Early Benefits of Lipitor in ACS Patients

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Disclosure Statement of Financial Interest

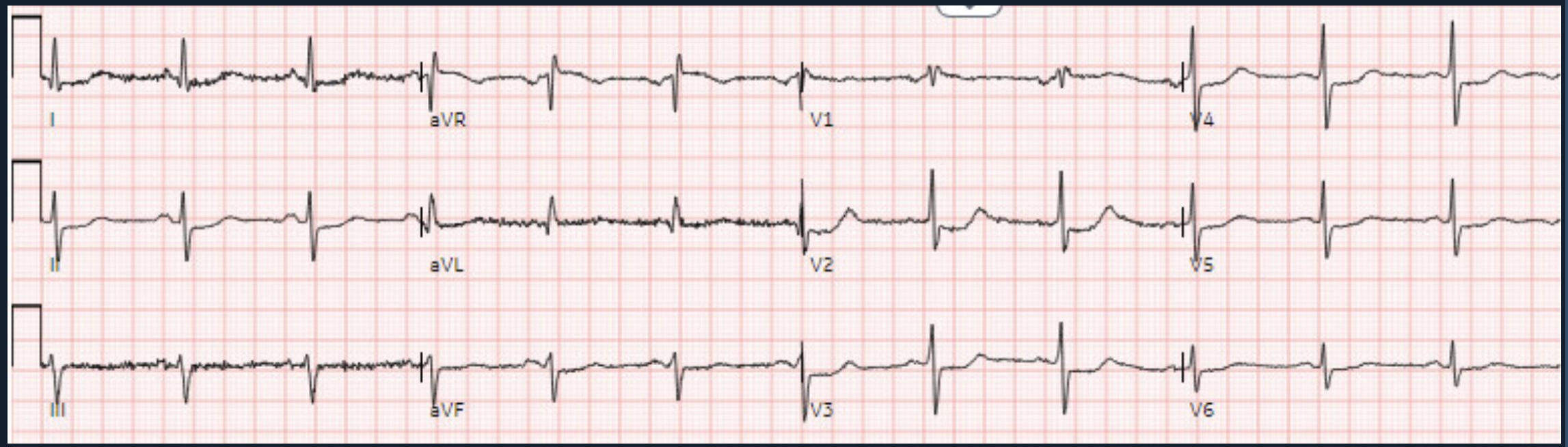
Advisory board/Honoraria: Amgen, Pfizer, Viatris.

74 y/o male with chest pain and NSTEMI

- Hx of HTN, HLD, CAD s/p DES to mid LAD (2016)
- Chest pain for 1 day
- Meds: ASA, Atorvastatin 20 mg, Amlodipine 2.5 mg, Imdur 30 mg, Metoprolol ER 25 mg

74 y/o male with chest pain and NSTEMI

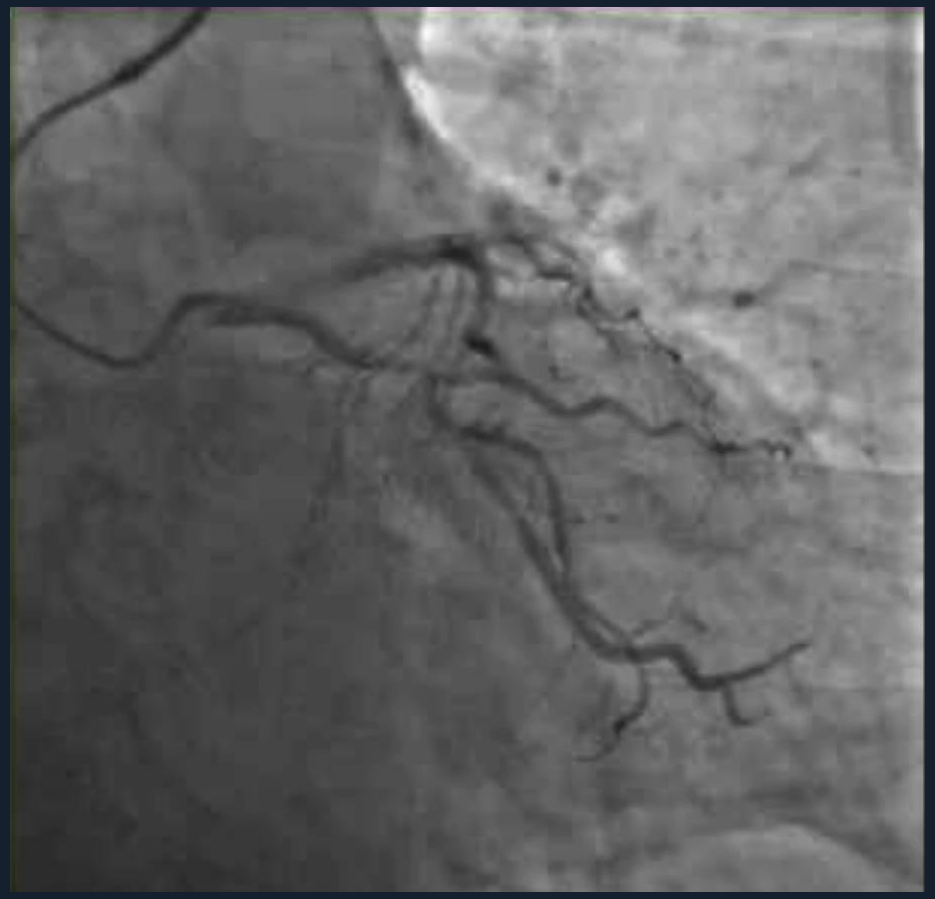
EKG



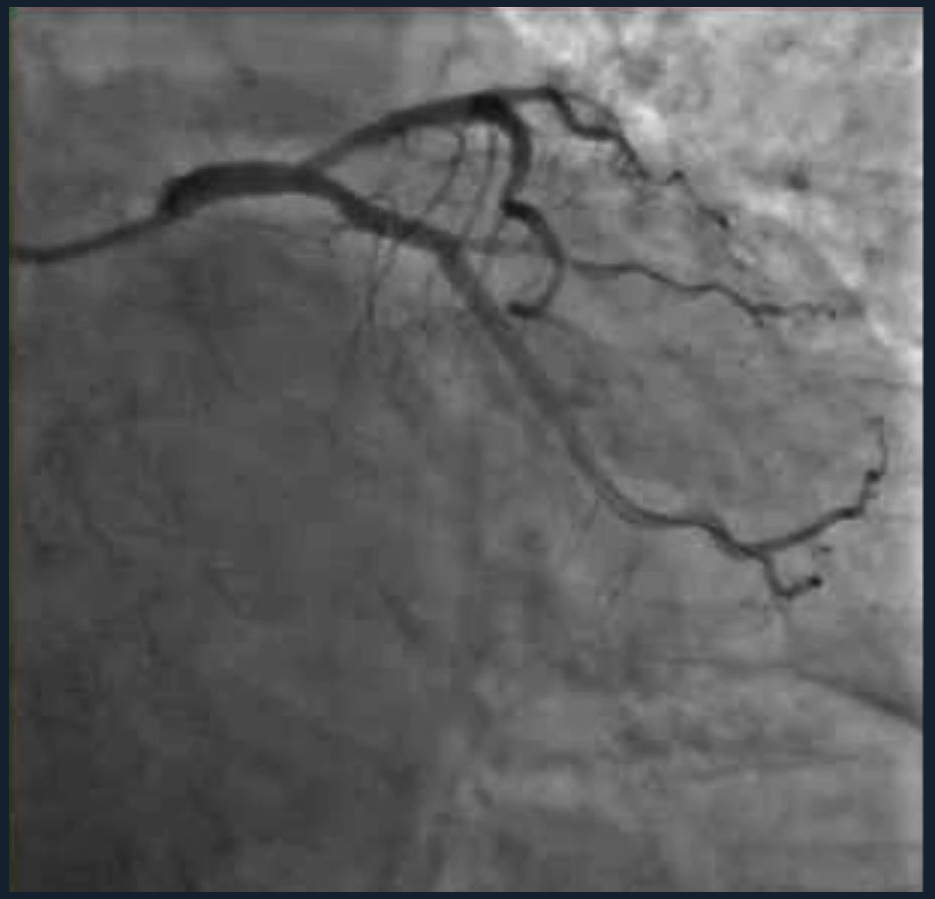
74 y/o male with chest pain and NSTEMI

Coronary Angiography

99% Proximal LCX with TIMI 2 flow



s/p DES x 1



74 y/o male with chest pain and NSTEMI

- Baseline Lipid panel: TC: 138 mg/dl; HDL: 47 mg/dl; TG 137 mg/dl; LDL 64 mg/dl

74 y/o male with known CAD on AT 20 mg p/w NSTEMI s/p DES with an LDL of 64 mg/dl.

Lipid Management Questions

- Should he be on a high intensity statin given an LDL of 64 mg/dl?
- What should be his target LDL-C level?
- Is there a benefit of administering high intensity statin prior to PCI and during the acute phase of NSTEMI?
- Does visit-to-visit variability in LDL-C levels matter?

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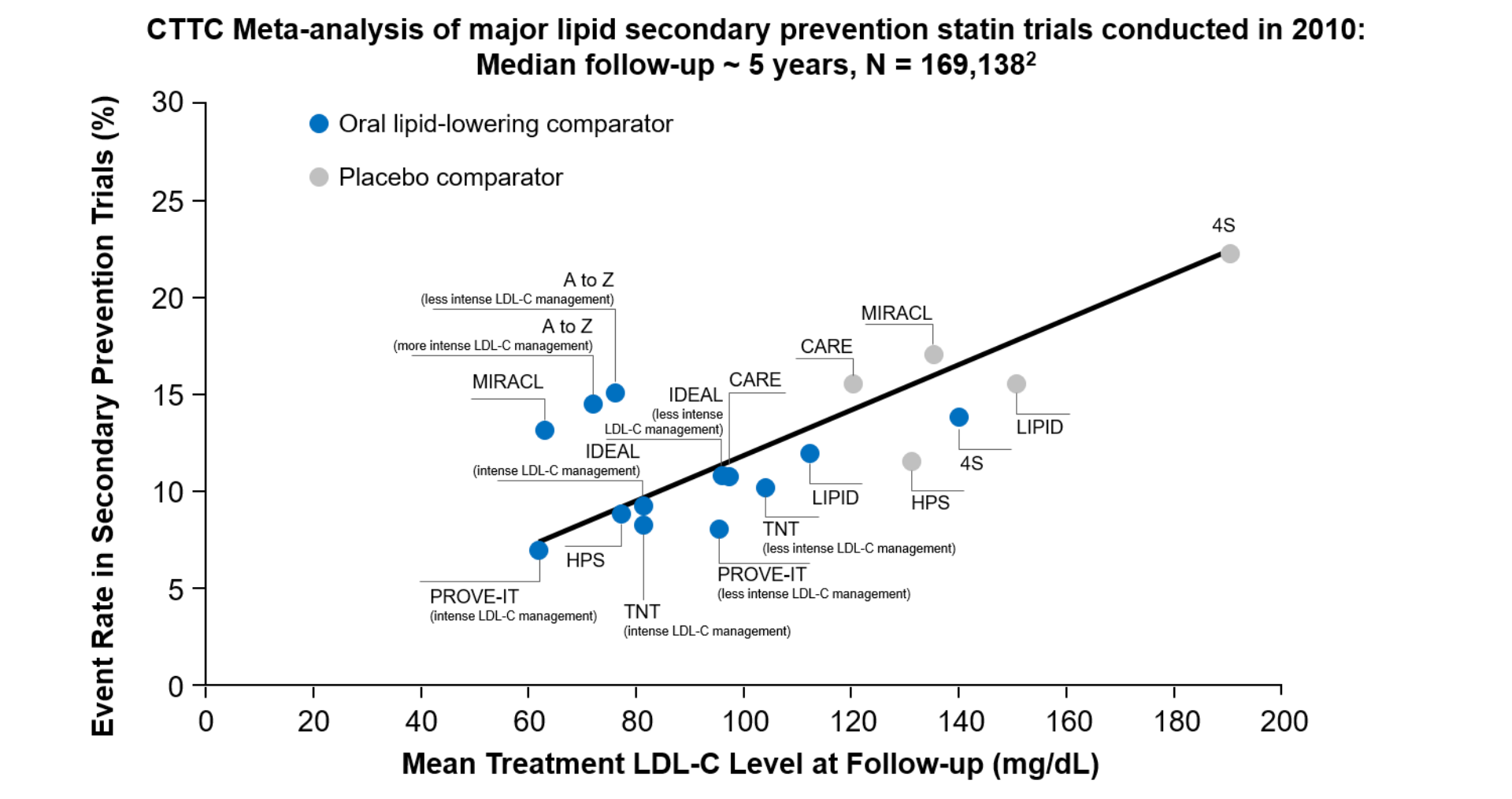
There Is a Linear Correlation Between LDL-C Lowering and Lowering Risk of CV Events in Statin Trials[1,2]



CTTC = Cholesterol Treatment Trialists' Collaboration.

1. Raymond C, et al. *Clev Clin J Med*. 2014;81:11-19. 2. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2010;376:1670-1681.

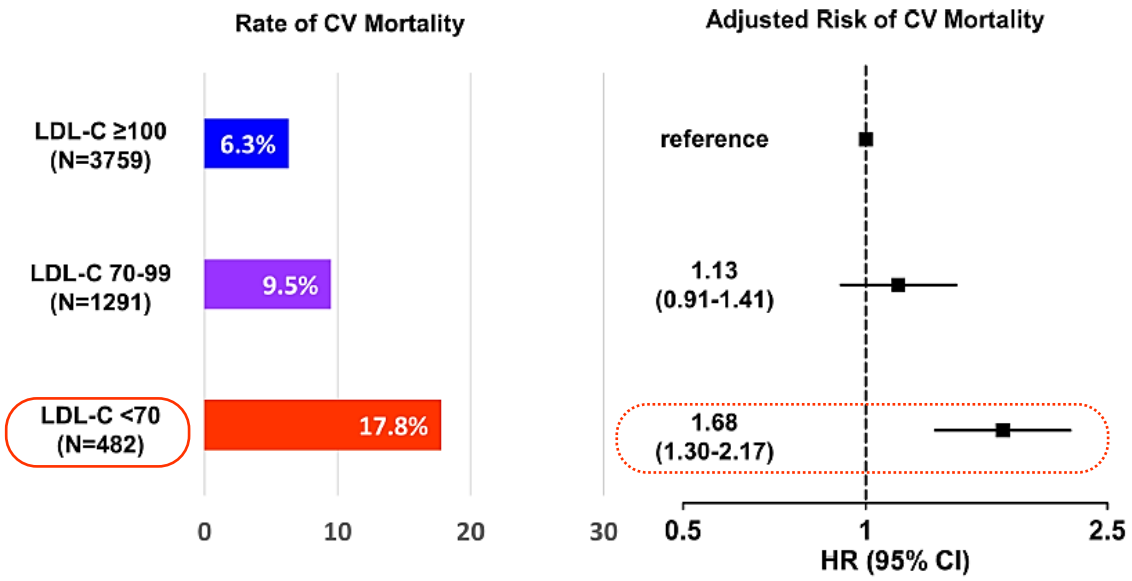
Benefits of More vs Less Intensive Statin Therapy (5 RCTs, N=39,612)

- Intensive therapy statin therapy resulted in a further reduction of LDL-C of 0.51mmol/L
- After 1 year:
    - 15% reduction in major vascular events
    - 13% reduction of coronary death or non-fatal MI
    - 16% reduction in ischemic stroke

CTT *Lancet* 2010; 376: 1670-81

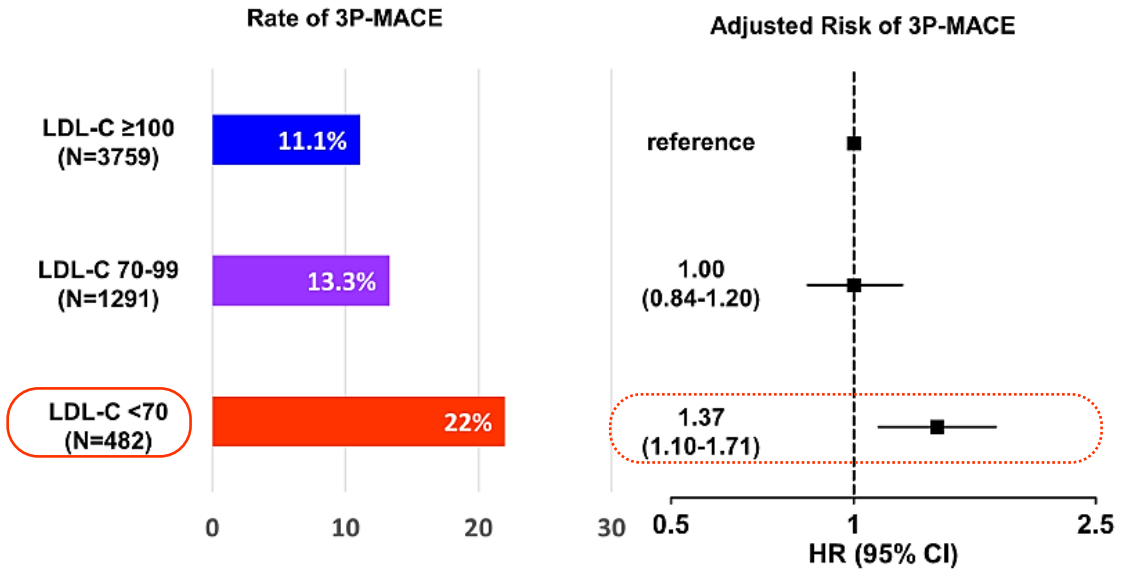
Impact of low baseline LDL-C on CV outcomes at 5 years in Korean patients with AMI having PCI

Adjusted risk of categorical LDL-C levels for CV mortality at 5 years



Adjusted risk of categorical LDL-C levels for 3P-MACE at 5 years

(nonfatal stroke, nonfatal MI, and CV death)



AMI, acute myocardial infarction; **PCI,** percutaneous coronary intervention; **COREA-AMI,** Cardiovascular Risk and Identification of Potential High-Risk Population-AMI (For evaluating the real-world features and long-term clinical outcomes in Korean patients with AMI, the participating university hospitals used web-based registries to enroll all consecutive patients with AMI prospectively. **3P-MACE**, 3-point major adverse cardiovascular event

Ref. Cho KH, et al. Impact of Low Baseline Low-Density Lipoprotein Cholesterol on Long-Term Postdischarge Cardiovascular Outcomes in Patients With Acute Myocardial Infarction. J Am Heart Assoc. 2022;11:e025958.

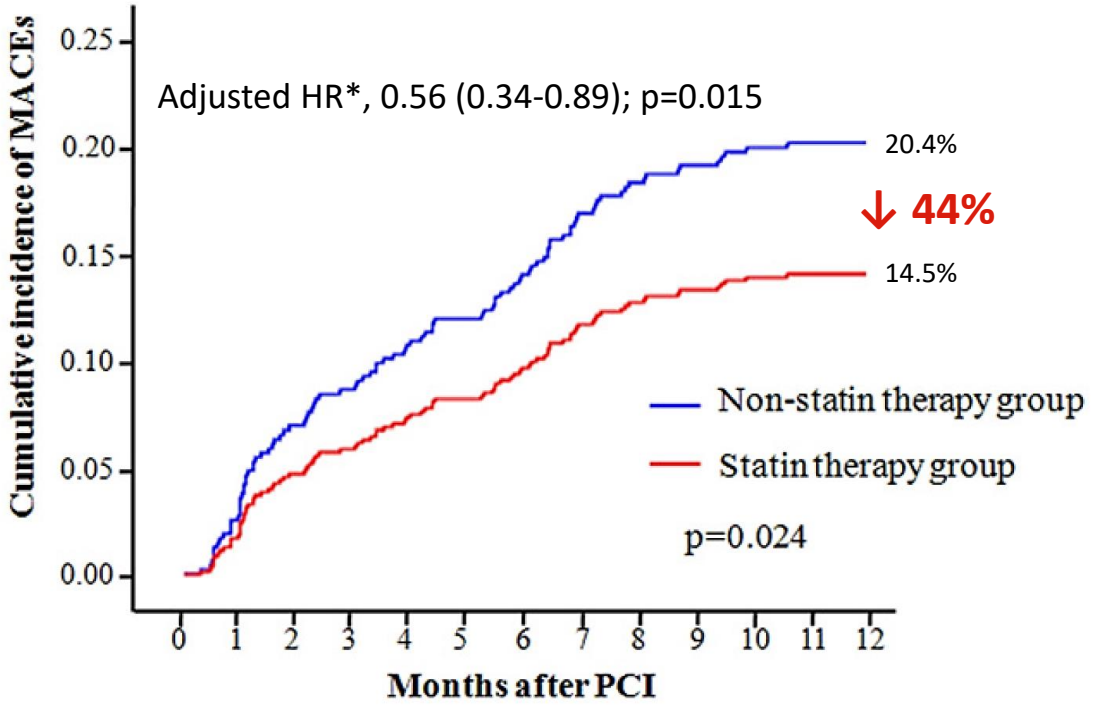
Benefit of statin in Korean patients with AMI and baseline LDL-C <70 mg/dL

A real-world observational study (KAMIR-NIH 2005-2007)

1,054 patients with AMI and baseline LDL cholesterol <70 mg/dL
(male 70%, mean 71 years old, mean LDL-C 58 mg/dL)

Estimates of the rate of the primary endpoint events

(Death, recurrent MI, TVR, and CABG)



Cumulative secondary endpoints at 12 months

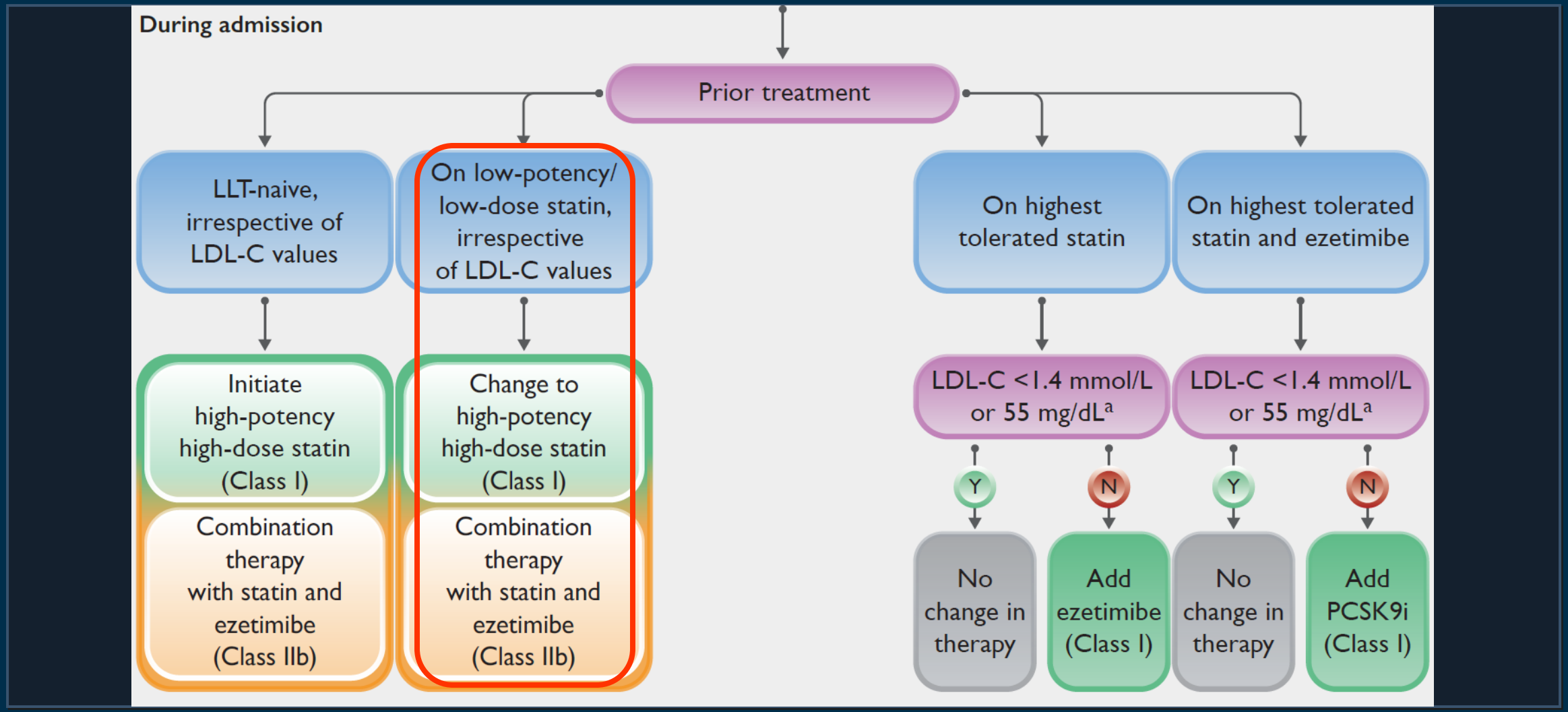
	Adjusted HR (95% CI)	p Value
Death	0.56 (0.26–1.20)	0.133
Cardiac death	0.47 (0.23–0.93)	0.031
Noncardiac death	0.89 (0.20–4.09)	0.885
MI	1.38 (0.45–4.19)	0.570
Coronary revascularization	0.45 (0.24–0.85)	0.013
Repeated PCI	0.63 (0.29–1.35)	0.232
TVR	0.51 (0.19–1.40)	0.191
CABG	0.15 (0.04–0.55)	0.004
MACE	0.56 (0.34–0.89)	0.015

*The HRs were adjusted for propensity score and important risk covariables that had significant effects (p <0.1) in the univariate analysis for clinical outcomes.

AMI, acute myocardial infarction; **KAMIR-NIH,** Korea Acute Myocardial Infarction Registry-National Institutes of Health; **MACE**, major adverse cardiac event; **PCI**, percutaneous coronary intervention; **TVR**, target vessel revascularization; **CABG**, coronary artery bypass grafting; **HR,** hazard ratio; **CI,** confidence interval

Ref. Lee KH, et al. Benefit of early statin therapy in patients with acute myocardial infarction who have extremely low low-density lipoprotein cholesterol. J Am Coll Cardiol. 2011 Oct 11;58(16):1664-71.

2023 ESC Guidelines for the management of acute coronary syndromes



Byrne RA, et al. Eur Heart J. 2023 Aug 25:ehad191.

2022 Korean guidelines for the management of dyslipidemia

- For patients with CHD, the treatment goal is to lower LDL-C levels to <55 mg/dL and by ≥ 50% from the baseline level for secondary prevention.
- If acute MI occurs, administer statins immediately regardless of the baseline LDL-C level.
- Statin is the first line drug for hypercholesterolemia and the dosage is recommended to be adjusted to reach the target LDL-C level according to risk.
- Combination with ezetimibe is recommended if LDL-C target is not achieved even after using maximum tolerable dose of statin.

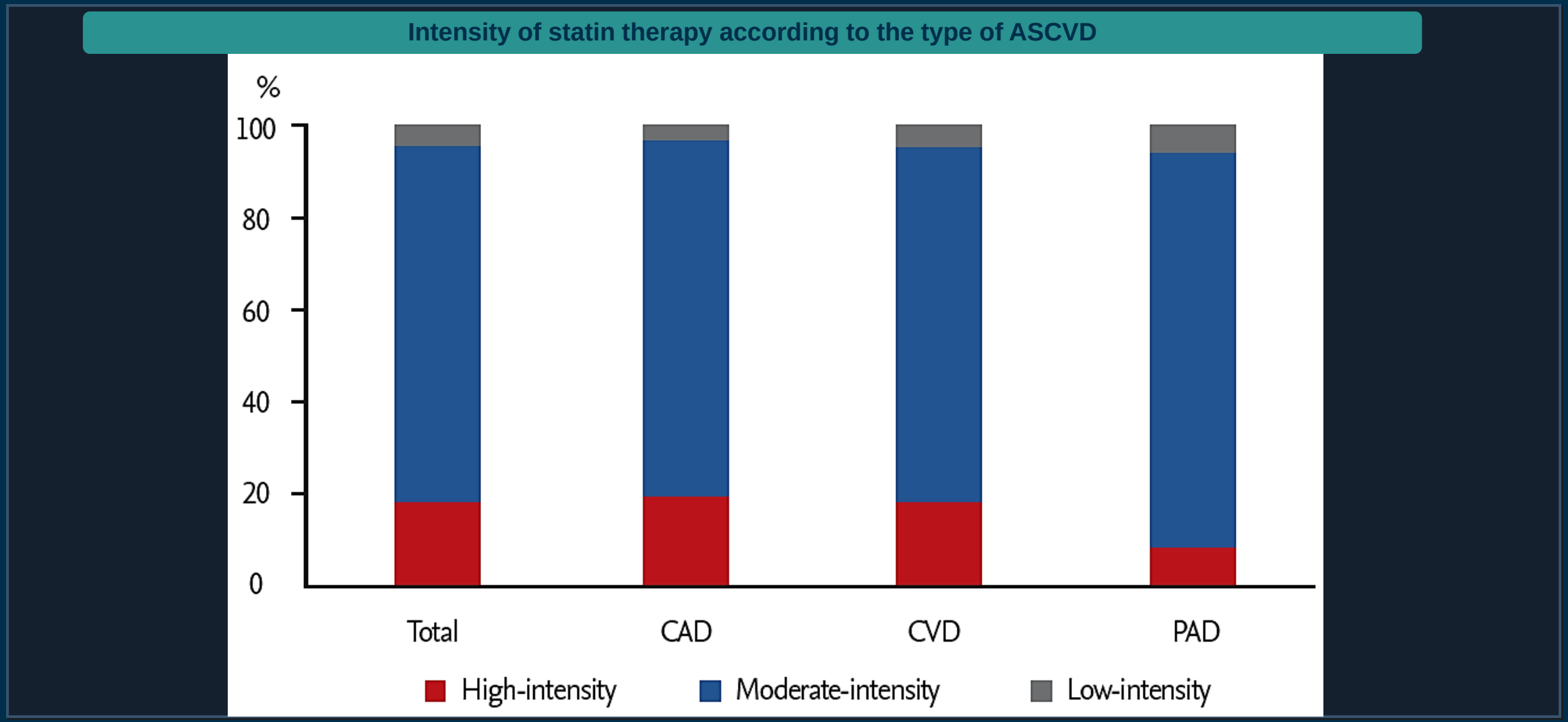
KSoLA, Korean guidelines for the management of dyslipidemia, 2022

74 y/o male with known CAD on AT 20 mg p/w NSTEMI s/p DES with an LDL of 64 mg/dl.

Lipid Management Questions

- Should he be on a high intensity statin given an LDL of 64 mg/dl? *Yes. Regardless of LDL-C levels*
- What should be his target LDL-C level?
- Is there a benefit of administering high intensity statin prior to PCI and during the acute phase of NSTEMI?
- Does visit-to-visit variability in LDL-C levels matter?

High-intensity statin underused in Korean patients with established ASCVD



Choi SY, et al. Korean J Intern Med 2020;35:593-604

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Guidelines and Recommendations Worldwide Advise LDL-C Lowering Based on CV Risk[1,2]

2018 AHA/ACC Guidelines

2 risk groups, including:

Very High-Risk

- **Multiple major ASCVD events** (recent ACS, history of MI, history of ischemic stroke, symptomatic PAD)

OR

- **One major ASCVD event and multiple high-risk conditions** (e.g. diabetes, hypertension)

2019 ESC/EAS Guidelines

5 risk groups, including:

Very High-Risk

- **Documented ASCVD**, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS*, stable angina, coronary revascularization†, stroke and TIA, and peripheral arterial disease‡
- **DM with target organ damage**, or at least three major risk factors, or early onset of T1DM of long duration (>20 years)
- **Severe CKD** (eGFR <30 mL/min/1.73 m^2)
- **A calculated SCORE ≥10%** for 10-year risk of fatal CVD
- **FH with ASCVD** or with another major risk factor

Statins are universally recommended as first-line therapy across guidelines and recommendations

LDL-C THRESHOLD of 70 mg/dL

Threshold = Trigger to intensify therapy by using non-statin medications

LDL-C GOAL < 55 mg/dL **AND** ≥ 50% reduction from baseline

Additionally, for ASCVD patients on maximally tolerated statin experiencing a 2nd vascular event within 2 years, a lower LDL-C goal of < 40 mg/dL (<1.0 mmol/L) may be considered

*MI or UA; †PCI, CABG, and other arterial revascularization procedures; ‡unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.
CT = computed tomography; FH = familial hypercholesterolemia.

1. Grundy SM, et al. *J Am College Cardiol*. 2019;73:e285- e350. 2. Mach F, et al. *Eur Heart J.* 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

2022 Korean guidelines for the management of dyslipidemia

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Lipid Management Questions

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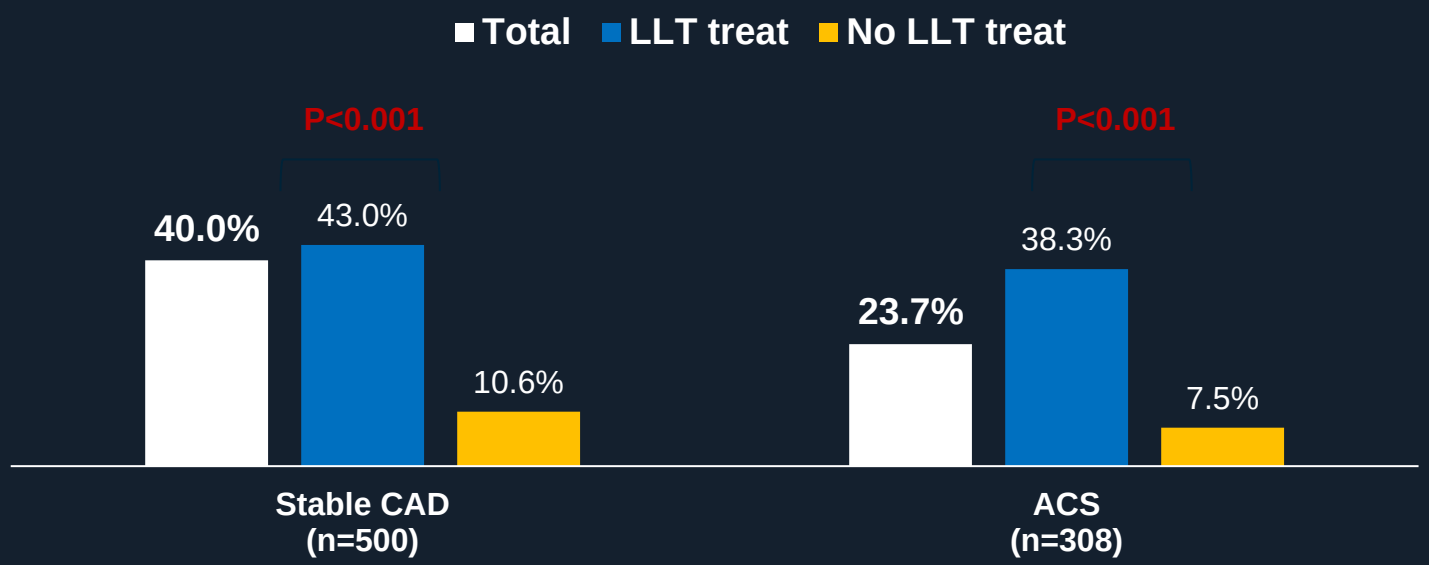
- What should be his target LDL-C level? *<55 mg/dl (consider <40 mg/dl)*
- Is there a benefit of administering high intensity statin prior to PCI and during the acute phase of NSTEMI?
- Does visit-to-visit variability in LDL-C levels matter?

Achievement of the LDL-C goal and statin use among patients with CAD or ACS in Korea

The international observational study (DYSIS II)
808 Korean patients with stable CAD or ACS



Statin daily dose – atorvastatin (mg/day)* * Statin dose normalised to atorvastatin potency	
Stable CAD : 17±10	ACS : 17±12

Poh KK, et al. Eur J Prev Cardiol. 2018, Vol. 25(18) 1950–1963_ Supplementary

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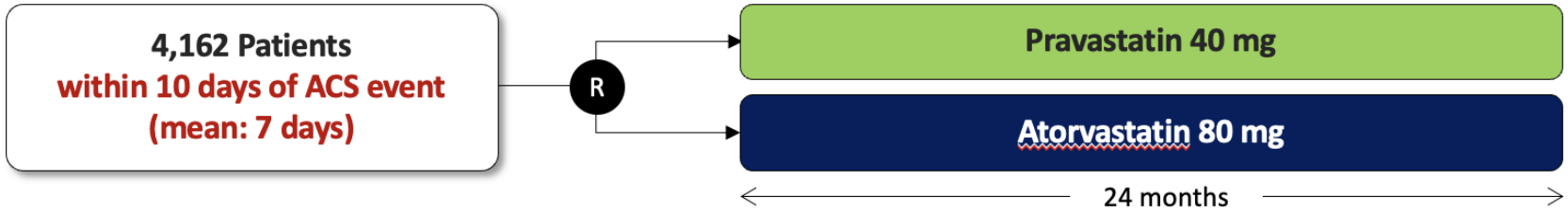
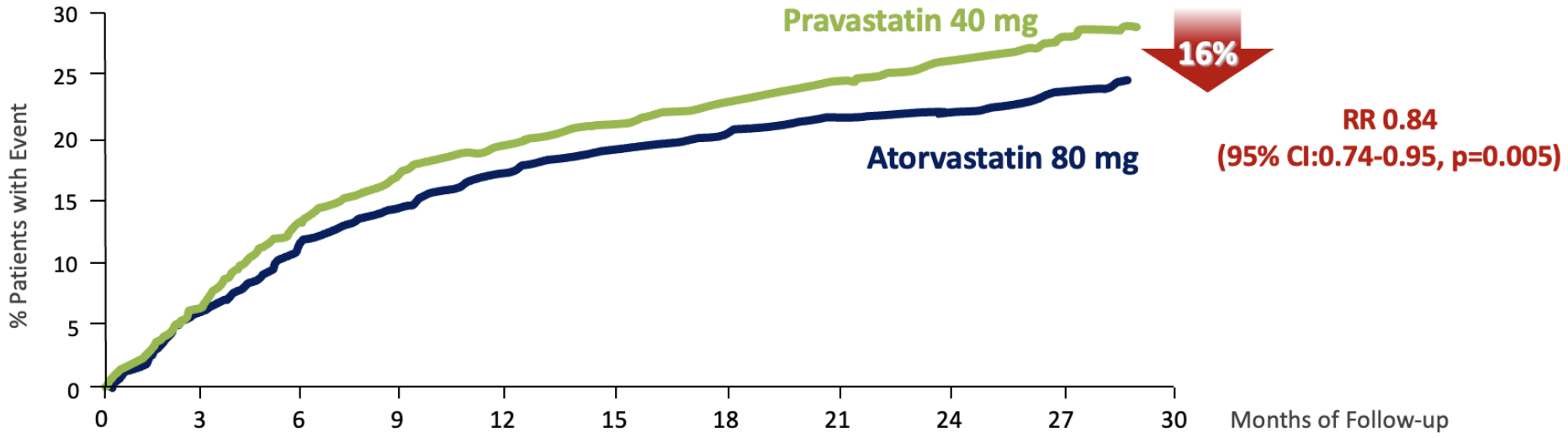
Early Atorvastatin 80 mg therapy after ACS

Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in MI (PROVE-IT 22) trial



Kaplan-Meier Estimates of Primary Outcome

(All-cause death, non-fatal MI, UA hospitalization, urgent revascularization, and/or stroke)

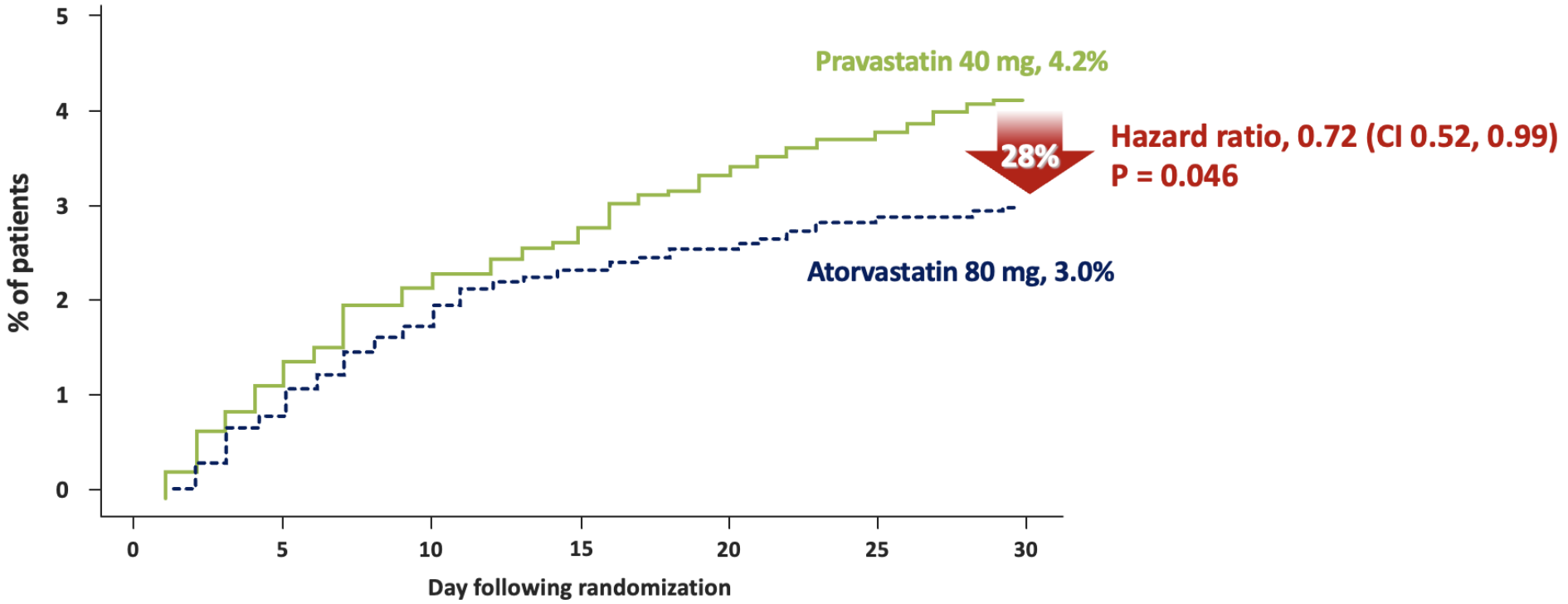


Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

Early Atorvastatin 80 mg therapy after ACS

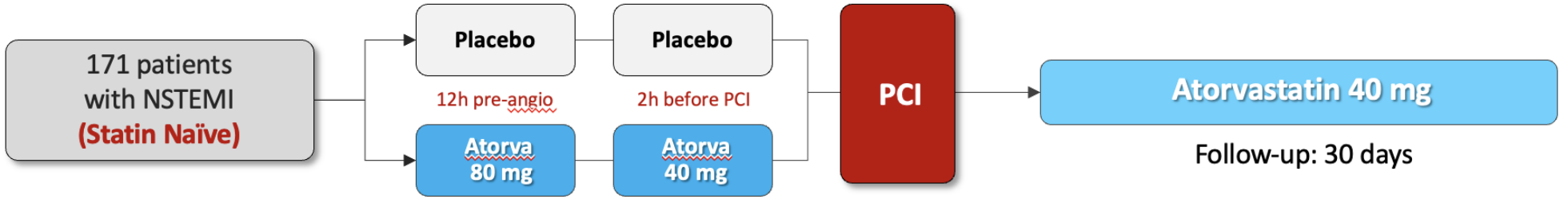
Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in MI (PROVE-IT 22) trial

Death, MI, or rehospitalization for ACS until 30 days

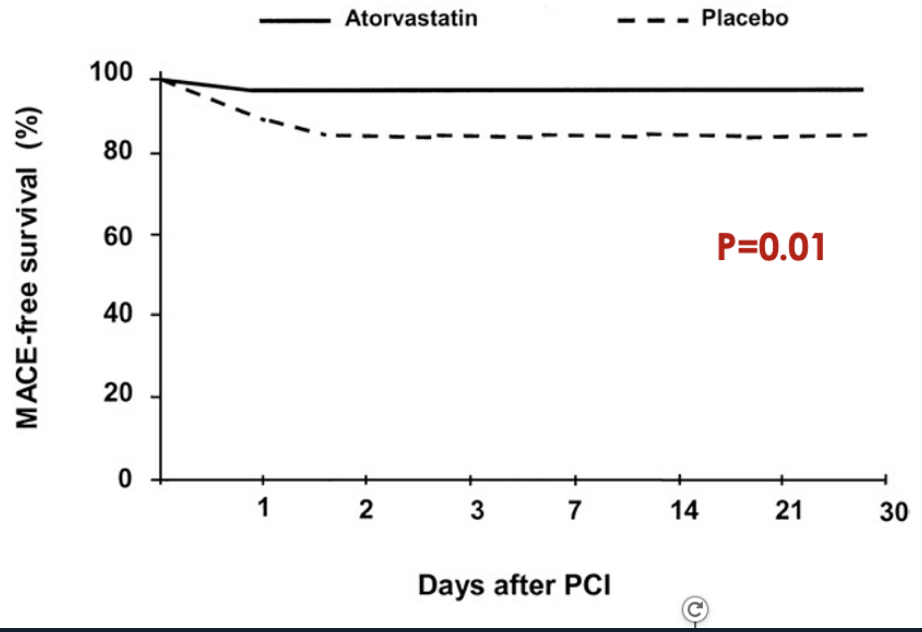


Ray KK, et al. J Am Coll Cardiol 2005;46:1405–10

ARMYDA-ACS: 30-day MACE of atorvastatin pretreatment in ACS patients undergoing early PCI



30-day incidence of MACE



	Atorvastatin (n=86)	Placebo (n=85)	P-value
Death	-	-	
MI	4(5)	13(15)	0.04
TVR	-	1(2)	1
Total MACE	**4(5)**	**14(17)**	**0.01**

*MACE, death, MI, target-vessel revascularization

Patti G, et al. J Am Coll Cardiol 2007;49:1272–8.

ARMYDA-RECAPTURE

Effect of atorvastatin reload in pts on chronic statin undergoing PCI

383 patients with stable angina(53%) or NSTEMI (47%)
(Statin chronic use)

- Placebo — 12h pre-angio
- Placebo — 2h before PCI
- Atorva 80 mg — 12h pre-angio
- Atorva 40 mg — 2h before PCI

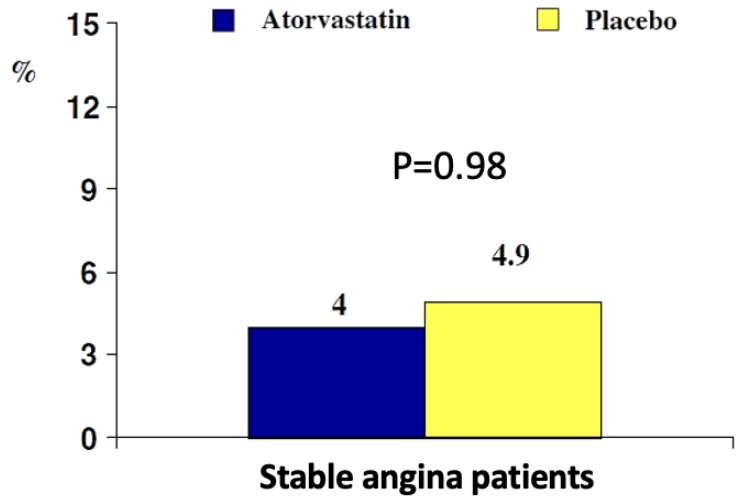
PCI

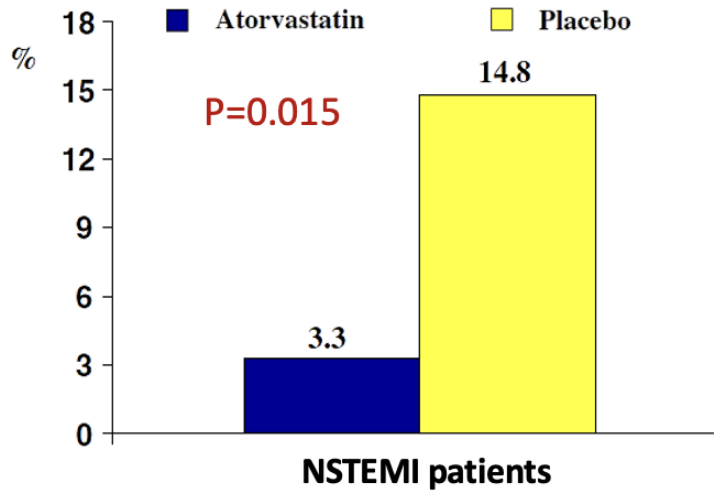
Atorvastatin 40 mg

Follow-up: 30 days

➲ **Primary endpoint(MACE) :** atorvastatin 3.7% vs. placebo 9.4%; p=0.037

Secondary endpoint (MACE according to clinical presentation)





Di Sciascio G, et al. J Am Coll Cardiol. 2009;54:558-65

Short-Term high-dose atorvastatin pretreatment in patients With ACS undergoing PCI

A Meta-Analysis of 9 RCTs published up to March 2013

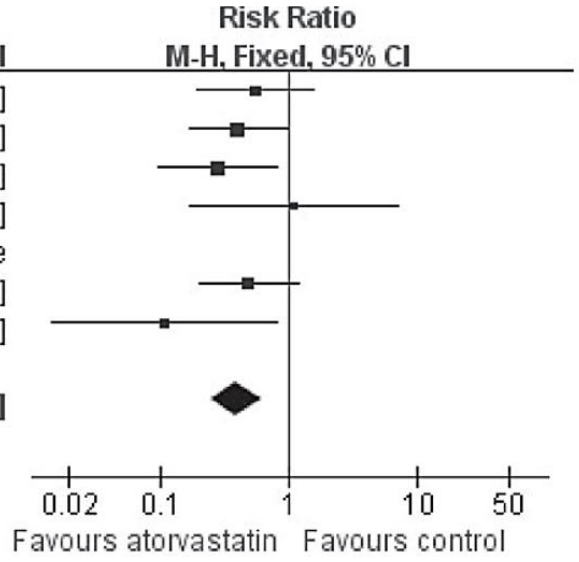
Atorvastatin 80 mg immediate or 12 hours before PCI (n=476) vs. placebo/10 mg(n=476)

Relative ratio of MACEs at 30 days

Study or Subgroup	atorvastatin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2010	5	86	9	85	15.0%	0.55 [0.19, 1.57]
Liu 2011	6	46	13	40	23.1%	0.40 [0.17, 0.96]
Patti 2007	4	86	14	85	23.4%	0.28 [0.10, 0.82]
Post 2012	2	20	2	22	3.2%	1.10 [0.17, 7.09]
Ren 2012	0	36	0	49		Not estimable
Wang 2013	6	40	12	39	20.2%	0.49 [0.20, 1.17]
Yu 2011	1	41	9	40	15.1%	0.11 [0.01, 0.82]
Total (95% CI)		**355**		**360**	**100.0%**	**0.39 [0.25, 0.61]**
Total events	24		59			

Heterogeneity: $Chi^2 = 3.74$, $df = 5$ ($P = 0.59$); $I^2 = 0\%$

Test for overall effect: $Z = 4.15$ ($P < 0.0001$)

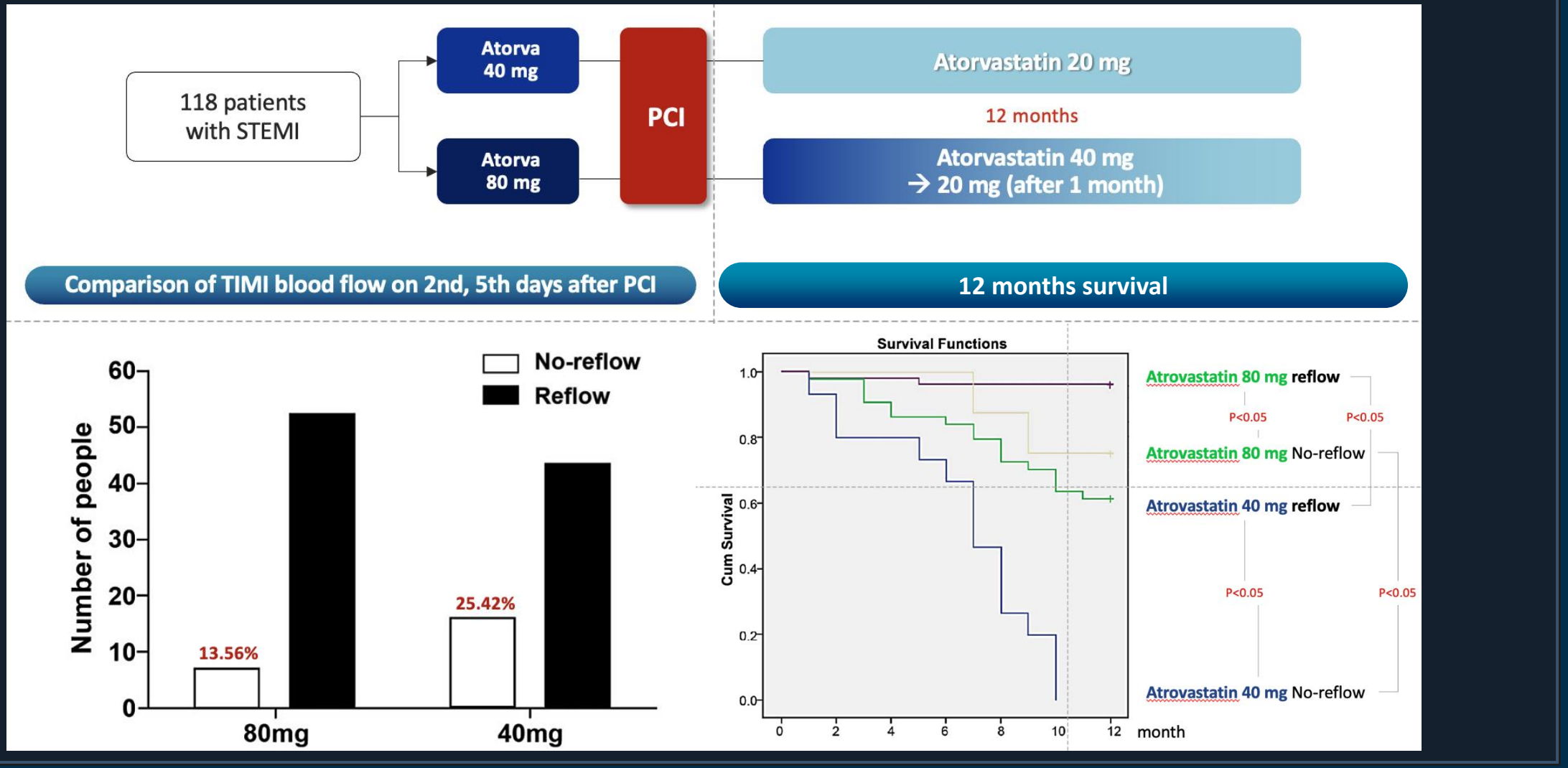


RR, 0.39 (0.25-0.61) **61% ↓**

* MACE was defined as the composite of death, MI and target-vessel revascularization

Liu Y, et al. Clin. Cardiol. 2013;36(12):E41–E48.

High Dose Atorvastatin Reduces No Reflow in STEMI

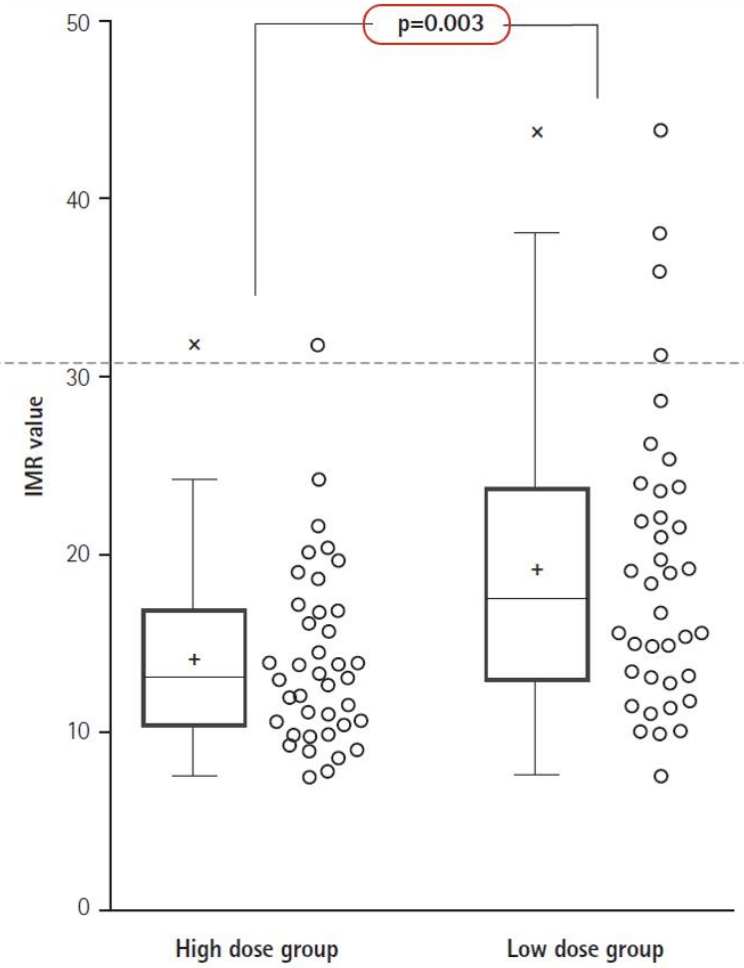


Li Q, et al. Am J Ther. 2018 May/Jun;25(3):e291-e298.

RESIST ACS Trial

Significantly lower post-PCI IMR value in high-dose atorvastatin group than low-dose in NSTE-ACS

Distribution of post-PCI IMR values

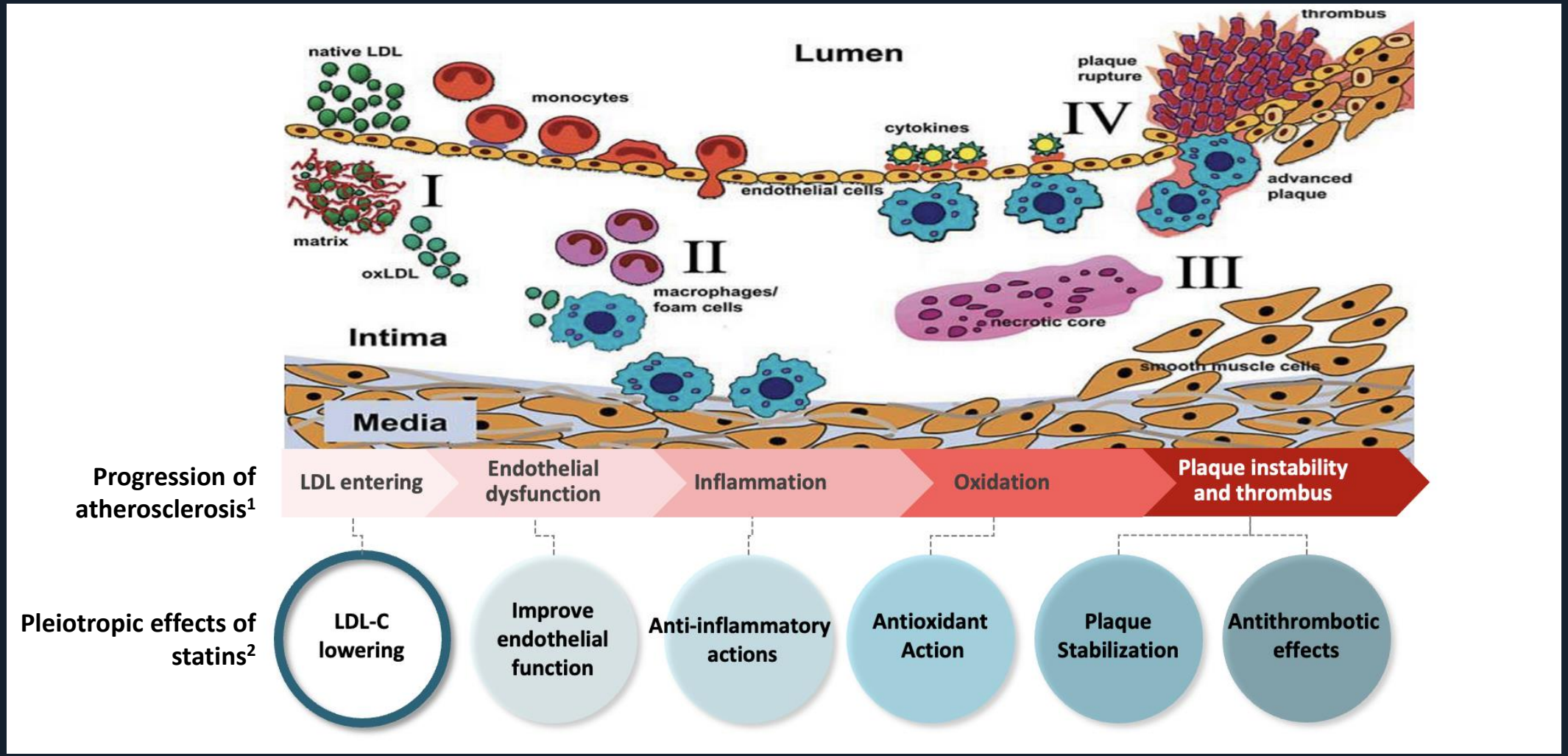


Coronary physiological parameters

Variable	High dose group (N=39)	Low dose group (N=38)	p
FFR, pre-PCI	0.57±0.20	0.64±0.17	0.202
FFR, post-PCI	0.90±0.05	0.91±0.07	0.748
CFR, post-PCI	1.86 (1.36-2.86)	1.83 (1.12-3.73)	0.611
IMR, post-PCI	14.1±5.0	19.2±9.3	0.003
Coronary wedge pressure, post PCI	24.7±12.4	25.3±15.5	0.853
Pw/Pa, post-PCI	0.24±0.11	0.25±0.15	0.569
Post-PCI IMR25	1 (2.6%)	9 (23.7%)	0.007

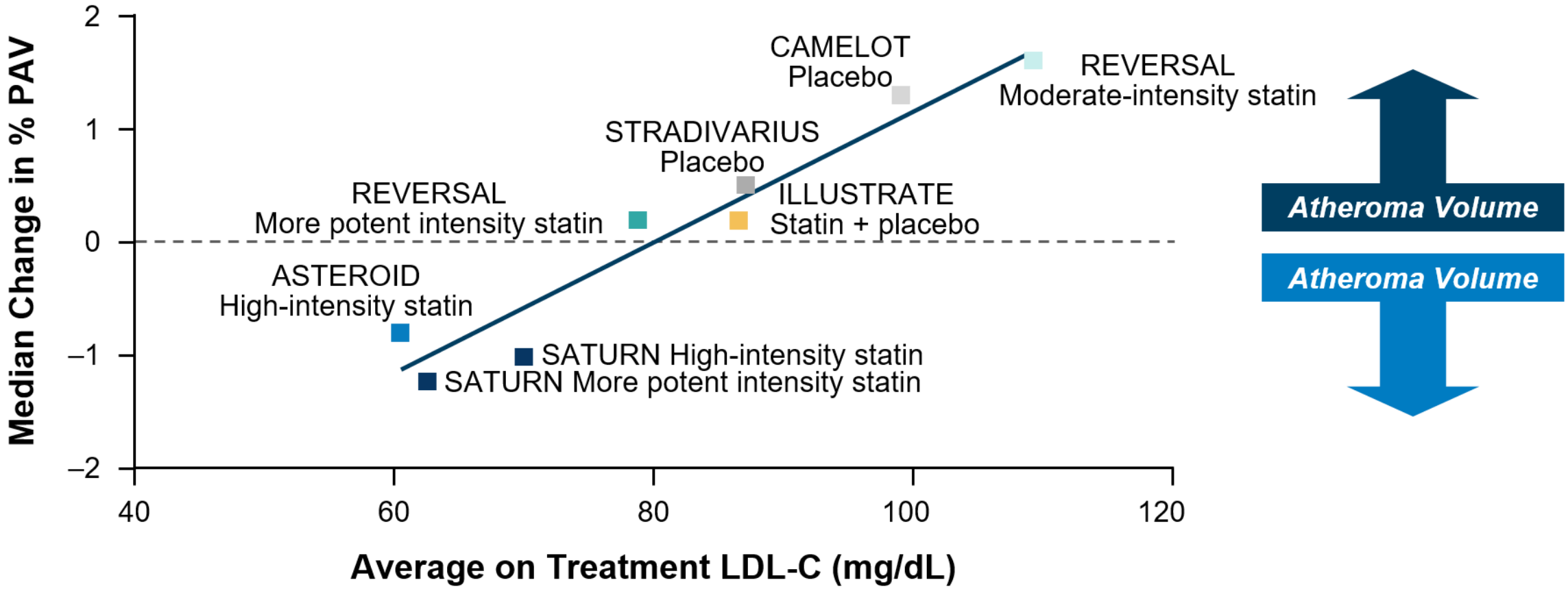
Lee BK, et al. Korean Circ J. 2016 Jul;46(4):472-80.

Benefits of statins beyond lipid lowering



Allayee H, et al. J Nutrigenet Nutrigenomics 2009;2(3):140-148. Libby P, et al. Circulation. 2001;104:365-372.

Reductions in Plaque Volume Have Been Shown With LDL-C Lowering



Median changes in PAV vs average on-treatment LDL-C in serial coronary IVUS trials.

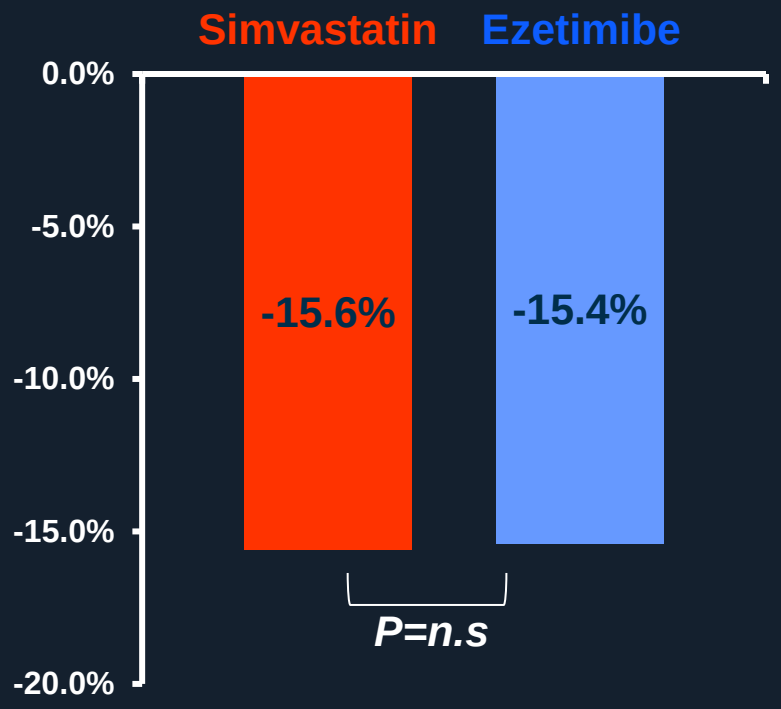
IVUS = intravascular ultrasound; PAV = percent atheroma volume.

Puri R, et al. *Am Heart J*. 2016;176:83-92.

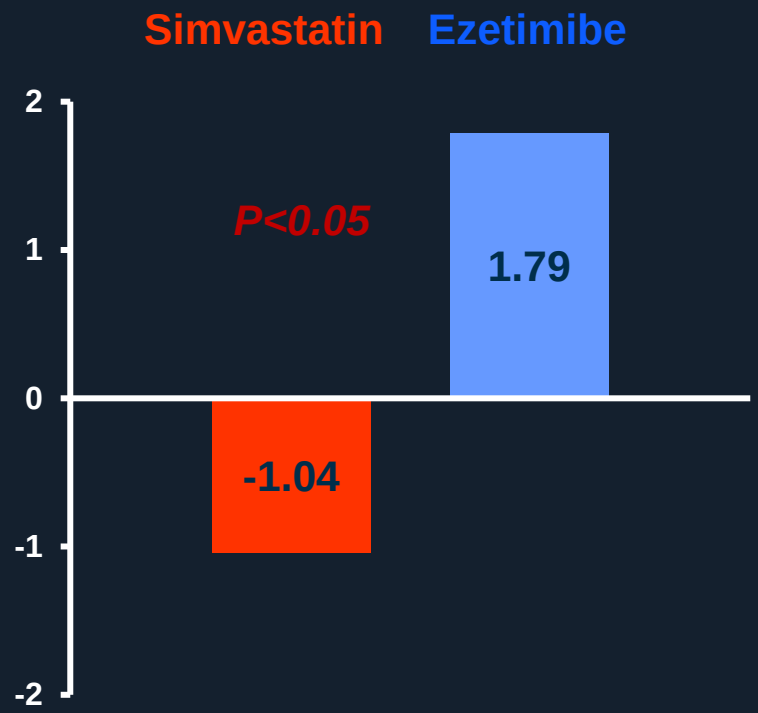
Pleotropic Effect: Statins vs. Ezetimibe

A randomized controlled trial 20 patients with chronic heart failure
Simvastatin 10 mg/d vs. Ezetimibe 10mg

Change in LDL –C after 4 weeks



Changes in plasma levels of mevalonate



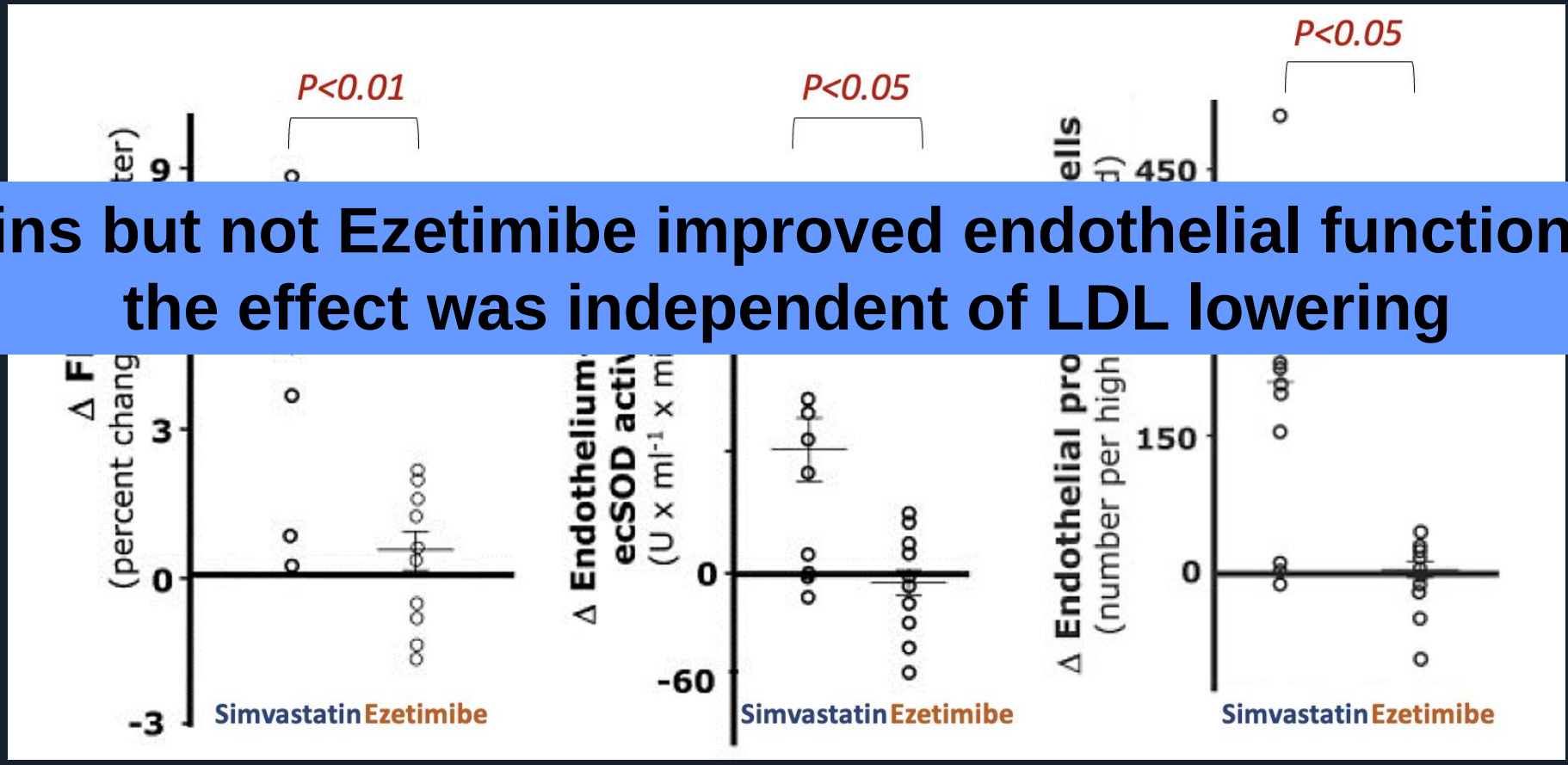
Landmesser U, et al. Circulation. 2005;111:2356–2363

Pleotropic Effect: Statins vs. Ezetimibe

Endothelial function in HF

A randomized controlled trial 20 patients with chronic heart failure
Simvastatin 10 mg/d vs. Ezetimibe 10mg

Change in Endothelial function after 4 weeks



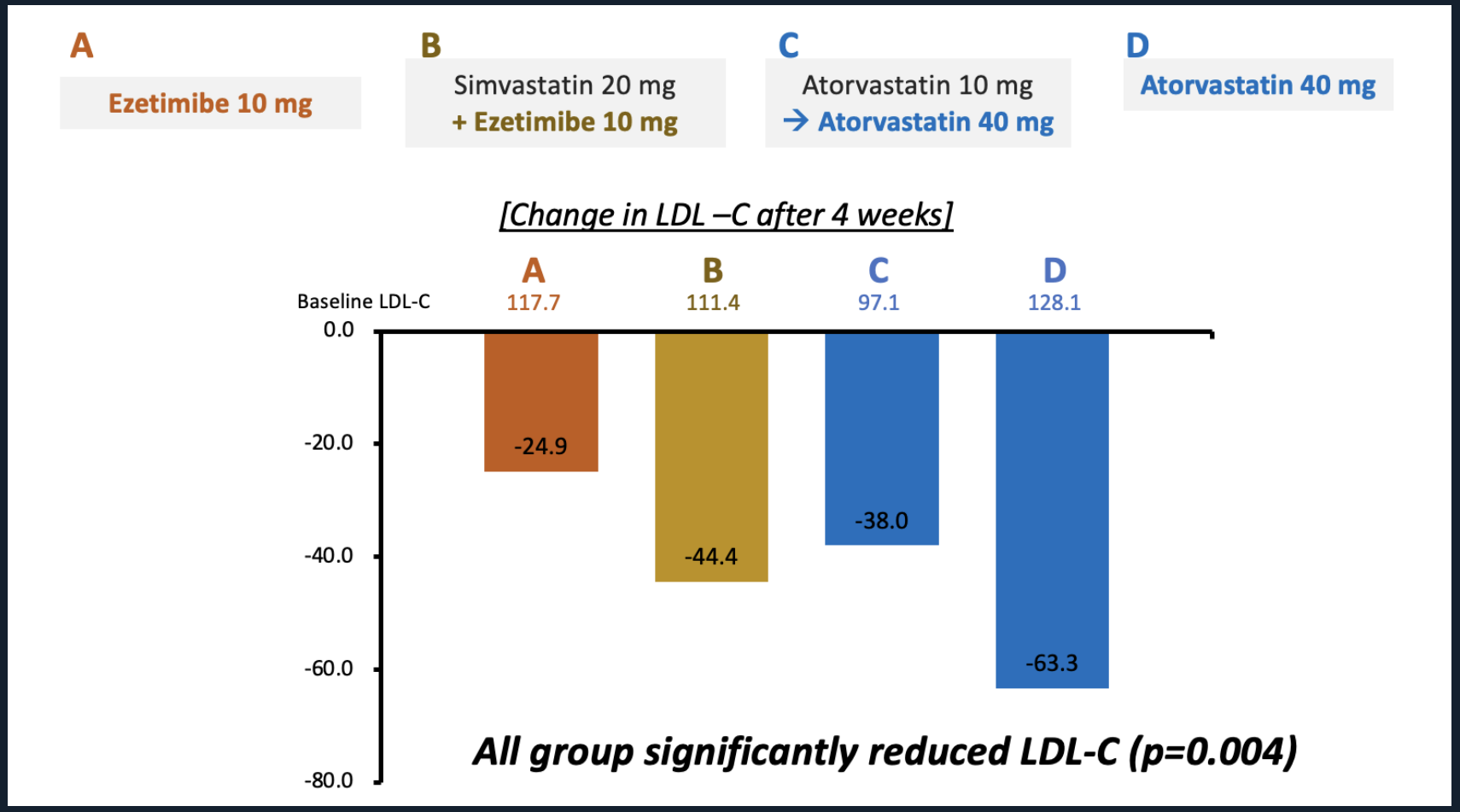
Statins but not Ezetimibe improved endothelial function and the effect was independent of LDL lowering

Landmesser U, et al. Circulation. 2005;111:2356–2363

Pleotropic Effect: High Intensity Statins vs. Statins + Ezetimibe

Endothelial function in CAD

A randomized controlled trial
60 patients with coronary artery disease
(30 statin naïve patients & 30 simvastatin 20 mg or atorvastatin 10 mg user)

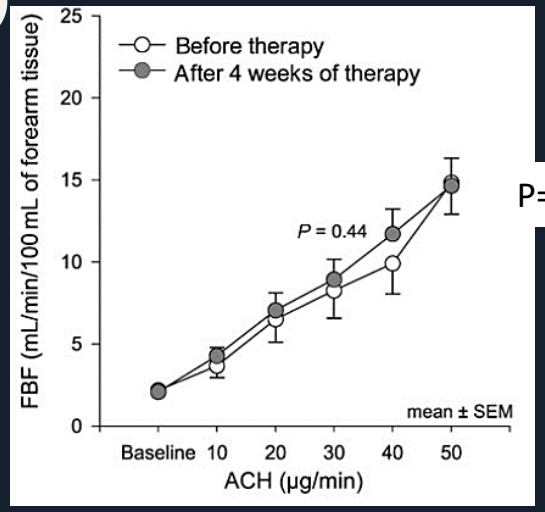


Fichtlscherer S, et al. Eur Heart J. 2006 May;27(10):1182-90

Pleotropic Effect: High Intensity Statins vs. Statins + Ezetimibe

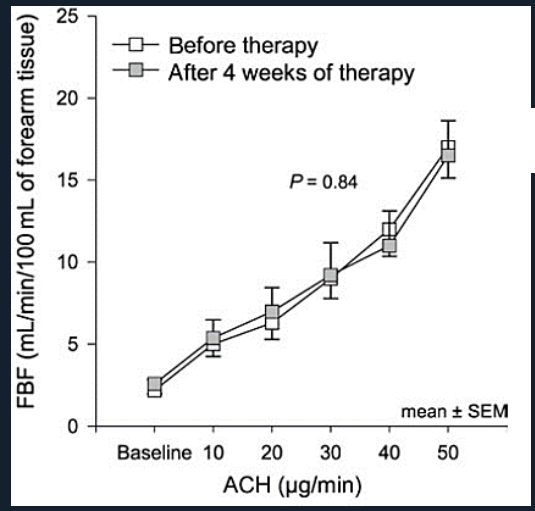
Endothelial function in CAD

A. EZE 10 mg



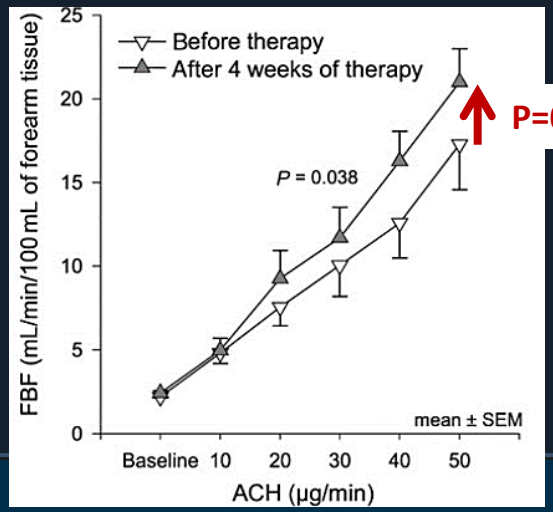
P=0.44

B. SMV/EZE 20/10 mg



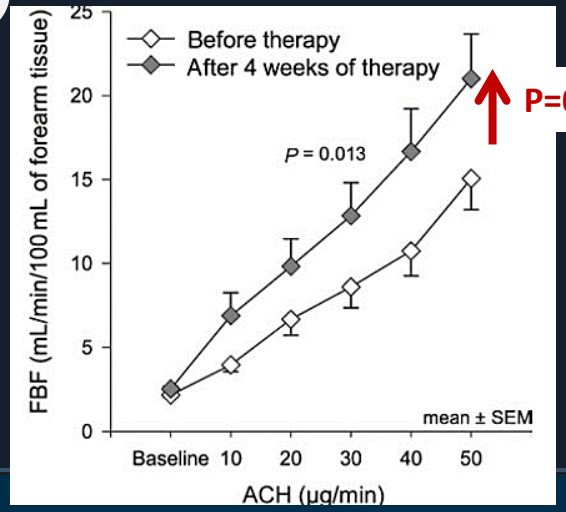
P=0.84

C. ATV 10 → 40 mg



P=0.038

D. ATV 40 mg



P=0.013

Fichtlscherer S, et al. Eur Heart J. 2006 May;27(10):1182-90

Pleotropic Effect: Statins vs. Ezetimibe

Endothelial function in CAD

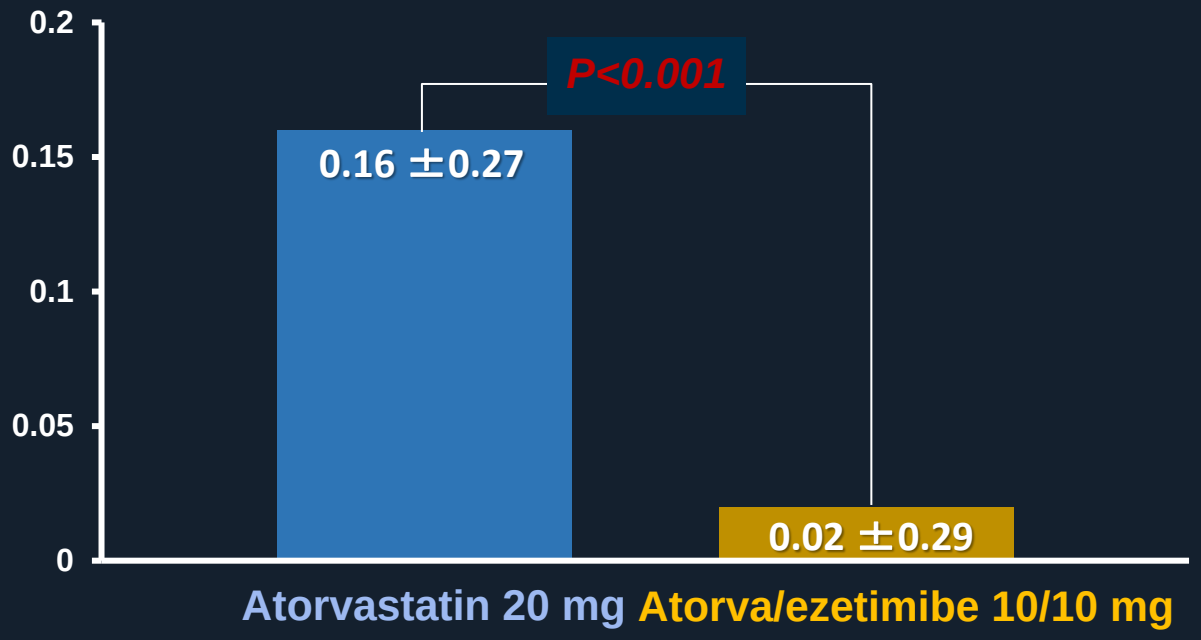
243 patients with coronary artery disease, LDL-C ≥ 70 mg/dL

Atorvastatin 10 mg → R

- **Atorvastatin 20 mg (n=133)**
- **Atorvastatin 10 mg + Ezetimibe 10 mg (n=117)**

12 weeks

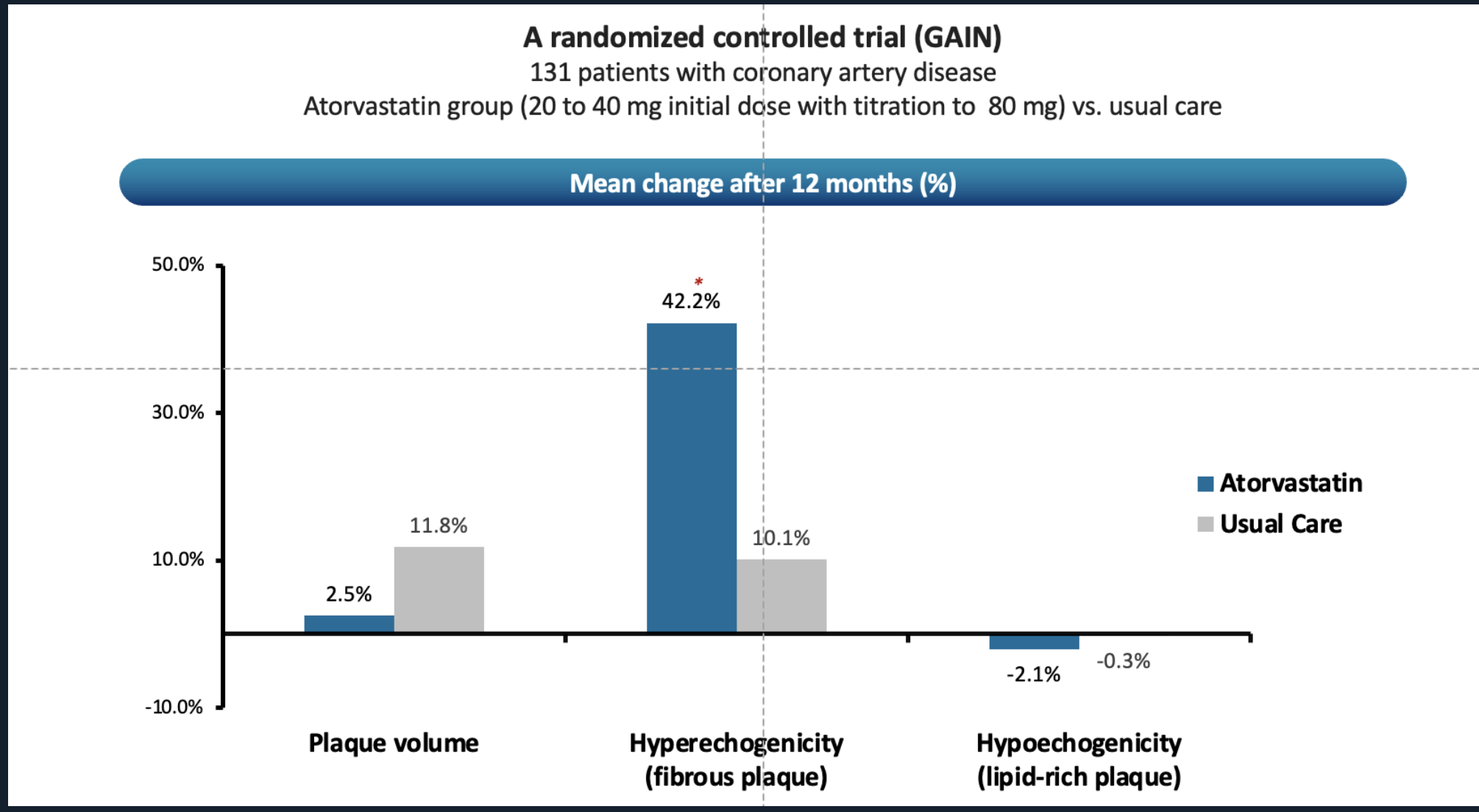
Change in reactive hyperemia index after 4 weeks



Matsue Y, et al. Circ J 2013; 77: 1791 – 1798.

Pleotropic Effects of Statins

Plaque Stabilization



Schartl M et al. Circulation. 2001;104:387-392.

74 y/o male with known CAD on AT 20 mg p/w NSTEMI s/p DES with an LDL of 64 mg/dl.

Lipid Management Questions

- Should he be on a high intensity statin given an LDL of 64 mg/dl?
- What should be his target LDL-C level?
- Is there a benefit of administering high intensity statin prior to PCI and during the acute phase of an MI? *Yes. Reduction in MACE (driven by lower MI), anti-inflammatory, antithrombotic, reduces no reflow, improves microvascular function and plaque stabilization.*
- Does visit-to-visit variability in LDL-C levels matter?

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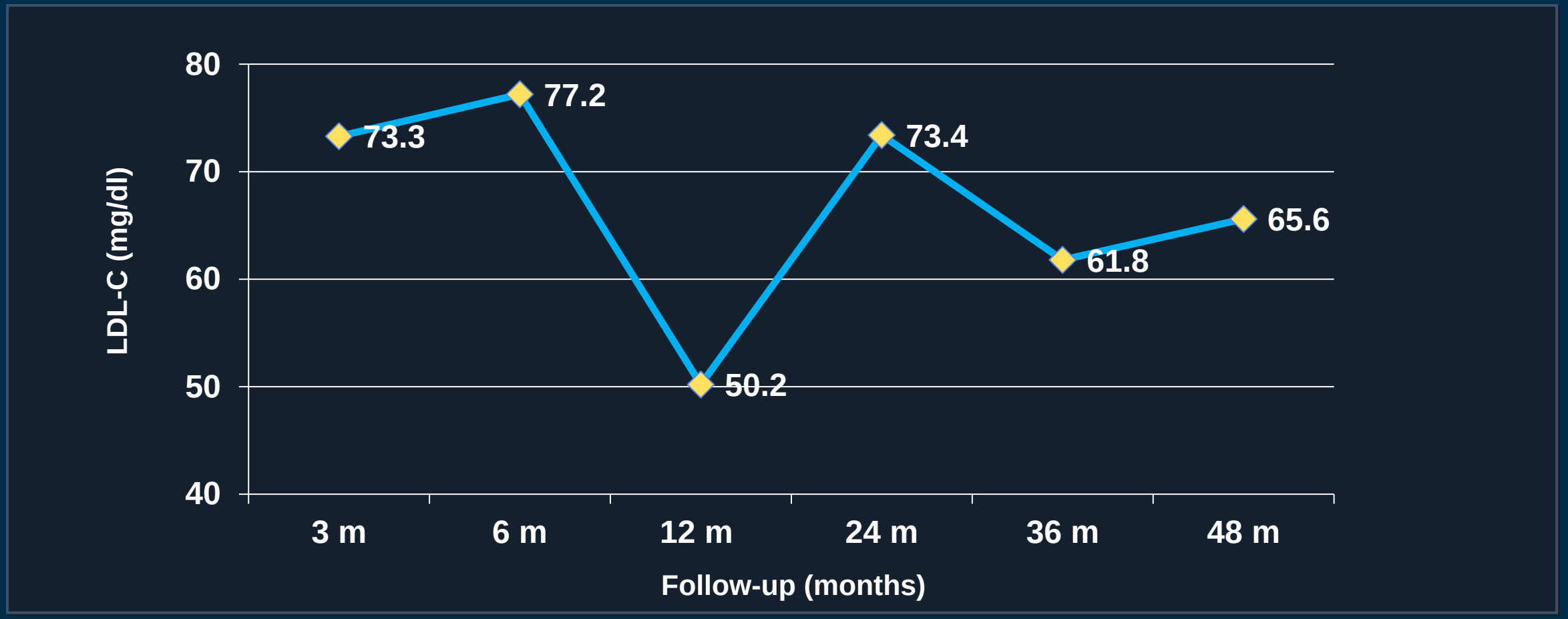
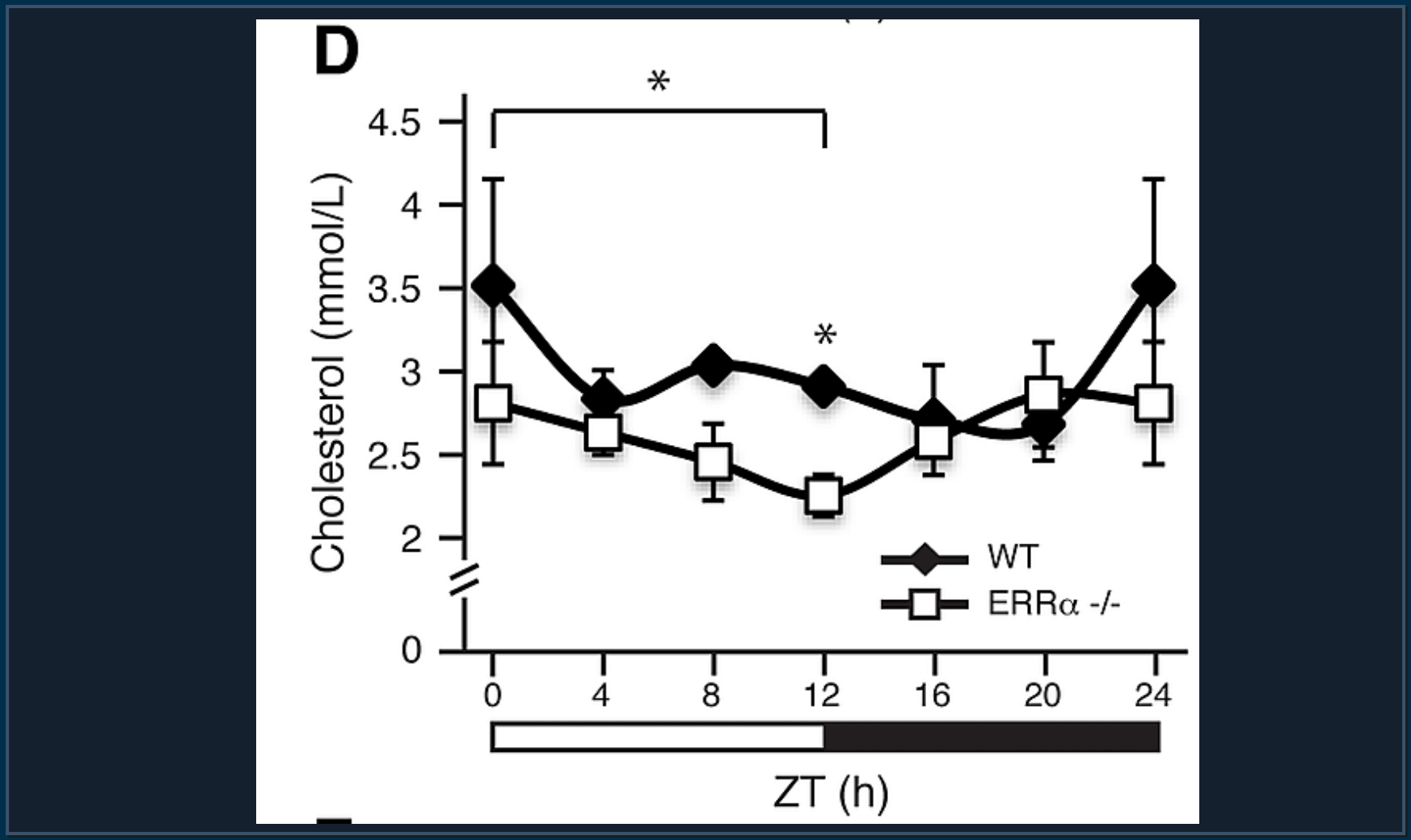


Does LDL-C variability matter?

Variability in LDL-C is everywhere!!!

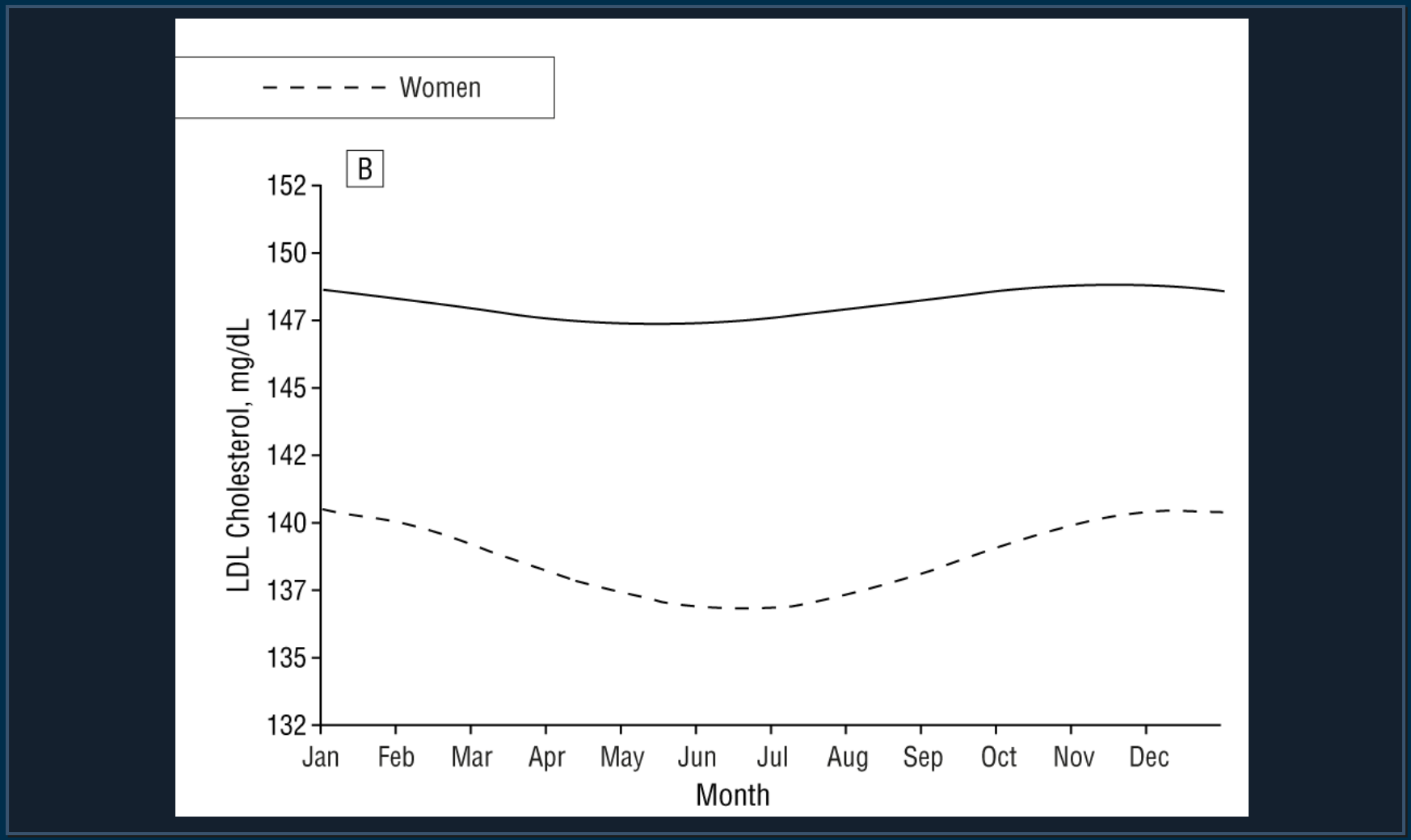
Diurnal



Dufour et al. PLOS Genetics. 10.1371/journal.pgen.1002143.g002

Variability in LDL-C is everywhere!!!

Seasonal

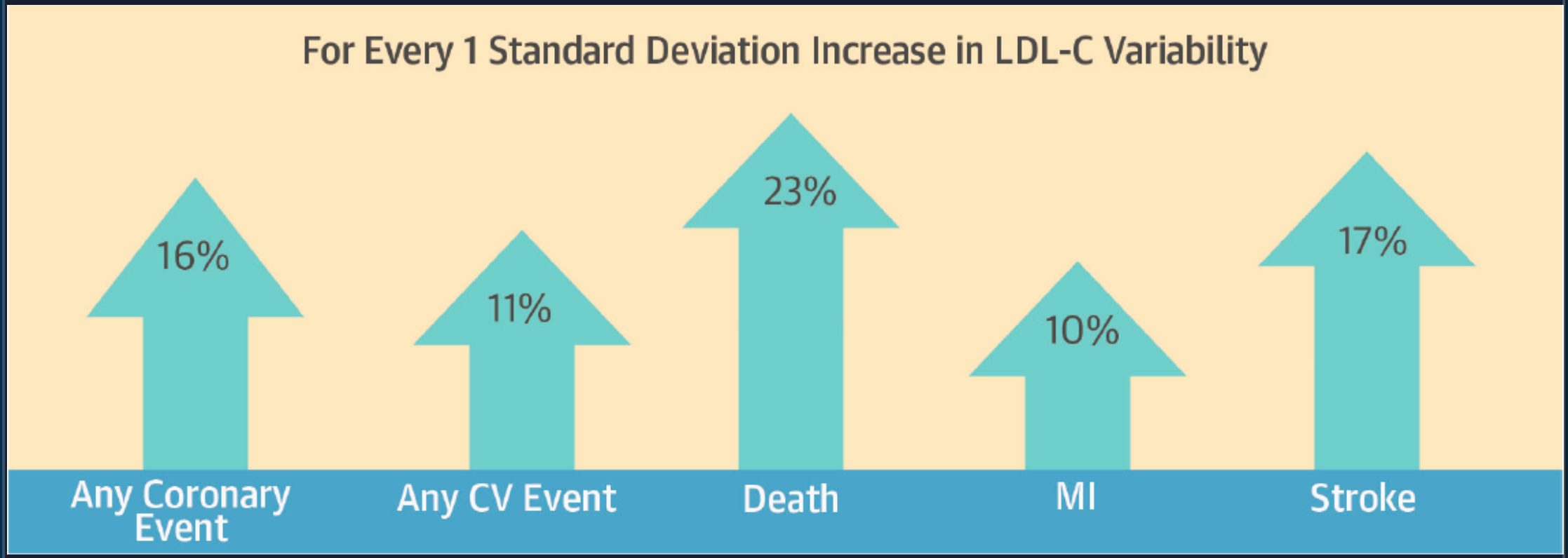


Ockene et al. Arch Intern Med. 2004;164(8):863-870

Does long-term variability in LDL-C matter?

TNT: VVV in LDL-C and Outcomes

9,572 patients with CAD



Bangalore et al. J Am Coll Cardiol. 2015 21;65(15):1539-48.

IDEAL: VVV in LDL-C and Outcomes

8658 patients with prior MI

Outcome	1 SD (10.8 mg/dl) increase in LDL-C VVV
Any coronary event	↑ 7%
Any CV event	↑ 8%
MI	↑ 11%
Stroke	NS
Death	↑ 20%

***Adjusted for treatment, mean LDL-C and baseline characteristics**

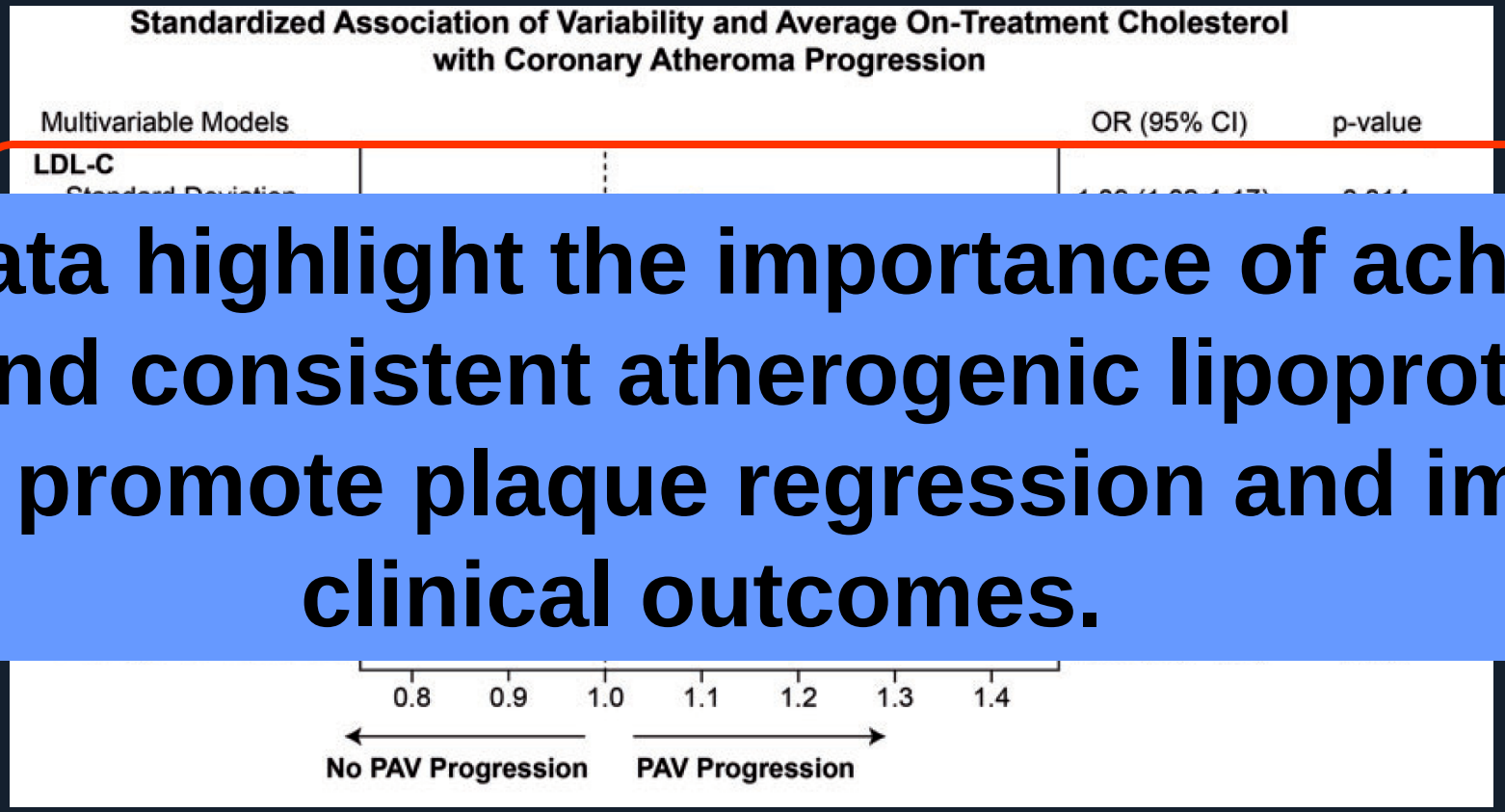
Bangalore et al. Am J Cardiol 2017;119:379e387

VVV in LDL-C: Mechanism of Adverse Effects

- Mechanism unknown. Few hypothesis
  - Endothelial dysfunction
  - Plaque instability
  - Marker for increased proportion of time where LDL-C is not at target
  - Marker for medication non-compliance

Visit-to-visit cholesterol variability correlates with coronary atheroma progression and clinical outcomes

4976 patients with CAD from 9 IVUS trials

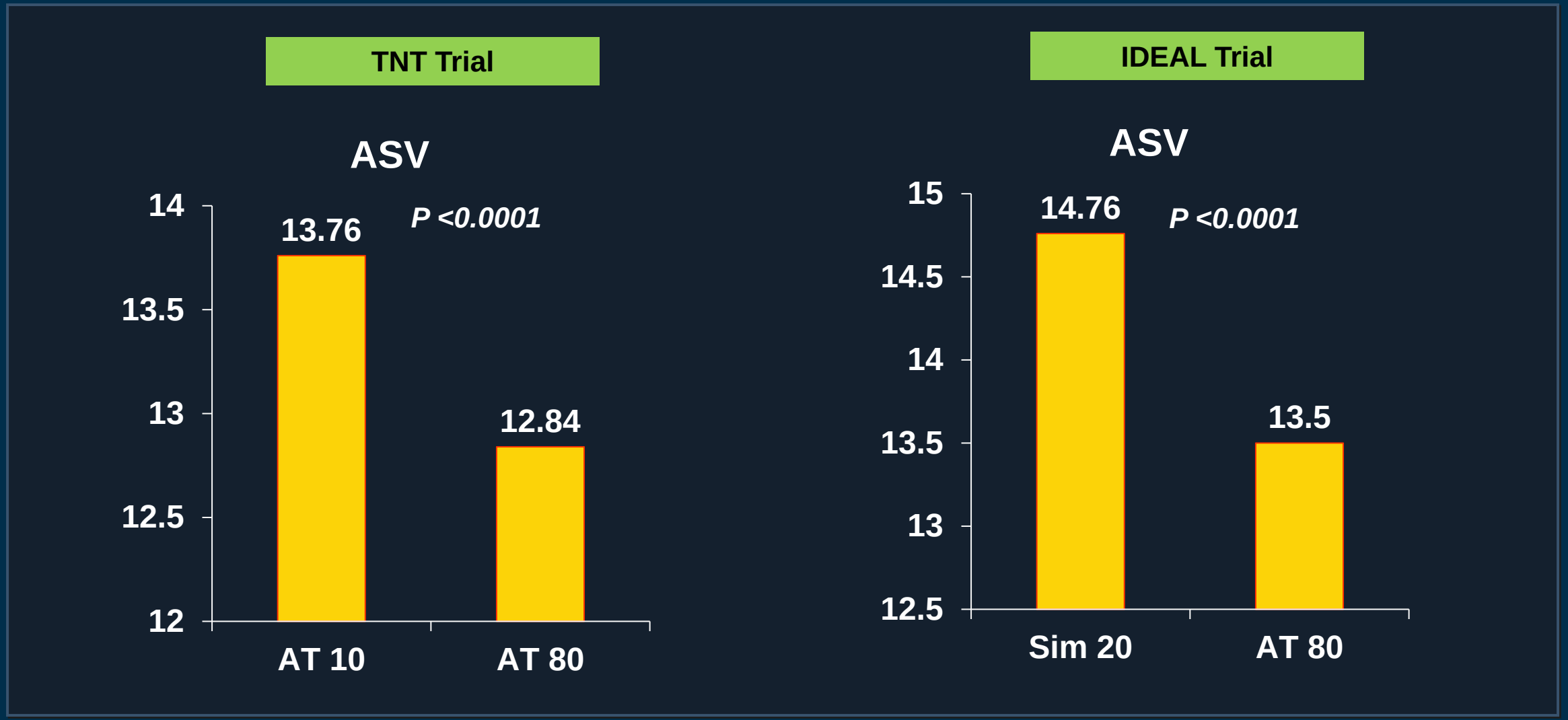


These data highlight the importance of achieving low and consistent atherogenic lipoprotein levels to promote plaque regression and improve clinical outcomes.

Clark D et al. European Heart Journal (2018) 39, 2551–2558

VVV in LDL-C: Therapeutic Implications

Lower LDL-C Variability with High Dose Atorvastatin



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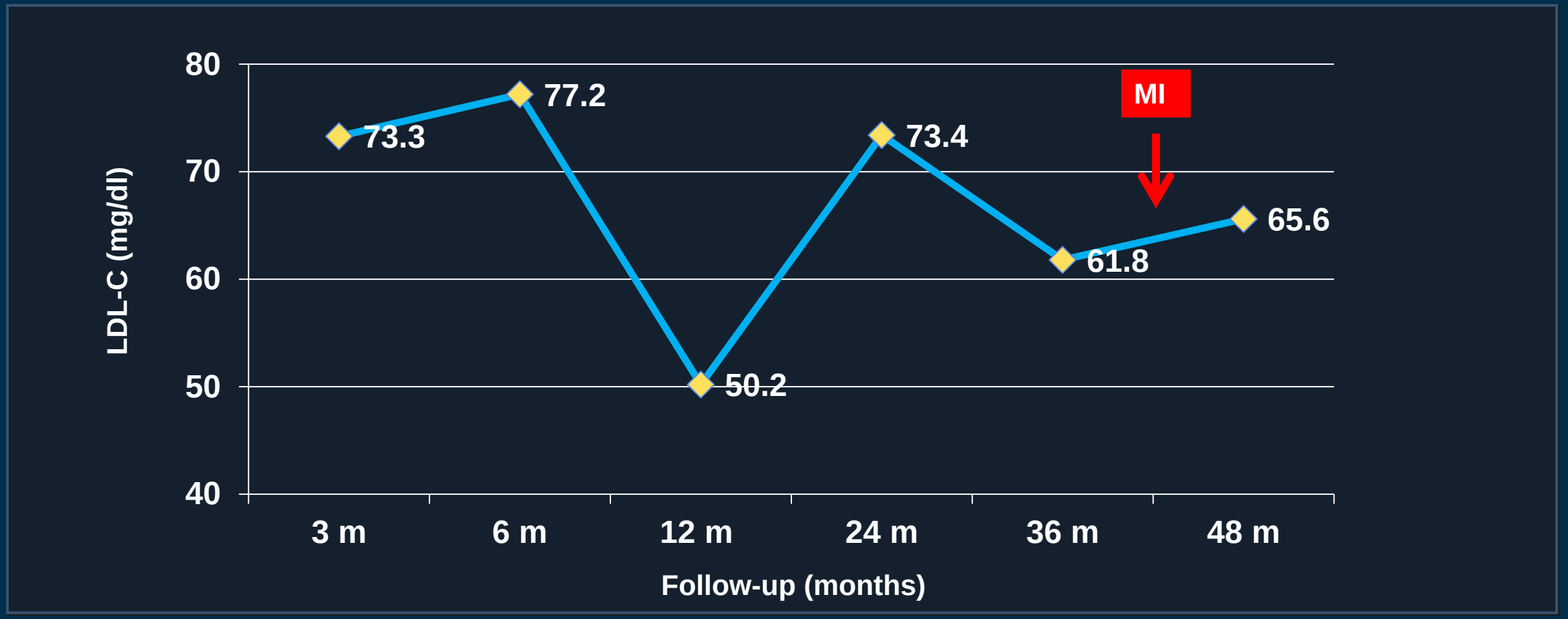

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Lipid Management Questions

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- Is there a benefit of administering high intensity statin prior to PCI and during the acute phase of an MI?
- Does visit-to-visit variability in LDL-C levels matter? ***Yes. Significant increase in CV events including death. Can be reduced with high intensity statins.***

74 y/o male with known CAD on AT 20 mg p/w NSTEMI s/p DES with an LDL of 64 mg/dl.

Lipid Management Questions

- Should he be on a high intensity statin given an LDL of 64 mg/dl? *Yes. Regardless of LDL-C levels*
- What should be his target LDL-C level? *<55 mg/dl (consider <40)*
- Is there a benefit of administering high intensity statin prior to PCI and during the acute phase of an MI? *Yes. Reduction in MACE (driven by lower MI), anti-inflammatory, antithrombotic, reduces no reflow, improves microvascular function and plaque stabilization.*
- Does visit-to-visit variability in LDL-C levels matter? *Yes. Significant increase in CV events including death. Can be reduced with high intensity statins.*