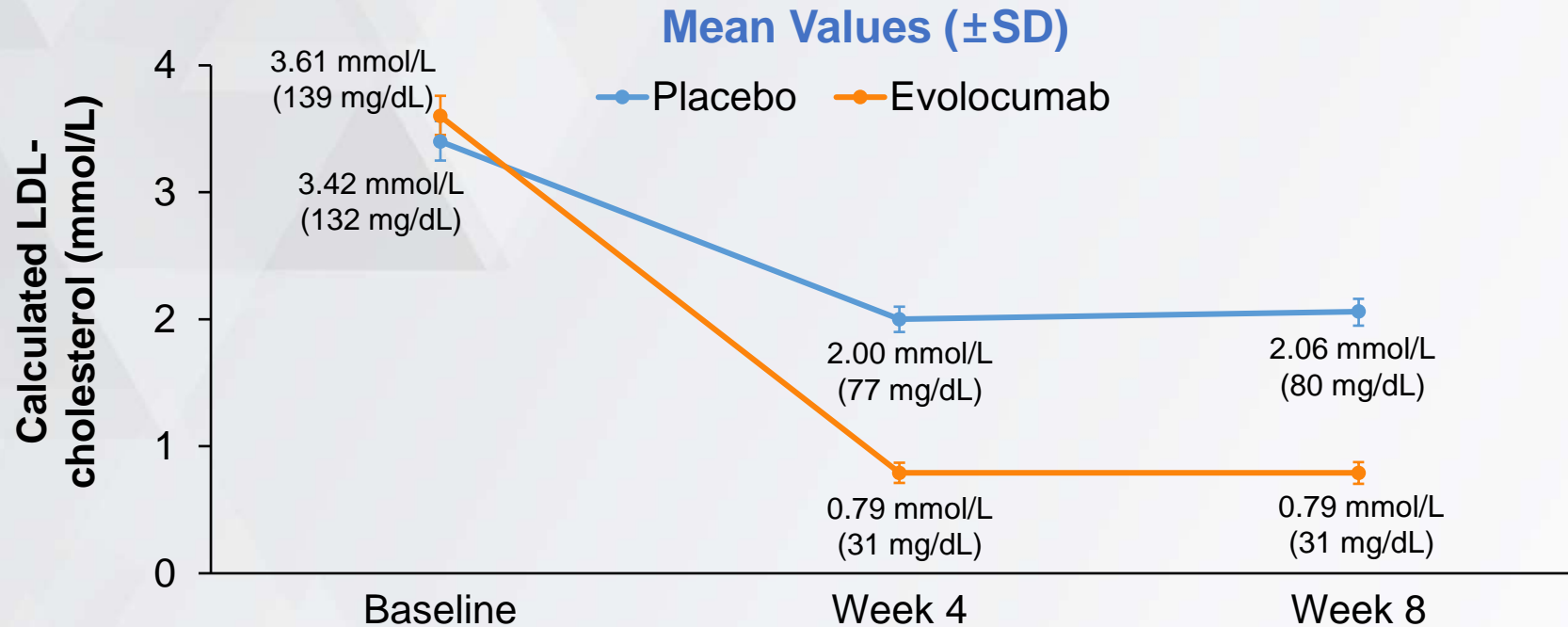
SECONDARY ENDPOINT

- Safety and tolerability

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

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



No. of patients

Placebo	148
Evolocumab	146

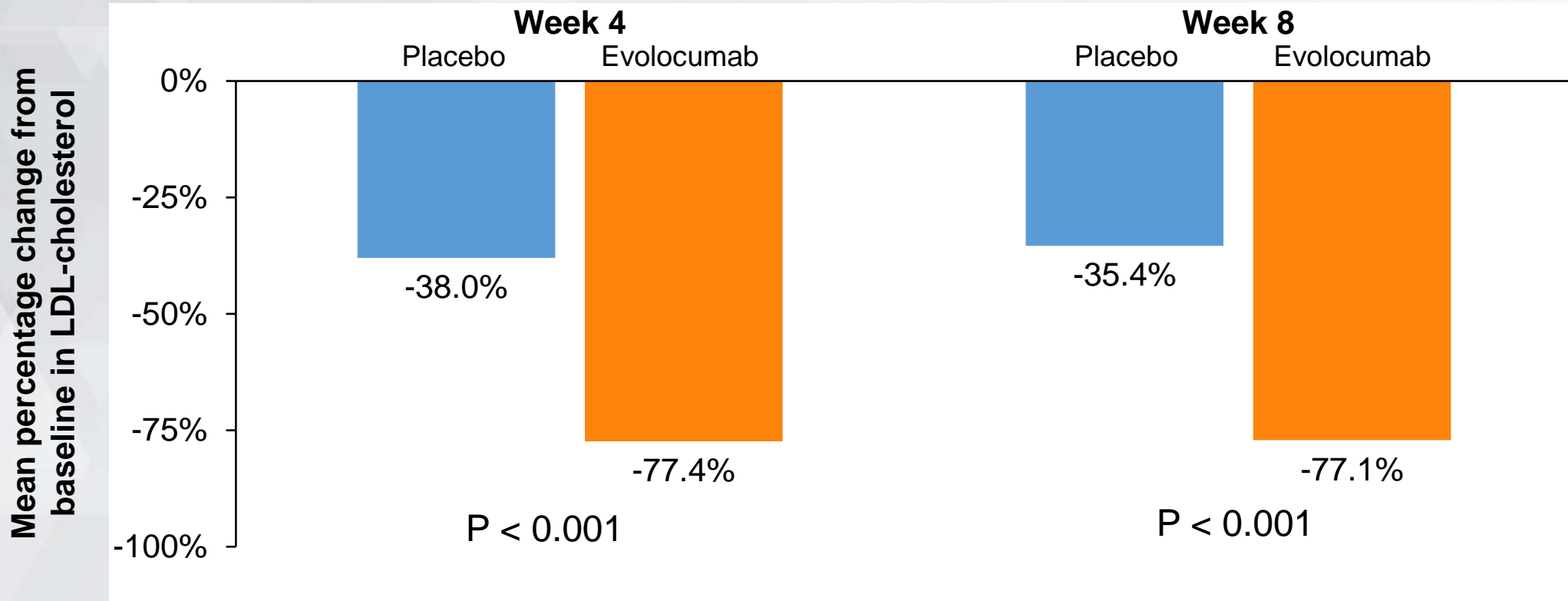
Absolute difference, LS means (mmol/L)

Percentage difference
P-value

	Week 4	Week 8
Absolute difference, LS means (mmol/L)	1.34	1.43
Percentage difference	38.4%	40.7%
P-value	<0.001	<0.001

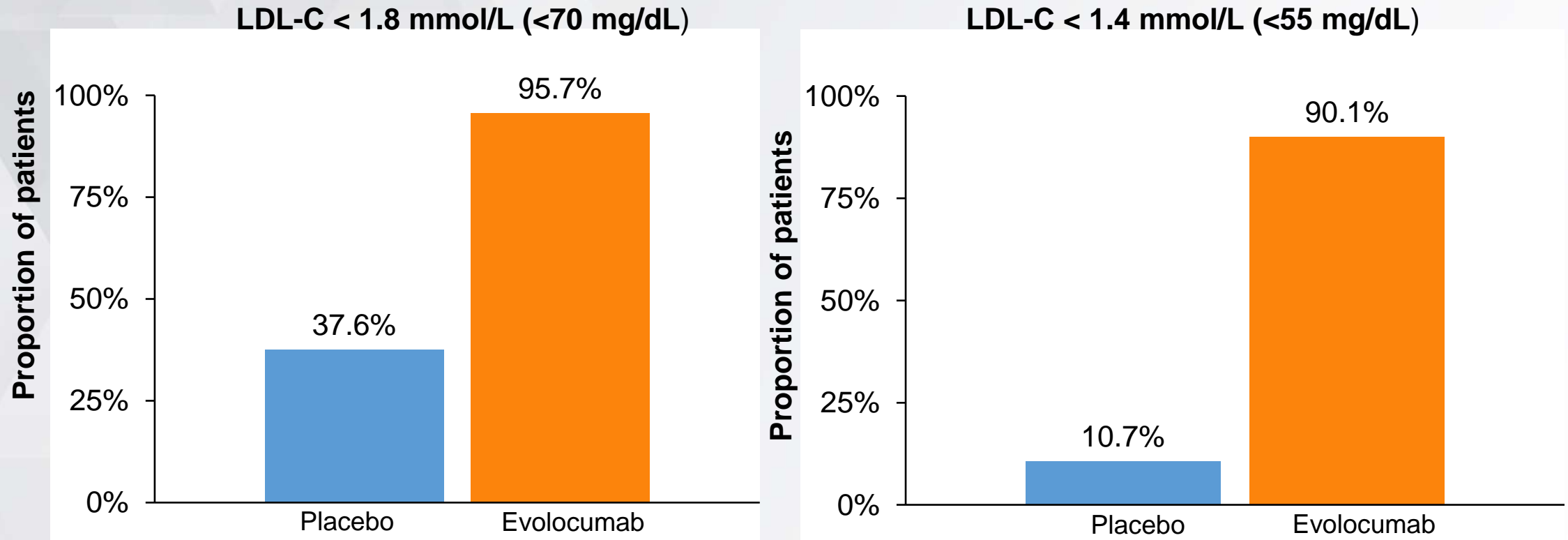
The reduction in LDL-C levels was evident at 4 weeks and maintained at 8 weeks

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

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>

Adverse Events of Special Interest Were Similar

	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.

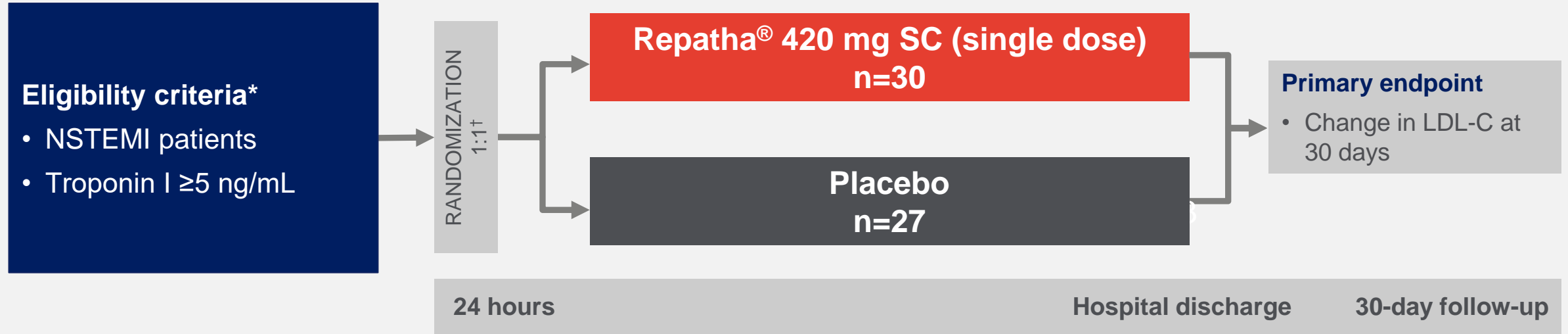
Number (proportion) of patients with each event type are reported, not counting multiple events of the same type. Fisher's exact tests in case of zero events in one group.

^aExcludes 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

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

EVACS Trial: Evolocumab Added to a Statin Was Administered in-hospital During the Early Postinfarction Period



- All patients received high-intensity statins unless contraindicated and were treated in accordance with current guidelines to treat ACS
- 57 patients met eligibility criteria and were included in the study

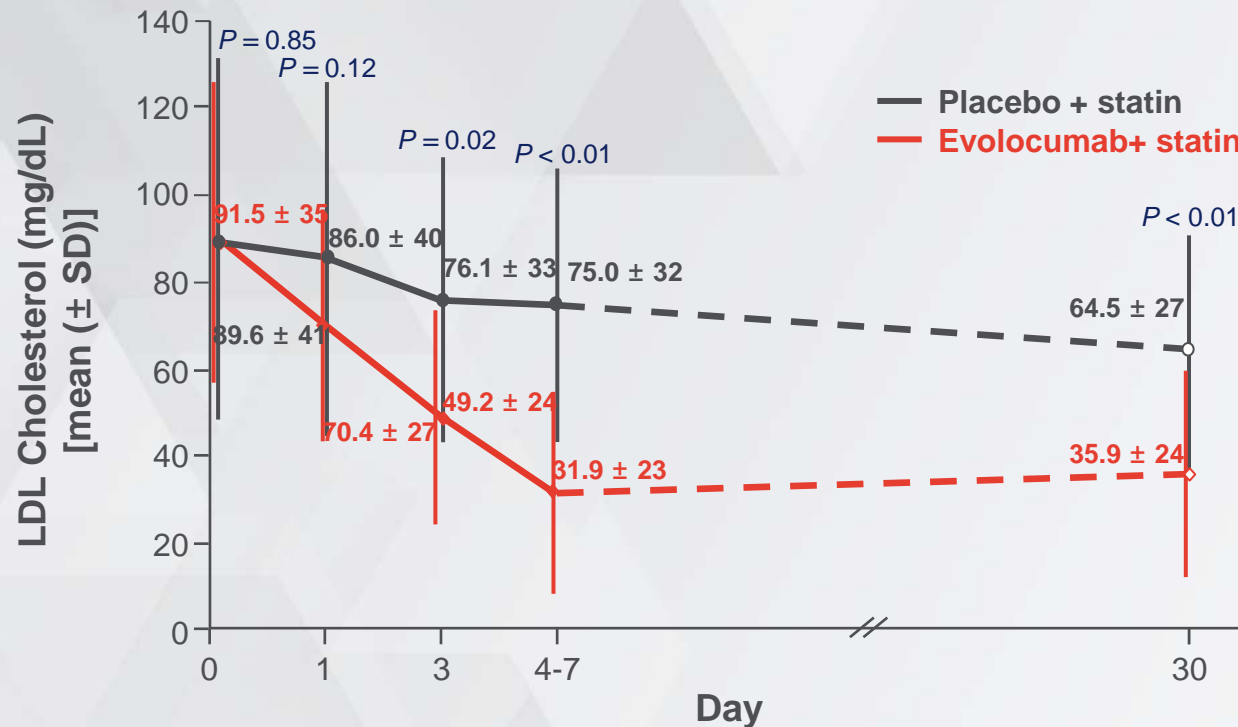
*Lipid values were not an inclusion criterion and were obtained at baseline, throughout hospitalization, and at 30 days. The principal reason for exclusion was a troponin I level of <5 ng/mL.

†Randomization occurred within 24 hours of presentation.

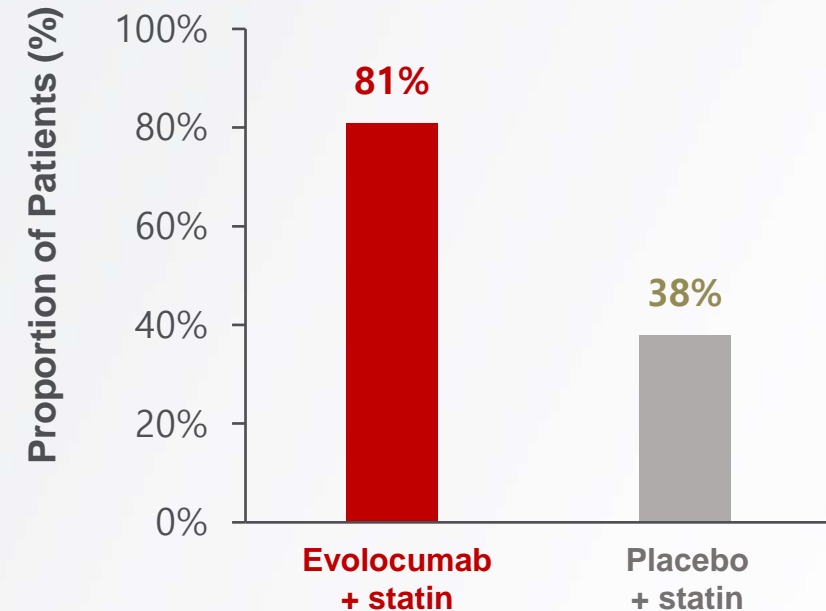
1. Leucker TM, et al. *Circulation*. 2020;142:419-421.

EVACS Trial: Evolocumab, Added to Statin Therapy, Reduced LDL-C Levels Throughout Hospitalization and at 30-day Follow-up

Mean LDL-C levels in the 2 study groups



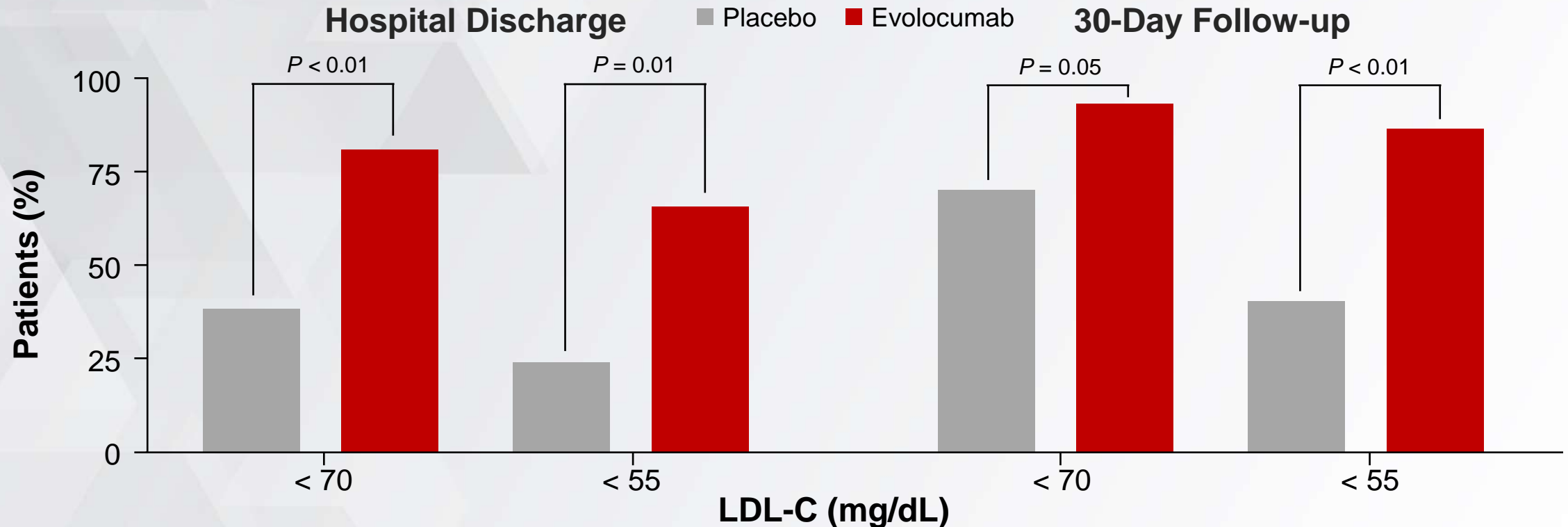
LDL-C <70 mg/dL at hospital discharge



This study demonstrated that evolocumab initiated in the hospital early after ACS rapidly and significantly reduces LDL-C in just 24 hours and 30 Days.

1. Leucker TM, et al. *Circulation*. 2020;142:419-421.

EVACS Trial: Evolocumab, Added to Statin Therapy, Reduced LDL-C Levels Throughout Hospitalization and at 30-day Follow-up



At hospital discharge^a (~Day 4), 80.8% and 65.4%, respectively, of evolocumab-treated patients achieved 2018 AHA/ACC and 2019 ESC guideline LDL recommendations compared with 38.1% and 23.8%, respectively, of placebo-treated patients

^aThe mean discharge day was 4±2 days. Discharge values were obtained within 24 hours of discharge (evolocumab n = 26; placebo n = 21).

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol.

Summary and Conclusions

- Mounting evidences and guidelines have been continuously emphasized “Lower is better” and “Earlier is better” in lipid-lowering therapy during last two decades.
- However, many interventionists or physicians have been underestimated residual ischemic risk and undertreated lipid lowering in ACS patients.
- Only high-intensity statin and ezetimibe can not achieve new LDL-c goal during acute phase in many ACS patients.
- We need new paradigm with preemptive use of PCSK9 inhibitor on top of high intensity statin and ezetimibe to get better and earlier achievement of LDL goal and prevention of recurrent ischemic events in ACS patients.