Eagle's Eye View:
How to Get Patients on a Statin Timely and Keep Them on It

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Disclosure

- Institutional grant/research funding to CardioVascular Research Foundation (CVRF, Korea) and/or Asan Medical Center from Abbott, Boston Scientific, Medtronics, Daiichi-Sankyo, Edwards Lifescience, HK InnoN, Daewoong Pharm, and ChongKunDang Pharm.

1. Lipid Lowering Guidelines for ACS Patients
2. Early Benefit of High-intensity Statin Therapy in ACS Patient
3. Effect of High-intensity Statin Pretreatment in ACS Patient Undergoing PCI
4. Plaque Regression in Stable ACS Patients
5. Inflammatory Risk and Statin Therapy in ACS Patient Undergoing PCI

Lipid Lowering Guidelines for ACS Patients

AHA/ACC Guideline
for the Management of Patients With NSTE ACS

Early Hospital Care

Recommendations	COR	LOE
Cholesterol management		
Initiate or continue high-intensity statin therapy in patients with no contraindications	*I*	*A*
Obtain a fasting lipid profile, preferably within 24 h	*IIa*	*C*

Key Evidence

PROVE IT-TIMI 22, MIRACL

Therapy with statins in patients with NSTE-ACS reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. High-risk patients, such as those with NSTE-ACS, derive more benefit in reducing these events from high-intensity statins, such as atorvastatin which lower low-density lipoprotein cholesterol levels by ≥50% as in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) and MIRACL (Myocardial Ischemia Reduction With Acute Cholesterol Lowering) trials,[273,274] than from moderate- or low-intensity statins.[18,272] These findings provide the basis for high-intensity statin therapy after stabilization of patients with NSTE-ACS. In addition, early introduction of this approach can promote improved compliance with this regimen.

Reference. Amsterdam EA, et al. Circulation. 2014;130:e344-e426.

ESC/EAS Guidelines
for the Management of Dyslipidemias

Recommendations in very high-risk patients with ACS patients

Recommendations	COR	LOE
In all ACS patients without any contraindication or definite history of intolerance, it is recommended high-dose statin is initiated or continued as early as possible, regardless of initial LDL-C values	*I*	*A*

Recommendations in very high-risk patients undergoing PCI

Recommendations	COR	LOE
Routine pre-treatment or loading (on a background of chronic therapy) with a high-dose statin should be considered in patients undergoing PCI for an ACS or elective PCI.	*IIa*	*B*

Reference. Mach F, et al. European Heart Journal, 2019,00, 1-78

Korean Society of Myocardial Infarction

2020 Expert Consensus Document on Pharmacotherapy for Acute MI

Recommendations for lipid-lowering therapy in acute MI

- It is recommended to obtain a lipid profile in all patients with AMI as soon as possible after presentation.
- It is recommended to start high-intensity statin therapy as early as possible after AMI, unless contraindicated, and maintain it during the long term.
- Treatment goals are recommended as an LDL-C reduction of ≥50% from baseline or an LDL-C level of <70 mg/dL in patients with AMI.
- In patients with AMI with LDL-C ≥70 mg/dL despite a maximally tolerated statin dose, combination with ezetimibe is recommended.
- In patients with AMI with LDL-C ≥70 mg/dL despite a maximally tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

Reference. Korean Society of Myocardial Infarction. Expert Consensus Document on Pharmacotherapy for Acute Myocardial Infarction

2022 Updated Korean Cholesterol management guideline

Recommendations for ASCVD Patients

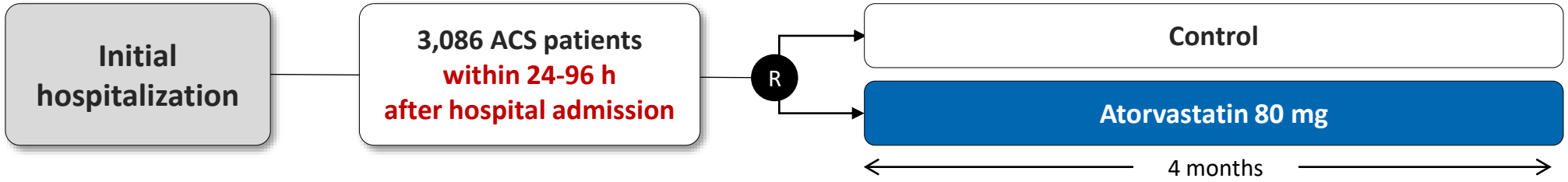
Recommendation	Class	LOE
For ASCVD patients, Target LDL cholesterol < 55 mg/dL or more than 50% reduction of baseline value	I	A
For AMI patients, use of high-dose statin regardless of baseline LDL cholesterol value	I	A

Reference. 한국지질동맥경화학회, 이상지질혈증 치료지침, 2018 & 2022

Early Benefit of High-intensity Statin Therapy in ACS Patient

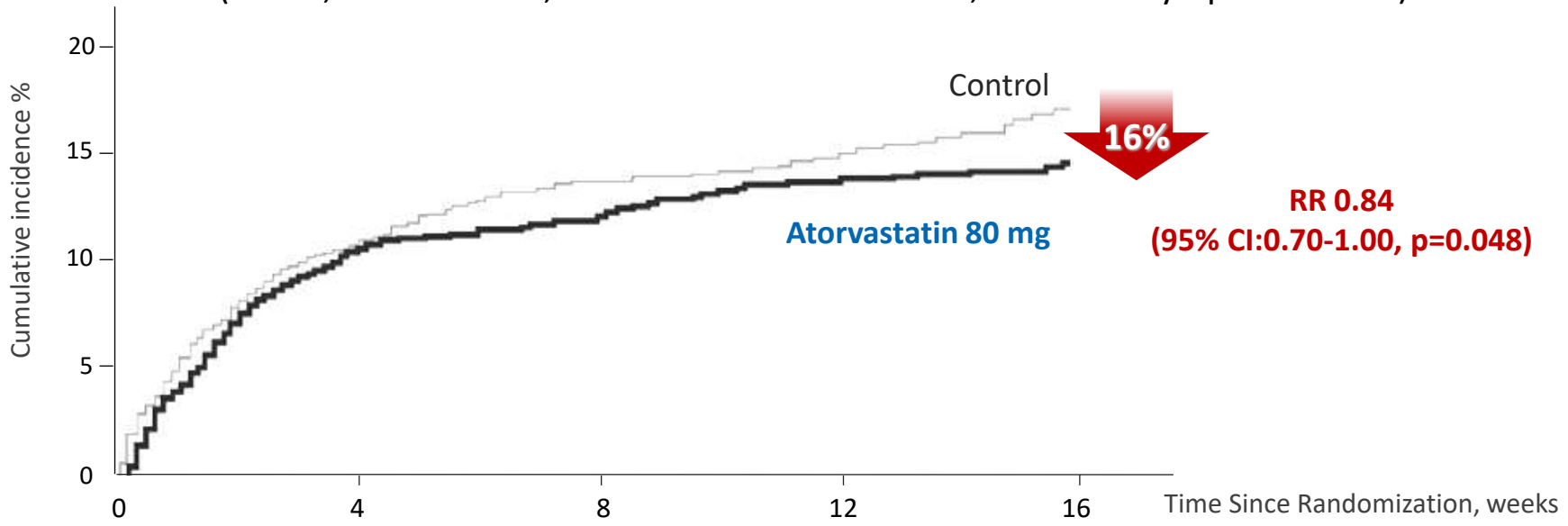
Early Atorvastatin 80 mg therapy after ACS: MIRACL Trial

Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial



Kaplan-Meier Estimates of Primary Outcome

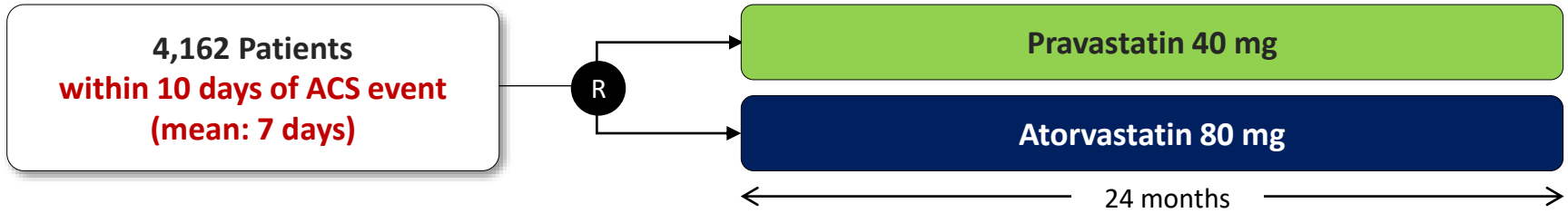
(Death, nonfatal AMI, resuscitated cardiac arrest, recurrent symptomatic MI)



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

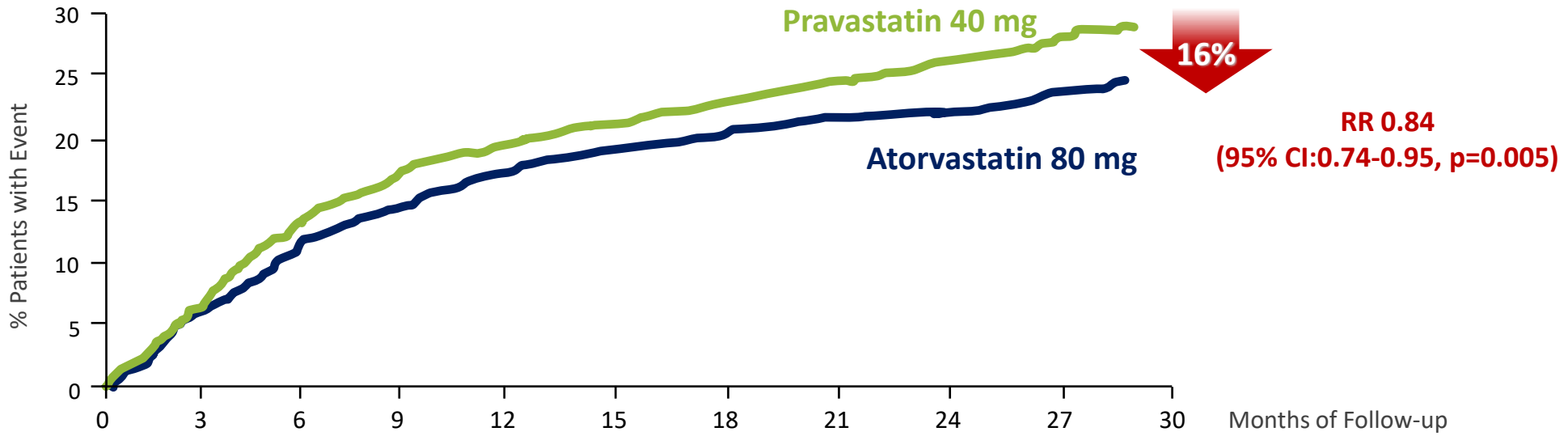
Atorvastatin 80 mg therapy after ACS: PROVE-IT 22

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)

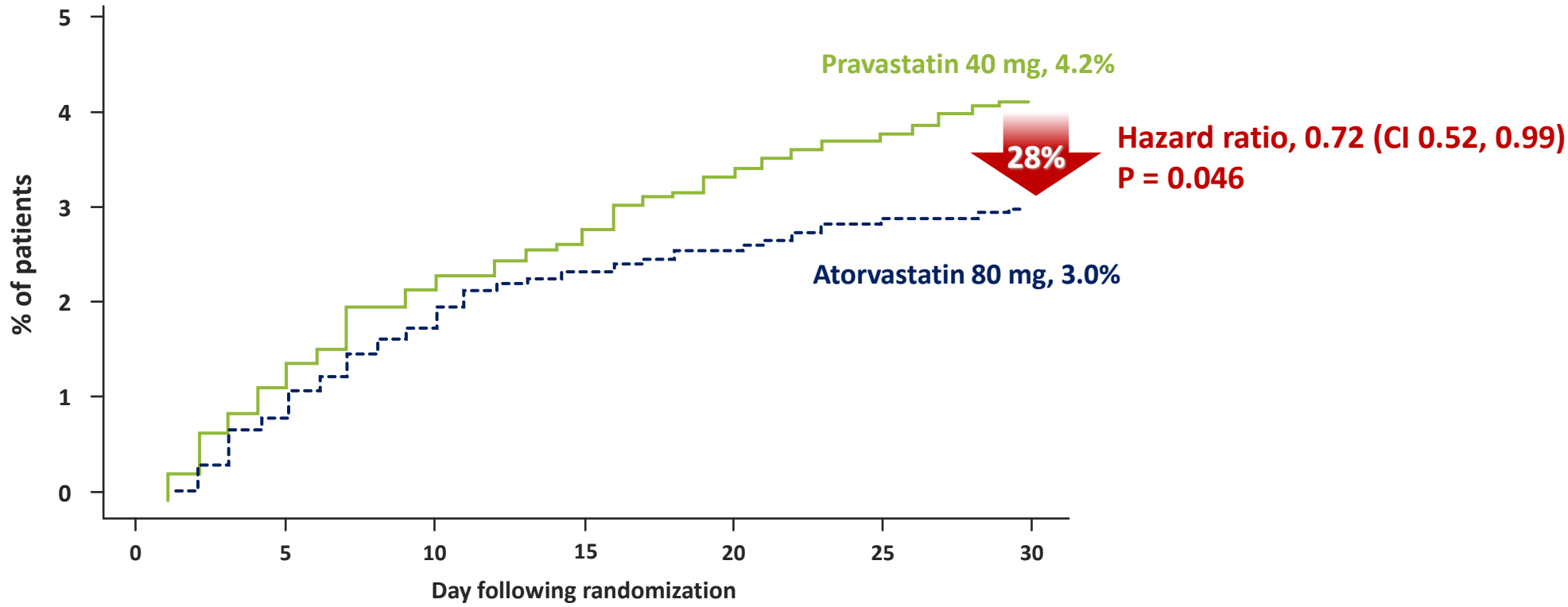


Reference. Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

Early benefit at 30 days of Atorvastatin 80 mg therapy after ACS: PROVE-IT 22

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

Death, MI, or rehospitalization for ACS until 30 days



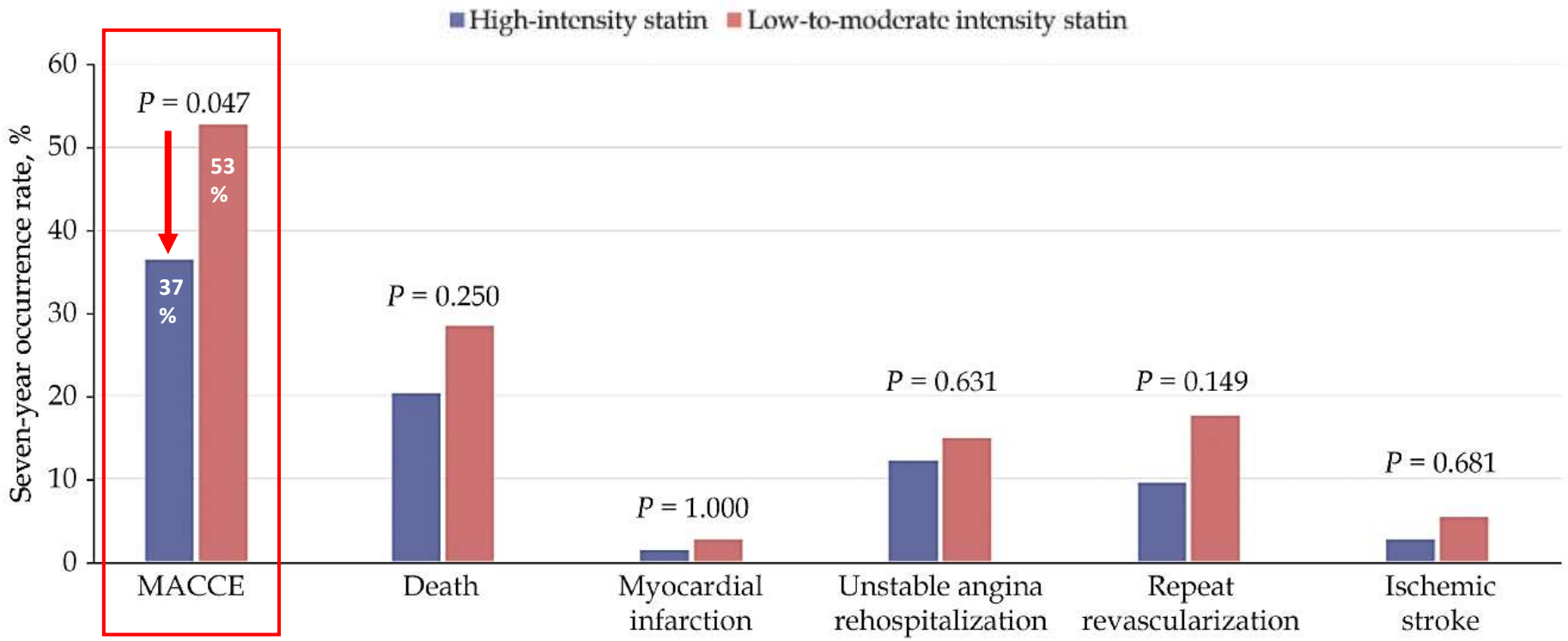
Reference. Ray KK, et al. J Am Coll Cardiol 2005;46:1405–10.

In Korean older patients with MI, High-intensity statin showed significantly lowered MACCE than low-to-moderate intensity statin

A retrospective cohort study in KOREA

546 elderly (>75 years) patients with MI, Follow-up: ~ 7 years

Incidence curve of MACCE for up to seven years in propensity score-matched† cohort



†The matching variables comprised mostly of the baseline characteristics, including age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking history, prior MI, prior PCI, prior CABG, prior stroke, prior congestive HF, prior CKD, height, body weight, BMI, admission SBP, DBP, heart rate, Killip class, clinical diagnosis, troponin I, creatine kinase-MB isoform, serum creatinine, eGFR, total cholesterol, TG, HDL-C, LDL-C, plasma glucose, echocardiographic left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and left ventricular ejection fraction. *MACCE, major adverse cardiac and cerebrovascular events, defined as all-cause death, MI, rehospitalization due to unstable angina, repeat revascularization, and ischemic stroke

Reference. Moon IT, et al. J Geriatr Cardiol. 2021 Aug 28;18(8):609-622.

High-intensity statin therapy in patients achieving treatment target for LDL-C after PCI

A retrospective cohort study in KOREA

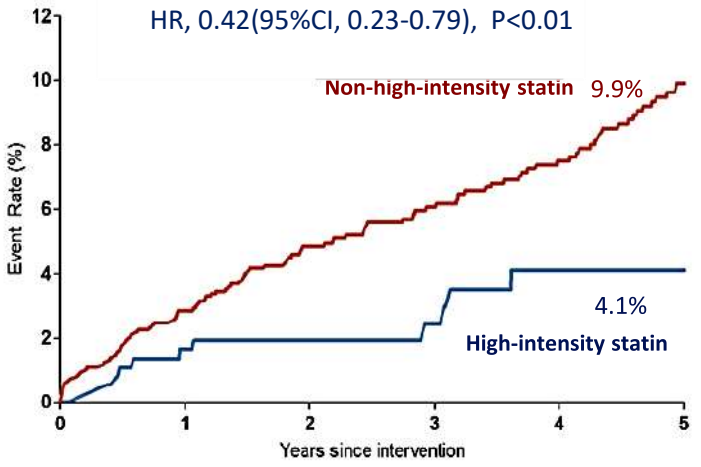
1,746 patients who achieved LDL-C target* after PCI

High-intensity statin (n=372)	Non high-intensity statin (n=1,374)
atorvastatin 40, 80 mg, rosuvastatin 20 mg	the other statin

Kaplan–Meier estimates of the incidence of the primary end point (cardiac death, MI, or stroke)

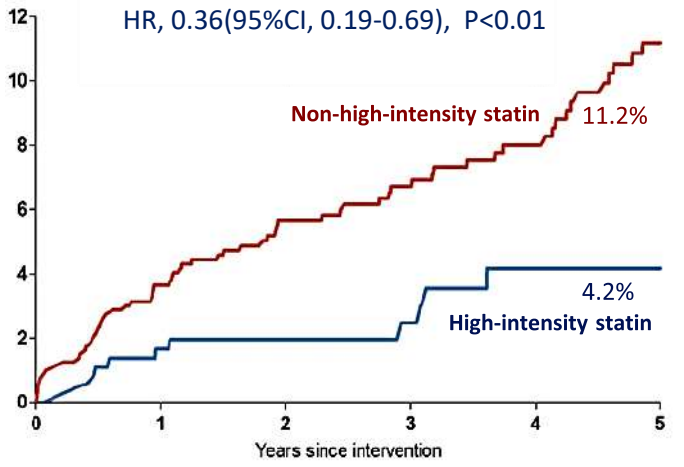
Overall population

HR, 0.42(95%CI, 0.23-0.79), P<0.01



Propensity-matched population

HR, 0.36(95%CI, 0.19-0.69), P<0.01



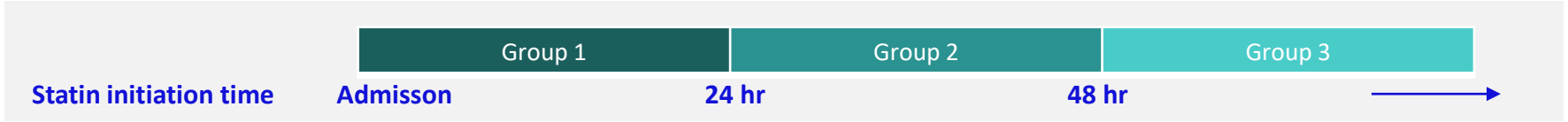
*LDL-C <70 mg/dL or >50% reduction from baseline level

Reference. Kim J, et al. J Am Heart Assoc. 2018;7:e009517.

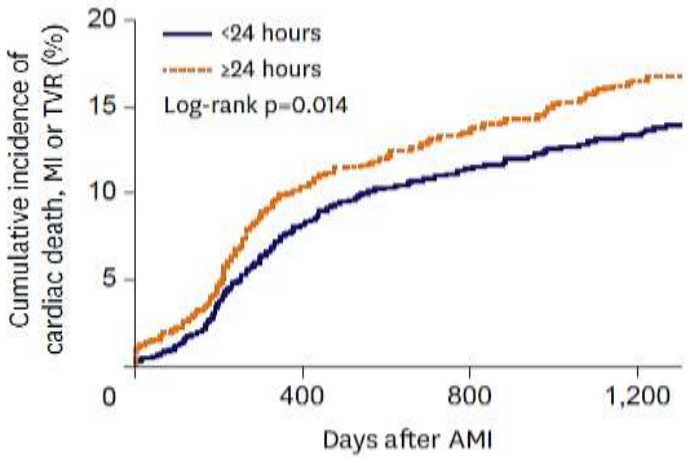
COREA-AMI: Early statin initiation in statin-naïve AMI patients undergoing PCI

The Convergent Registry of Catholic and Chonnam University for AMI (COREA-AMI)

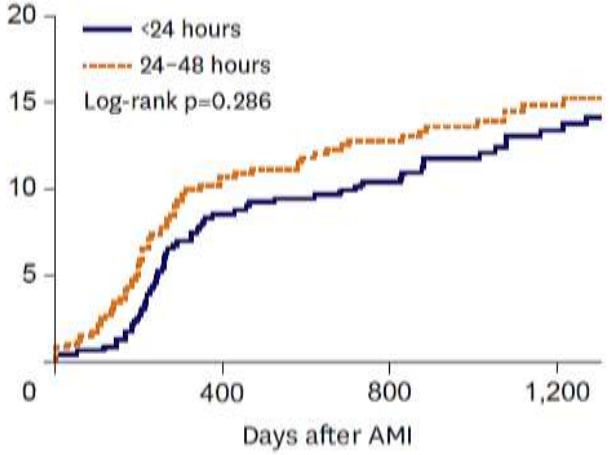
3,921 statin-naïve patients undergoing PCI



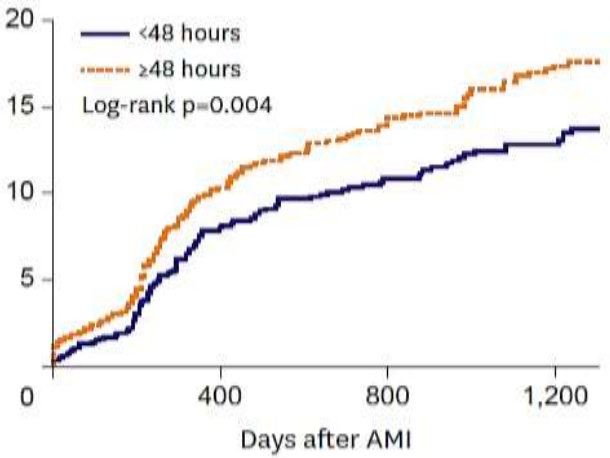
Kaplan-Meier curves for cumulative incidence of cardiac death, myocardial infarction or TVR



HR 0.78, 95% CI 0.64-0.95; p=0.011



HR 0.84, 95% CI 0.61-1.16; p=0.290



HR 0.69, 95% CI 0.54-0.89; p=0.005

TVR, target-vessel revascularization

Reference. Kim MC, et al. Korean Circ J. 2019 May;49(5):419-433.

Effect of High-intensity Statin Pretreatment in ACS Patient Undergoing PCI

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

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

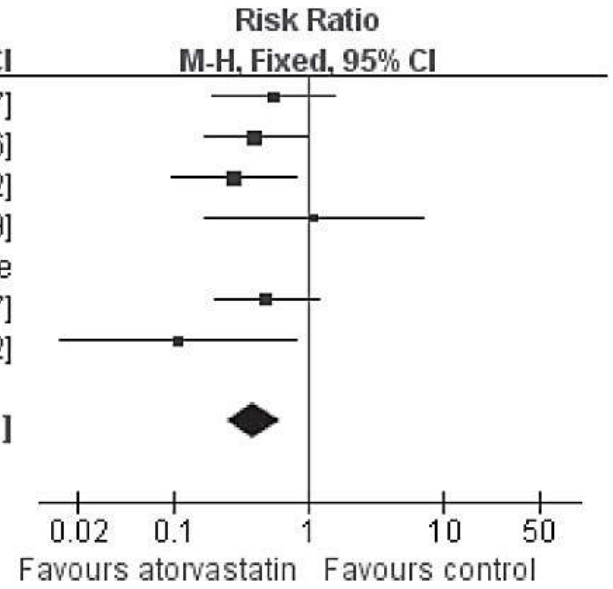
Atorvastatin 80 mg immediate or 12 hours before PCI (n=476) vs. placebo/10 mg(n=476)

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: Chi² = 3.74, df = 5 (P = 0.59); I² = 0%

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

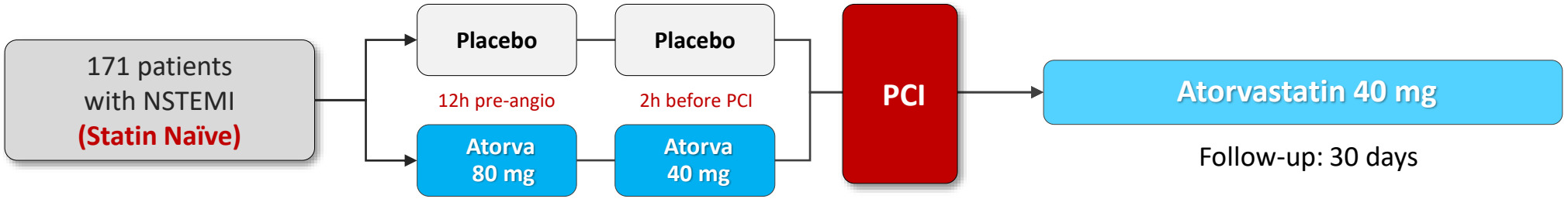


RR, 0.39 (0.25-0.61) **61% ↓**

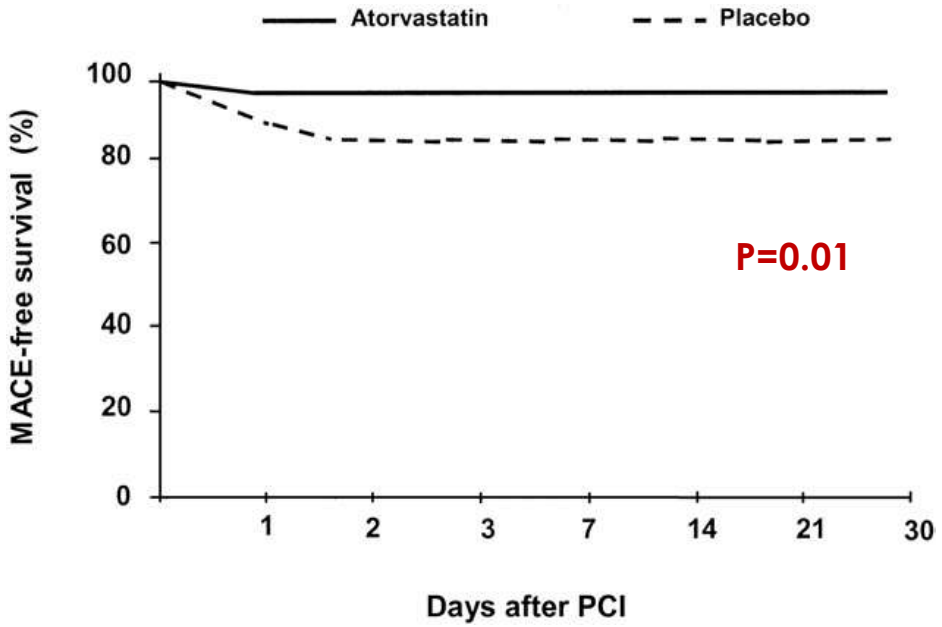
* MACE was defined as the composite of death, MI and target-vessel revascularization

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

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

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

ARMYDA-RECAPTURE

Effect of atorvastatin reloading in patients on chronic statin undergoing PCI

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

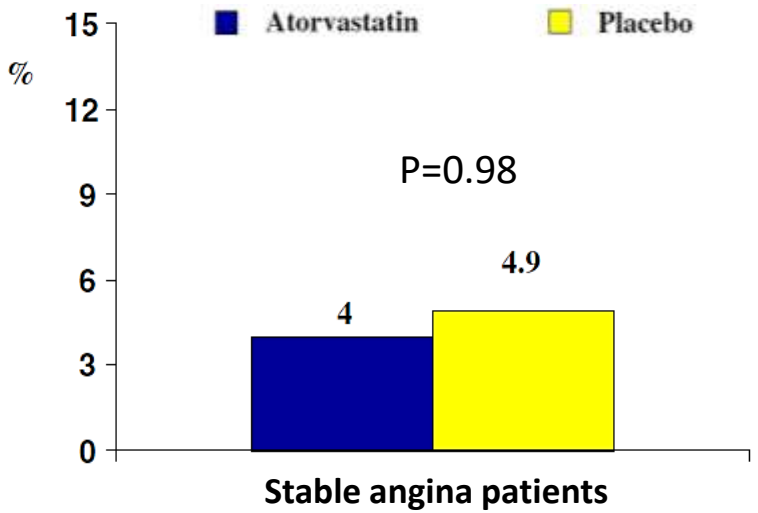
- **Placebo** (12h pre-angio) → **Placebo** (2h before PCI)
- **Atorva 80 mg** → **Atorva 40 mg**

→ **PCI** → **Atorvastatin 40 mg**

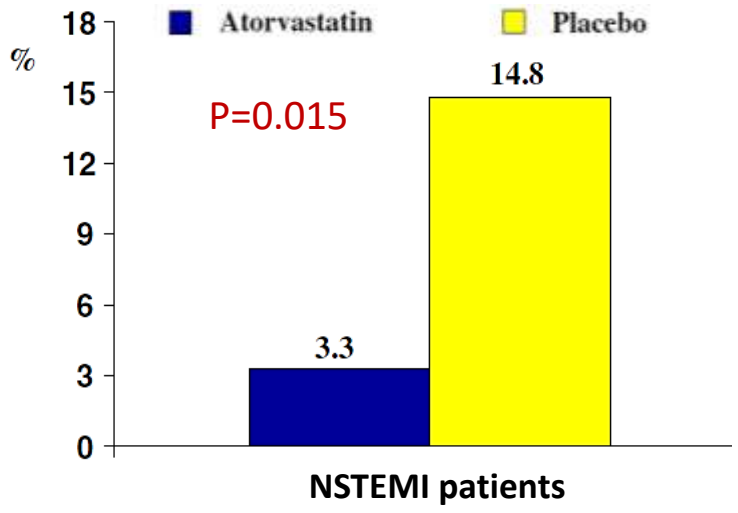
Follow-up: 30 days

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

Secondary endpoint (MACE according to clinical presentation)



Stable angina patients



NSTEMI patients

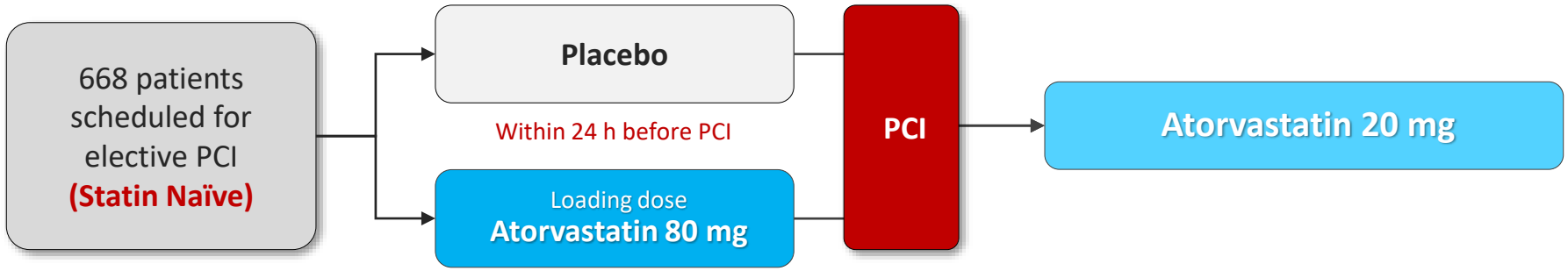
ARMYDA, Atorvastatin for Reduction of MYocardial Damage During Angioplasty; MACE, major adverse cardiac event; TVR, target vessel revascularization.

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

* MACE, death, MI, target-vessel revascularization

NAPLES trial

Effect on periprocedural MI of single, atorvastatin 80 mg before PCI



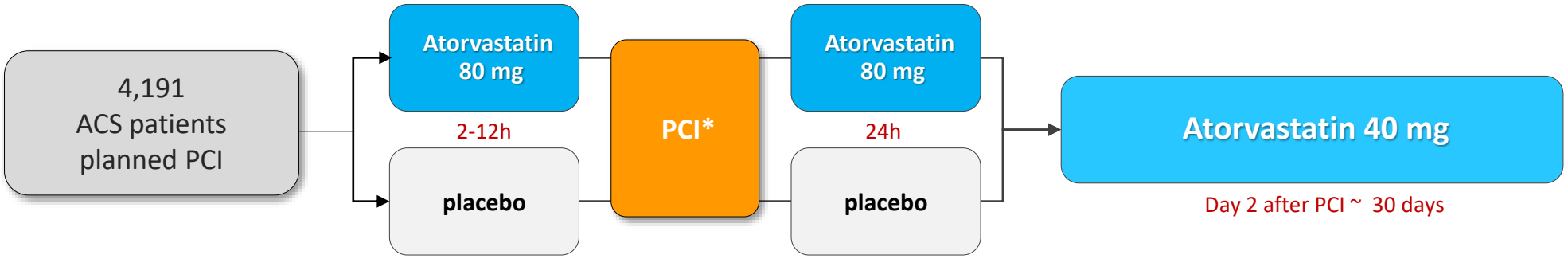
Creatine kinase myocardial isoenzyme(CK-MB) & Troponin I(TnI) increase at 6 and 12 h after PCI

	Atorvastatin (n=338)	Placebo (n=330)	P-value
Incidence of CK-MB increase >3x ULN	9.5%	15.8%	0.014
Incidence of TnI increase >3x ULN	26.6%	39.1%	<0.001

ULN, upper limit of normal

Reference. Briguori C, et al. J Am Coll Cardiol 2009;54(23):2157-2163.

SECURE-PCI
Statins Evaluation in Coronary Procedures and Revascularization



Patient Population

- Mean 61.8 years
- UA(14.5%), NSTEMI(60.7%), STEMI(24.8%)
- Planned invasive management within the next 7 days
- PCI(64.7%), CABG(8%), others(27.3%)

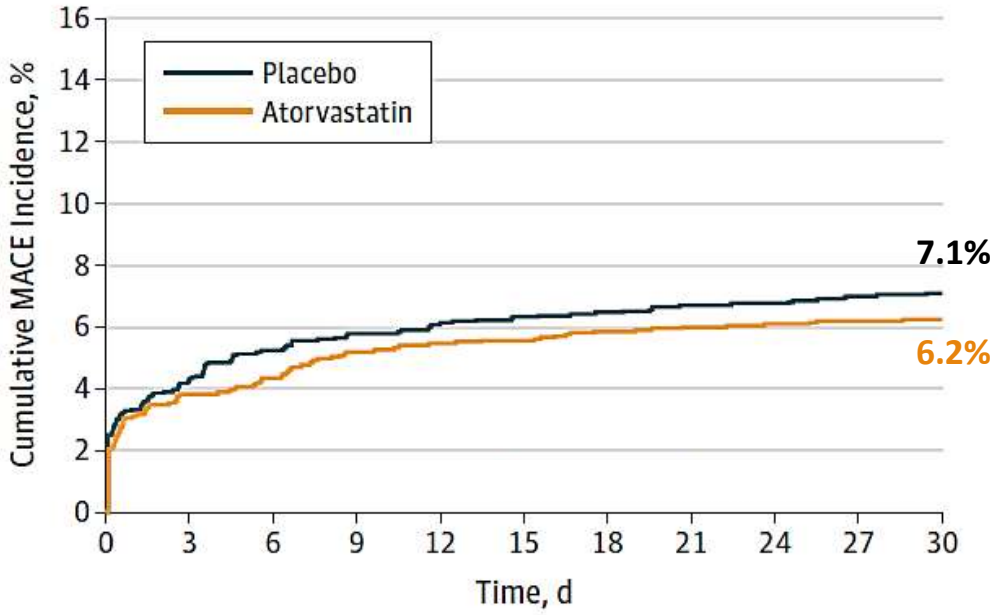
Primary End Point

- Major adverse cardiovascular events
  - All-cause mortality
  - MI
  - stroke
  - unplanned coronary revascularization

Reference. Berwanger O, et al. JAMA 2018;319:1331-40.

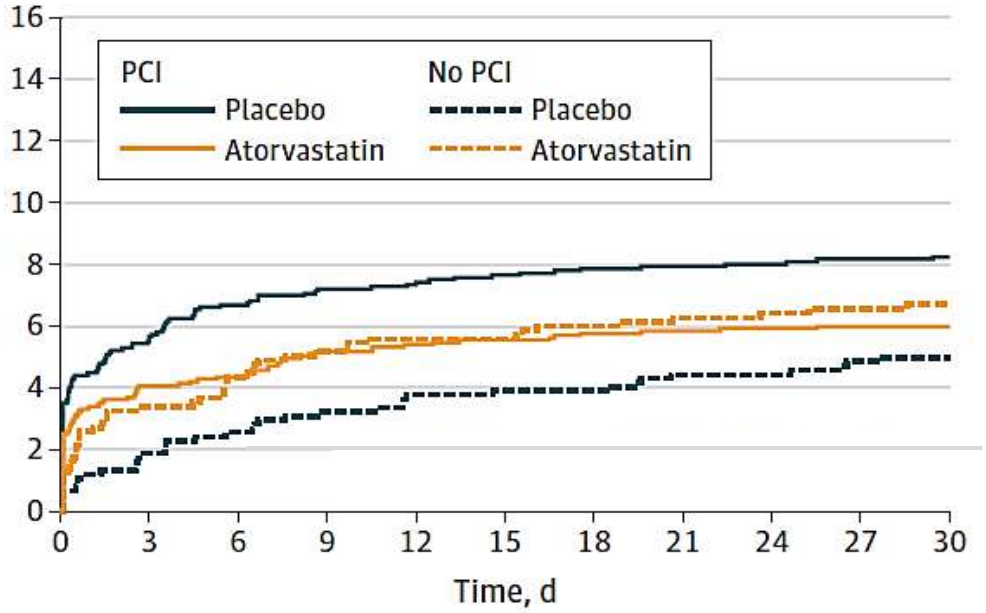
SECURE-PCI: Primary outcome

All patients (primary analysis)



HR, 0.88; 95% CI, 0.69-1.11; P = 0.27

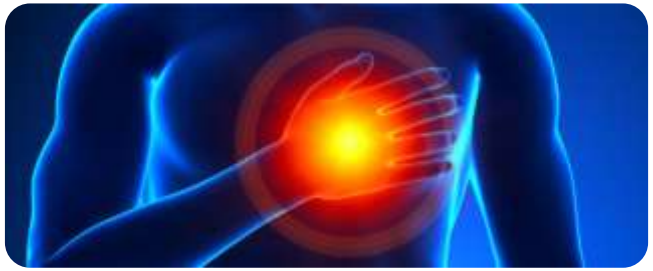
All patients by PCI (secondary analysis)

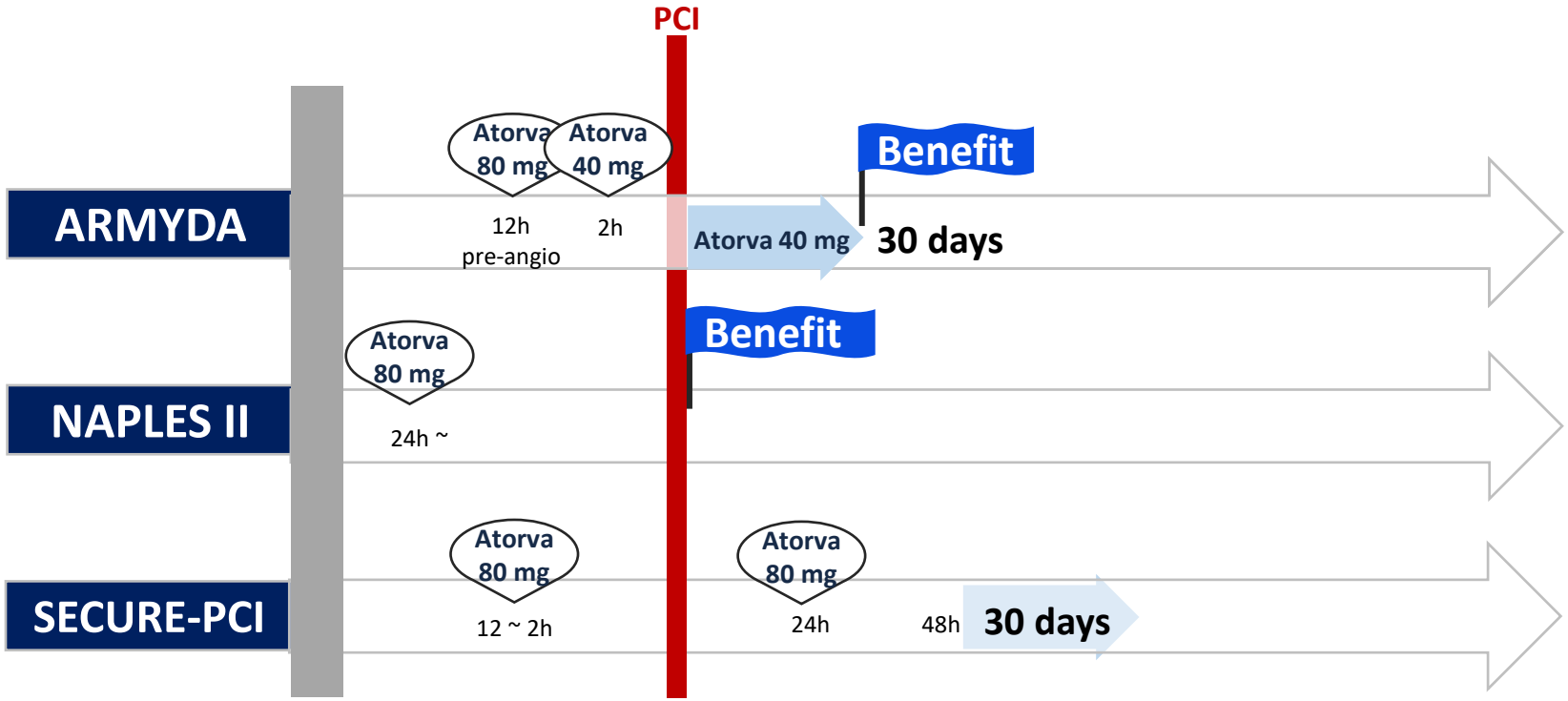


- **PCI**: HR, 0.72; 95% CI, 0.54-0.96; **P = 0.02**
- **No PCI**: HR, 1.36; 95% CI, 0.89-2.09; P = 0.15

Reference. Berwanger O, et al. JAMA 2018;319:1331-40.

Pretreatment in ACS Patients Undergoing PCI



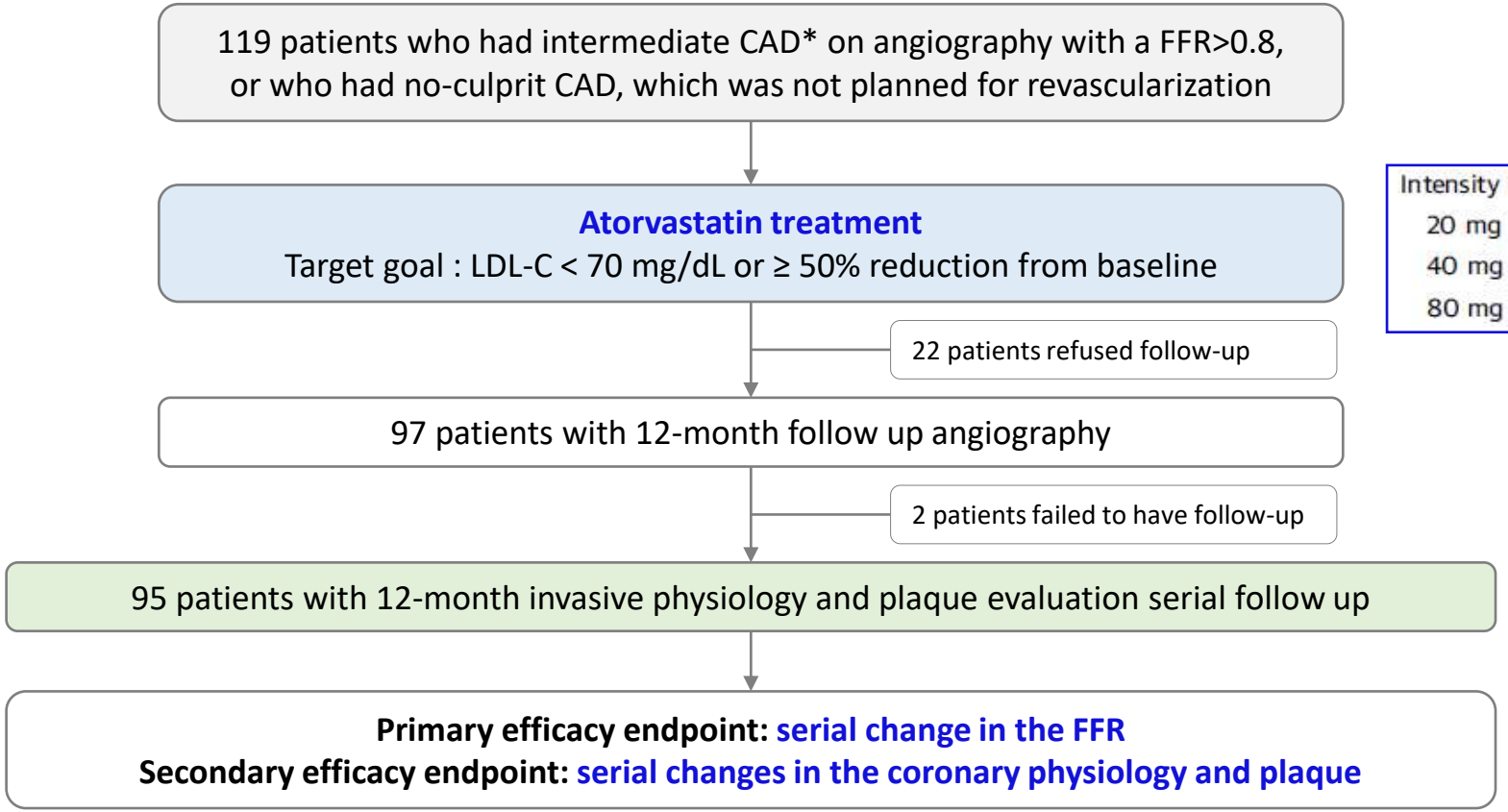


Reference. Berwanger O, et al. JAMA 2018;319:1331-40.

Plaque Regression
in Stable ACS Patients

Effect of Atorvastatin on coronary flow index and plaque parameters in patients with CAD

A prospective multicenter observational study(FORTE)

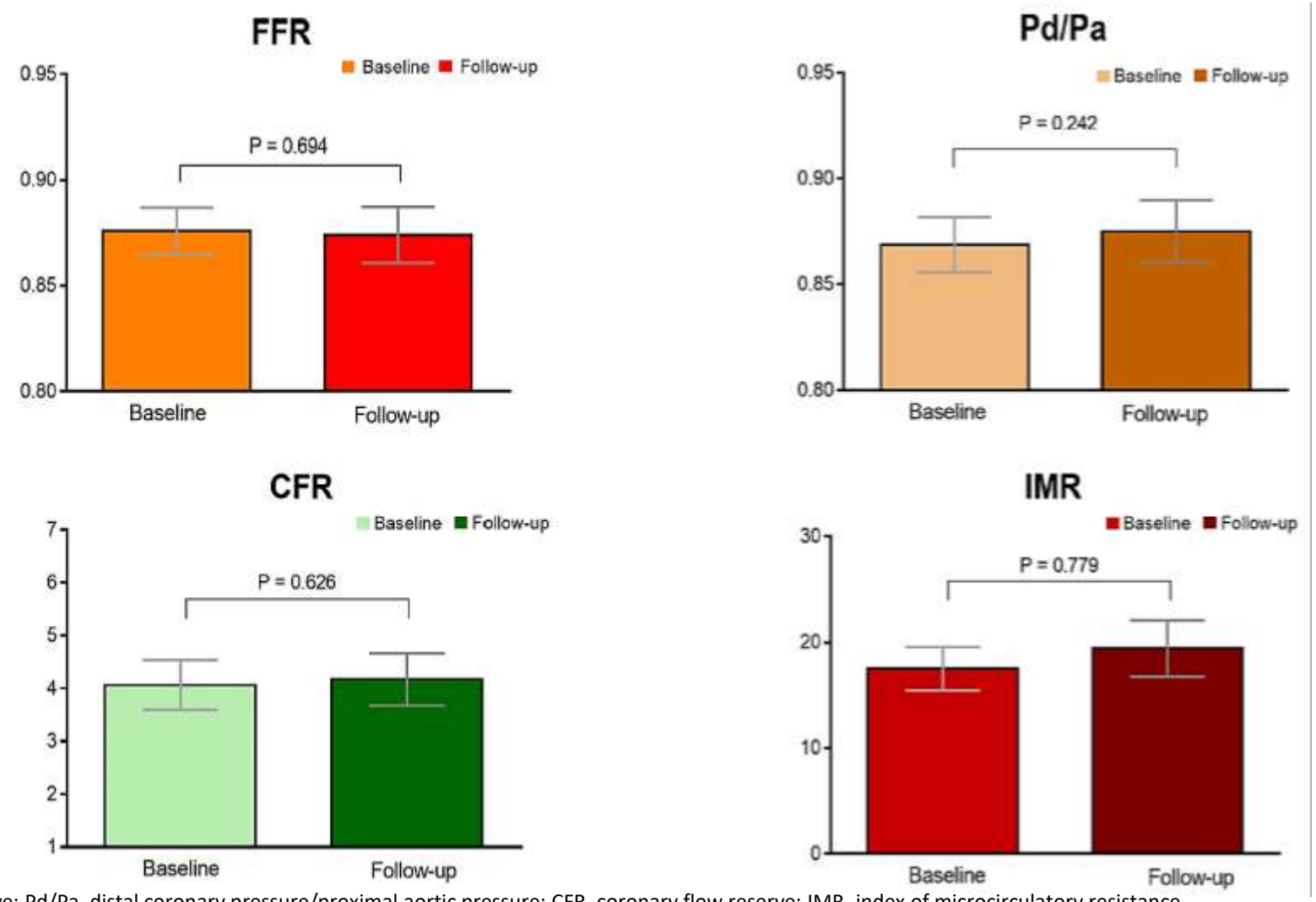


Intensity of atorvastatin	
20 mg	48 (50.5)
40 mg	32 (33.7)
80 mg	15 (15.8)

FORTE, Effect of Atorvastatin on Fractional Flow Reserve in Coronary Artery Disease; FFR, fractional flow reserve
*30-80% diameter stenosis by visual estimation

Reference. Lee CH, et al. JACC: Asia 2022;2:691–703.

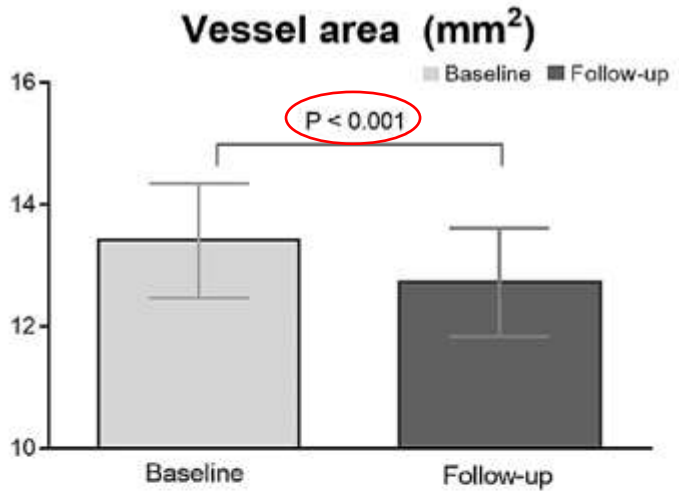
Changes of Coronary Flow after Atorvastatin therapy

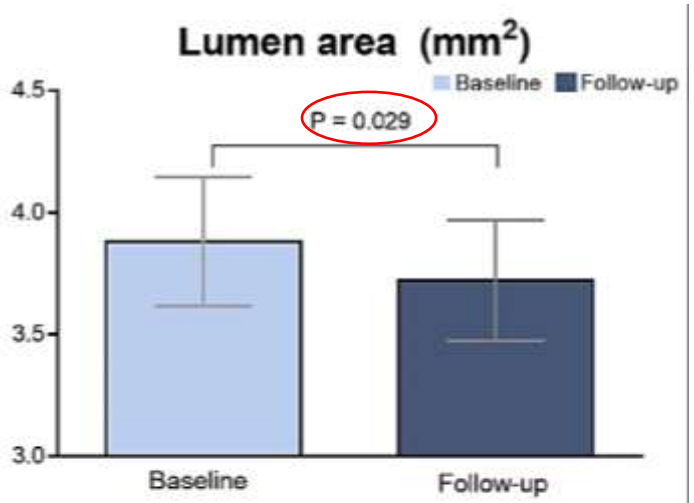


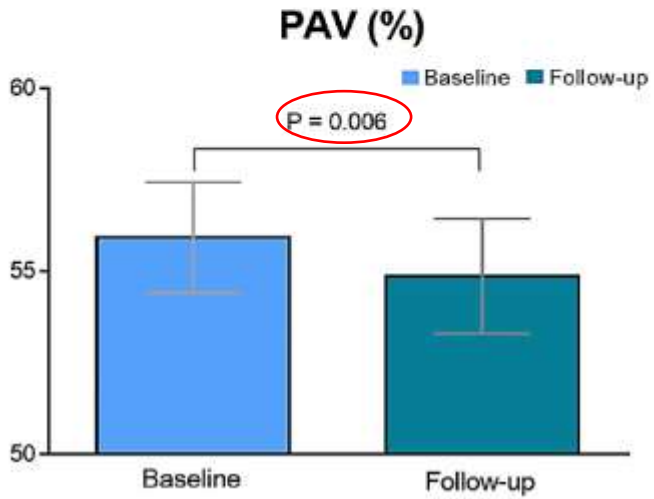
FFR, fractional flow reserve; Pd/Pa, distal coronary pressure/proximal aortic pressure; CFR, coronary flow reserve; IMR, index of microcirculatory resistance

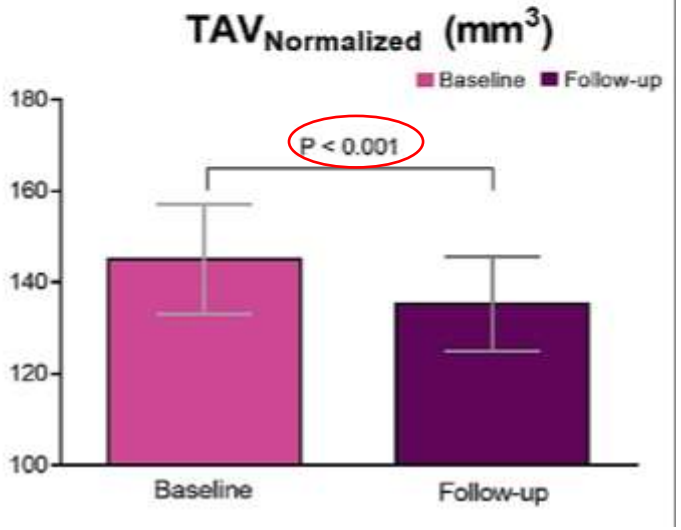
Reference. Lee CH, et al. JACC: Asia 2022;2:691–703.

Changes of Coronary Plaque after Atorvastatin therapy







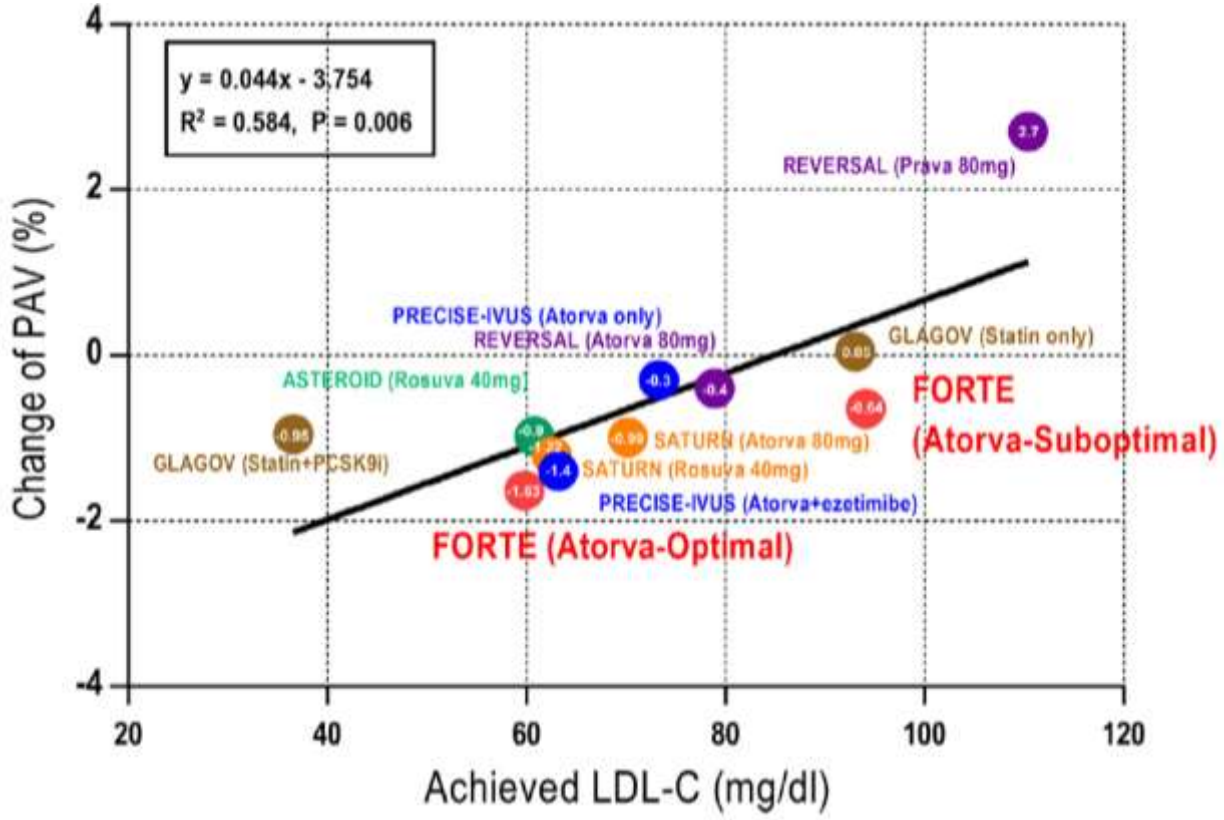


PAV, percent atheroma volume; TAV, total atheroma volume

Reference. Lee CH, et al. JACC: Asia 2022;2:691–703.

Relationship Between Achieved LDL-C Levels and Change in PAV

	Optimal Treatment (n = 39)				Suboptimal Treatment (n = 56)			
	Baseline	12 month	Change (%)	P value	Baseline	12 month	Change (%)	P value
LDL-C (mg/dL)	114.8	**59.8**	-55.0 (-47.9%)	<0.001	123.5	**94.1**	-29.4 (-23.8)	<0.001
PAV, %	56.81	55.18	**-1.63 (-2.9%)**	0.031	55.28	54.64	**-0.64 (-1.2%)**	0.092



Reference. Lee CH, et al. JACC: Asia 2022;2:691–703.

Inflammatory Risk and Statin Therapy in ACS Patient Undergoing PCI

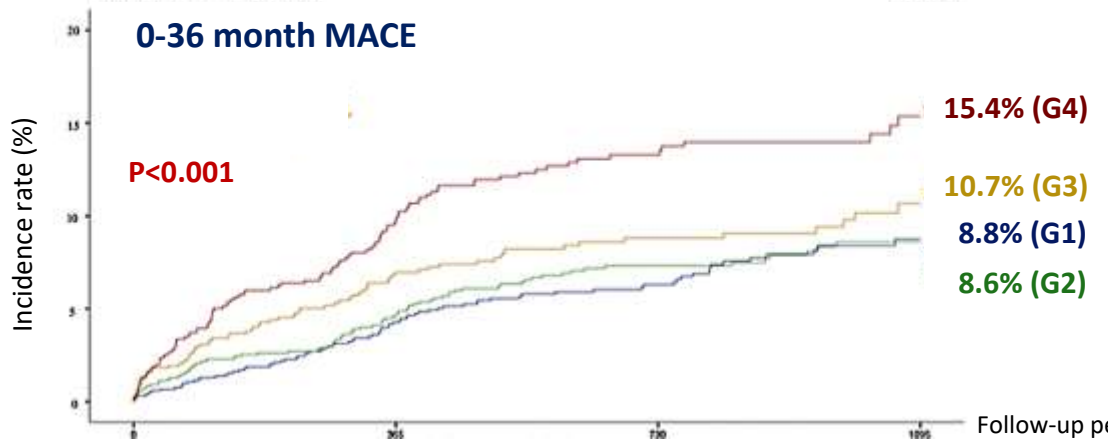
KAMIR-NIH, Korea Acute Myocardial Infarction-National Institutes of Health

Time-dependent prognostic effect of hs-CRP in AMI

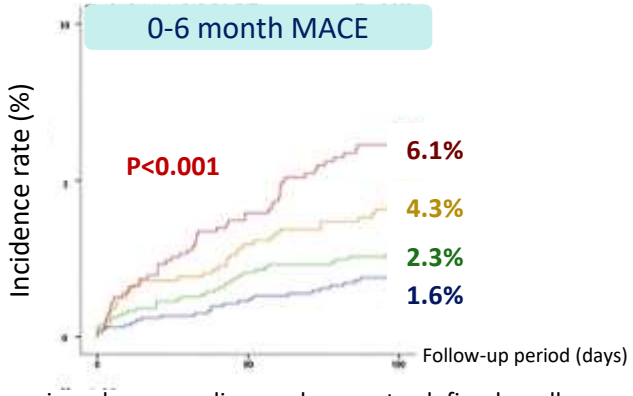
A retrospective cohort study

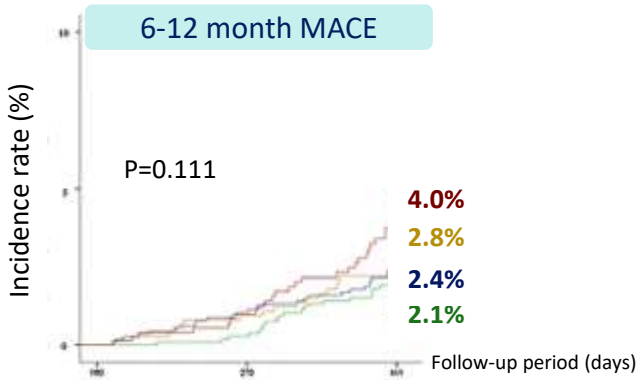
4,410 AMI patients underwent successful PCI with statin therapy

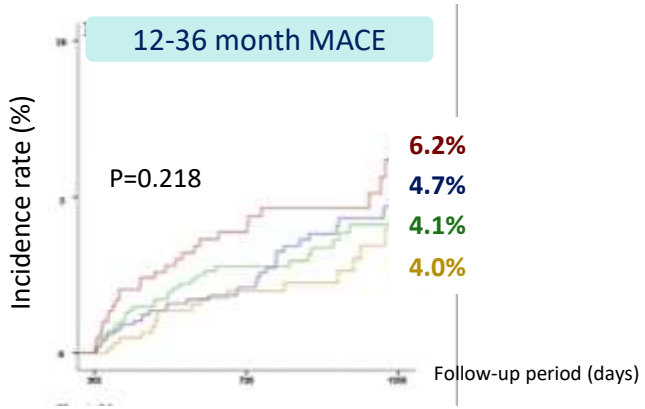
Incidence of MACE according to pre-specified time-periods and baseline Hs-CRP levels



Group	hs-CRP (mg/L)
G4	> 10.0
G3	3-10
G2	1-3
G1	≤ 1.0







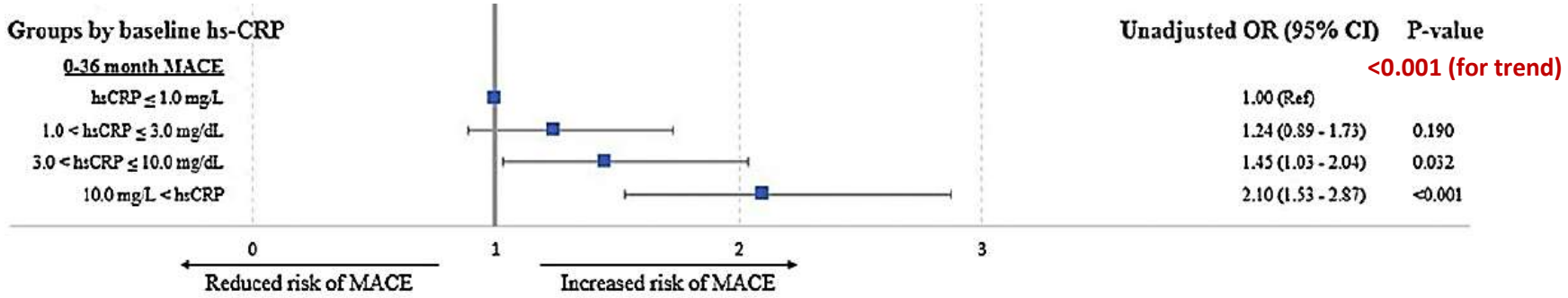
* MACE, major adverse cardiovascular events, defined as all-cause mortality, any MI, and repeat revascularization

Reference. Kang DO, et al. J Cardiol. 2019 Jul;74(1):74-83.

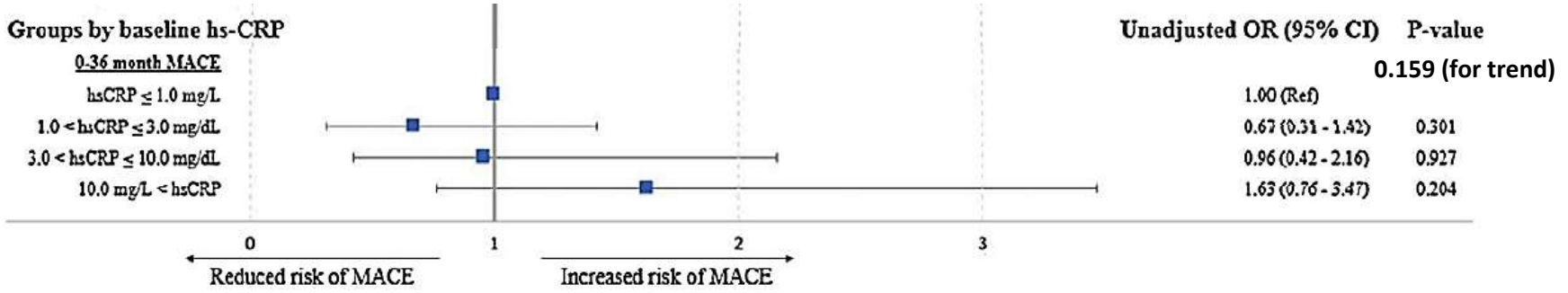
Effect of high-intensity statin therapy by baseline hs-CRP in AMI patients undergoing successful PCI

Incidence of MACE according to baseline Hs-CRP levels

Non-high-intensity Users



High-intensity Users



* MACE, major adverse cardiovascular events, defined as all-cause mortality, any MI, and repeat revascularization

Reference. Kang DO, et al. J Cardiol. 2019 Jul;74(1):74-83.

Residual inflammatory risk(RIR) in Korean patients with CAD undergoing PCI

A retrospective cohort study

PCI-treated patients with serial hs-CRP values (on admission & 1-month post PCI) (n=4,562)

4 group according to serial hs-CRP
hs-CRP cutoff: 2 mg/L

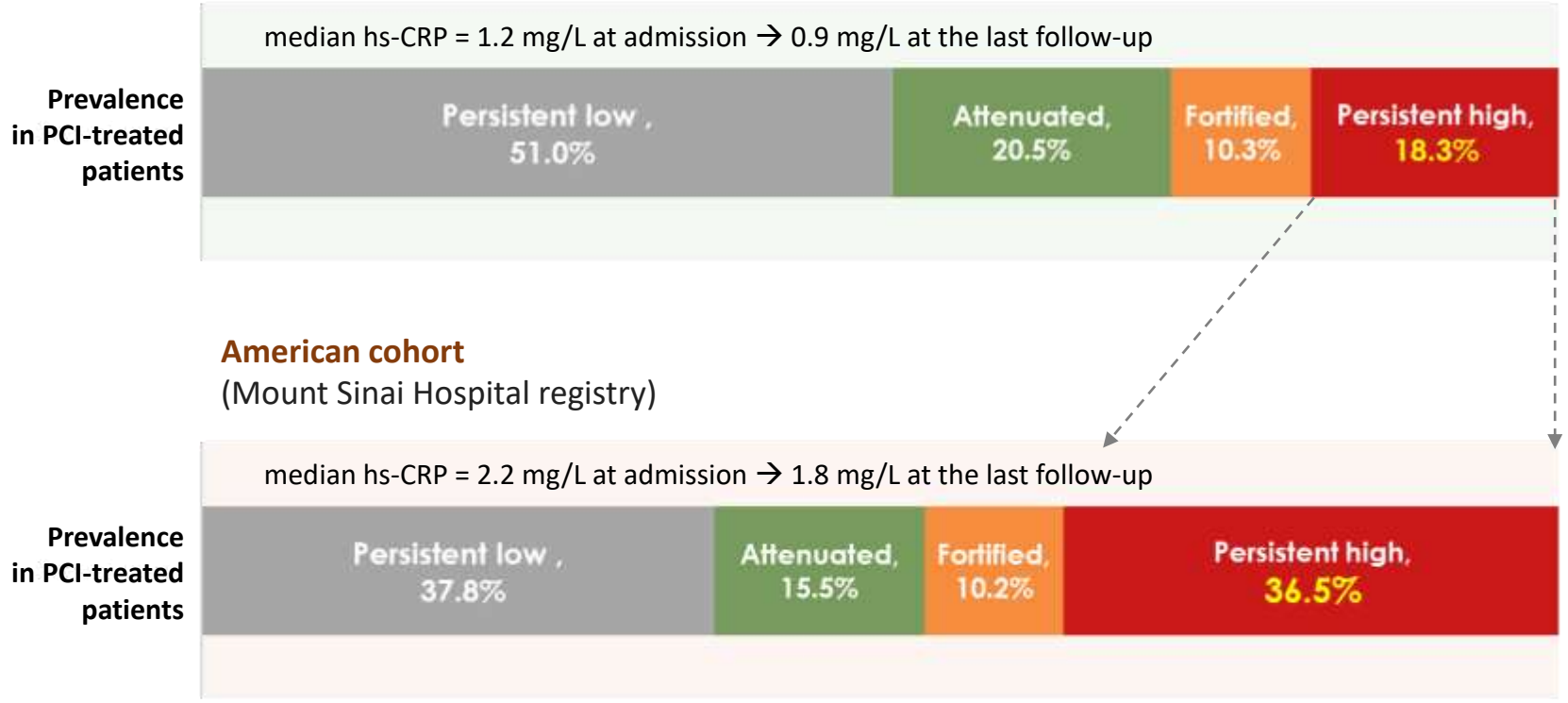
Phenotype of RIR	Persistent low RIR	Attenuated RIR	Fortified RIR	Persistent high RIR
	Low on-admission **Low** 1-month	**High** on-admission **Low** 1-month	**Low** on-admission **High** 1-month	**High** on-admission **High** 1-month

RIR, residual inflammatory risk; hs-CRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention

Reference. Ahn JH, et al. JACC Asia. 2022 Apr 12;2(3):323-337.

East Asian had a lower prevalence of persistent high RIR compared with American

East Asian cohort : median hs-CRP = 1.2 mg/L
(Prospective 2-center database in Korea)



RIR, residual inflammatory risk; hs-CRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention

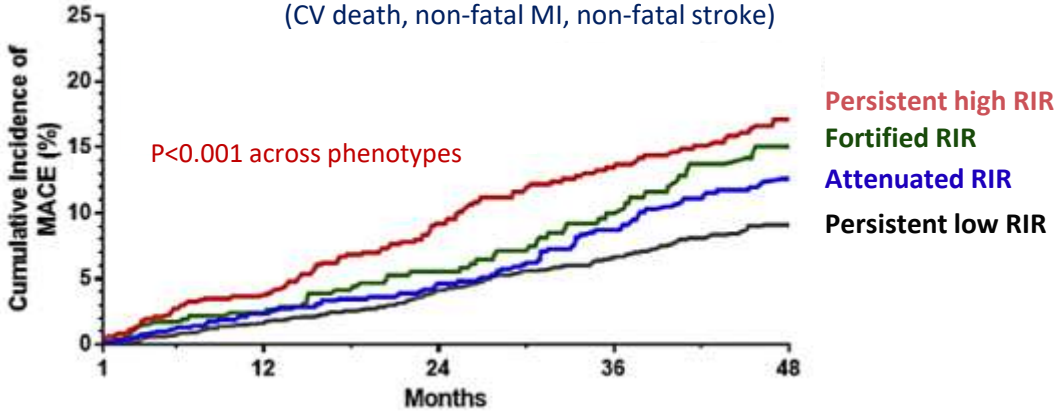
Reference. Ahn JH, et al. JACC Asia. 2022 Apr 12;2(3):323-337.

Risks of clinical events were significantly different across phenotype of residual inflammatory risk

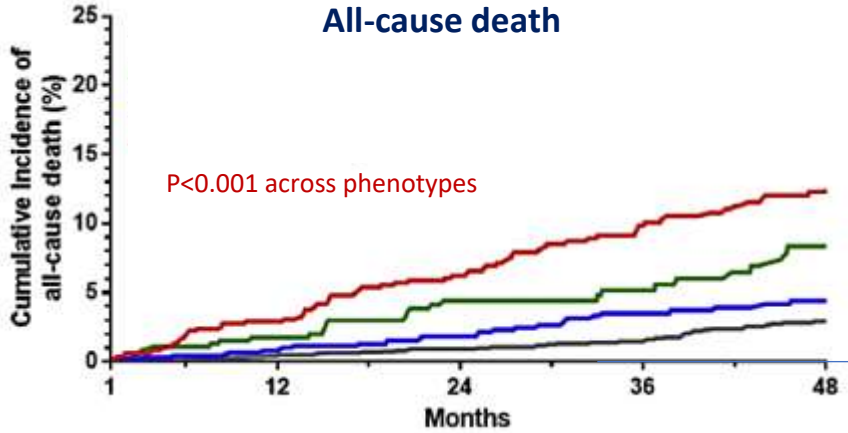
Kaplan-Meier curves for adverse clinical events, stratified by phenotype of residual inflammatory risk (RIR)

MACE

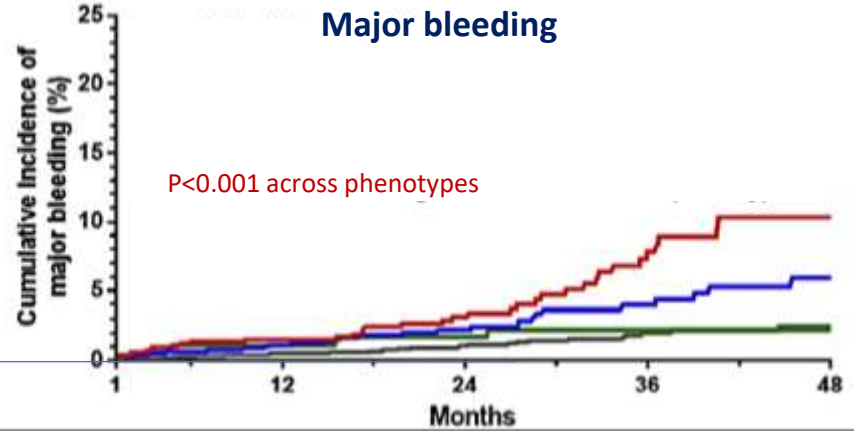
(CV death, non-fatal MI, non-fatal stroke)



All-cause death



Major bleeding



RIR, residual inflammatory risk; MACE, Major adverse cardiac events

Reference. Ahn JH, et al. JACC Asia. 2022 Apr 12;2(3):323-337.

Persistent high RIR was significantly associated with baseline characteristics and statin therapy

The Determinants of Persistent High RIR vs Other RIRs

	Multivariable Analysis	
	OR (95% CI)	***P* value**
Index presentation with MI	-	-
Age (per 1-y increase)	1.02 (1.01-1.02)	<0.001
Smoking	1.57 (1.30-1.89)	<0.001
Diabetes mellitus	-	-
Chronic kidney disease	1.91 (1.55-2.35)	<0.001
Hemoglobin (per 1 g/dL increase)	0.90 (0.85-0.94)	<0.001
Previous stroke	-	-
WBC (per $10^3/mm^3$ increase)	1.07 (1.04-1.09)	<0.001
LDL cholesterol (per 1 mg/dL increase)	1.00 (1.00-1.01)	<0.001
HDL cholesterol (per 1 mg/dL increase)	0.99 (0.98-0.99)	<0.001
Multivessel disease	1.30 (1.10-1.52)	0.002
Medication: statin	0.65 (0.46-0.92)	0.016

35% ↓

RIR, residual inflammatory risk; WBC, white blood count

Reference. Ahn JH, et al. JACC Asia. 2022 Apr 12;2(3):323-337.

Key Messages

- Contemporary clinical guideline emphasize mandatory use of high-dose statin in ACS or PCI patients on the basis of pivotal RCTs.
- Benefit of high-dose statin was remarkable when it used as soon as possible in the early period.
- High-intensity statin pretreatment was beneficial in patients with stable CAD or ACS who are undergoing PCI.
- Statin therapy was beneficial for plaque stabilization and/or regression in ASCVD patients and reduction of residual inflammatory risk in ACS patient undergoing PCI.