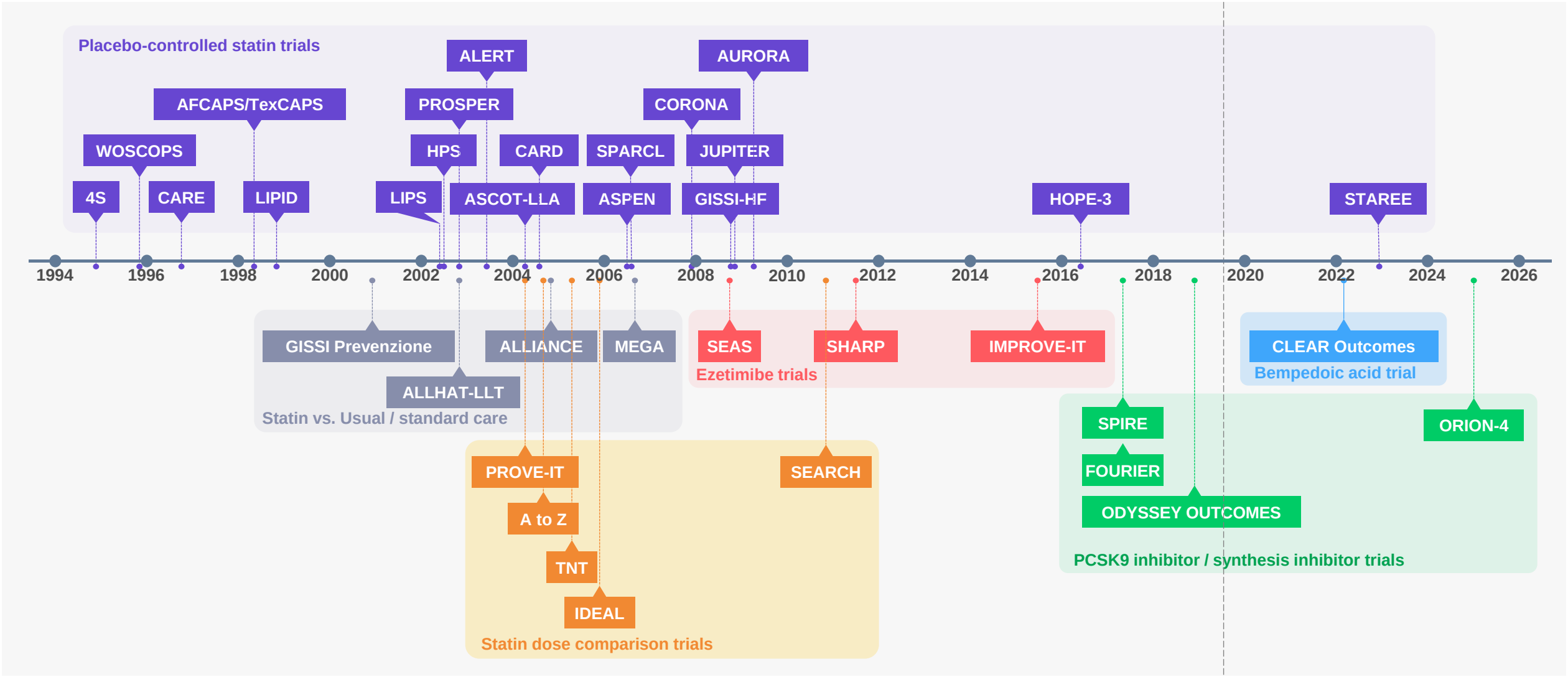
Individual Treatment Strategy for Dyslipidemia in CAD

Chung-Ang University Gwangmyeong Hospital

Jun Hwan Cho

DAEWOONG

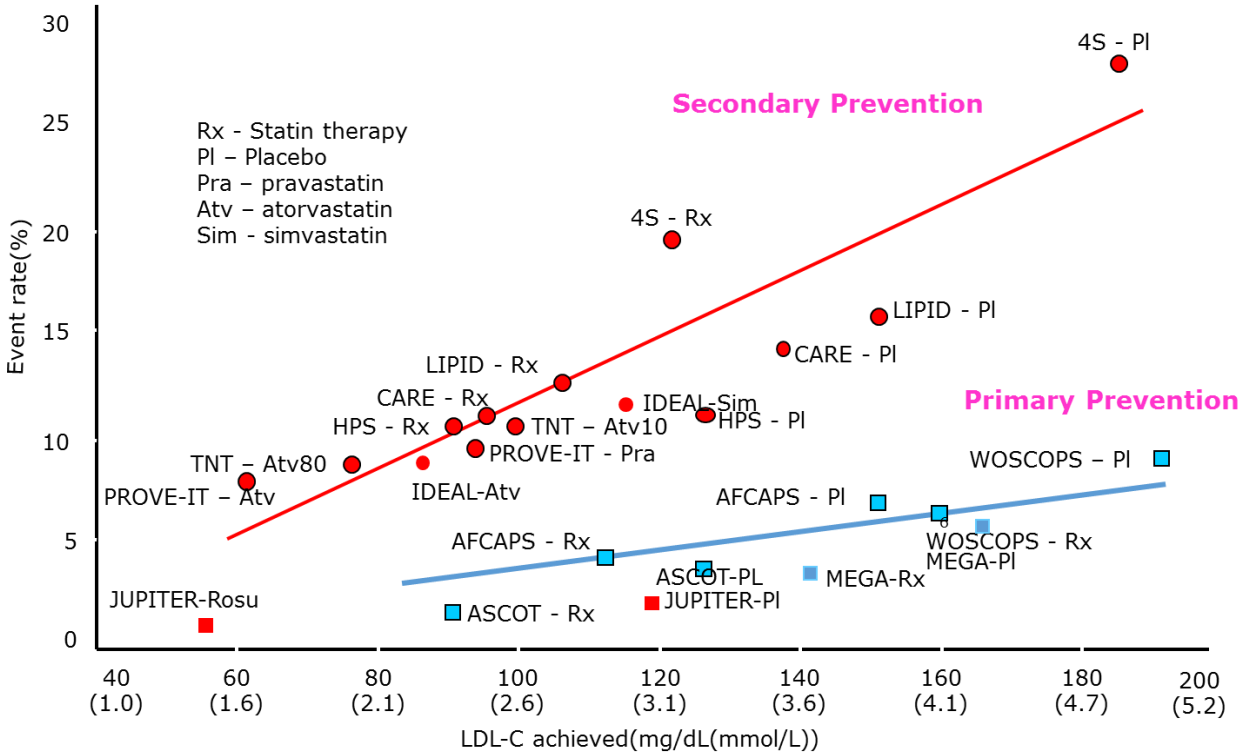
CV outcome trials : LDL-C Lowering Treatment



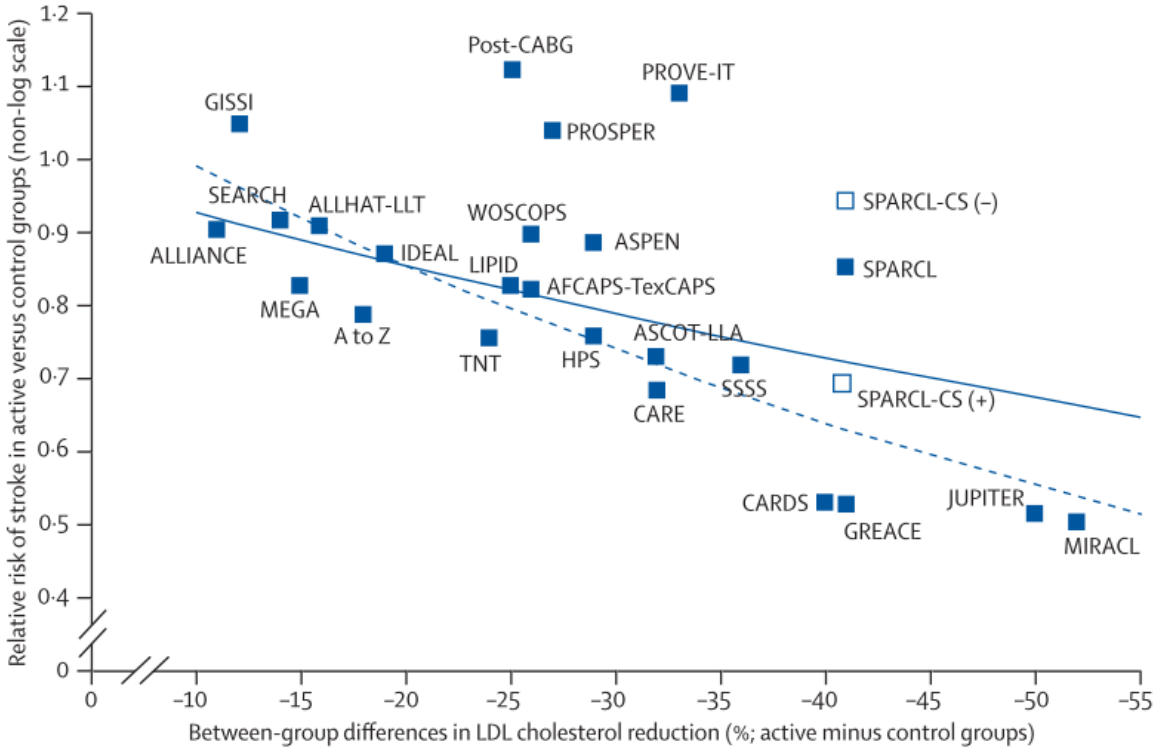
Association between LDL-C and ASCVD

Lower LDL-C may reduce risk of cardiovascular events and stroke

Reduced cardiovascular events with LDL-C lowering[1-4]



Reduced stroke events with LDL-C lowering[5]

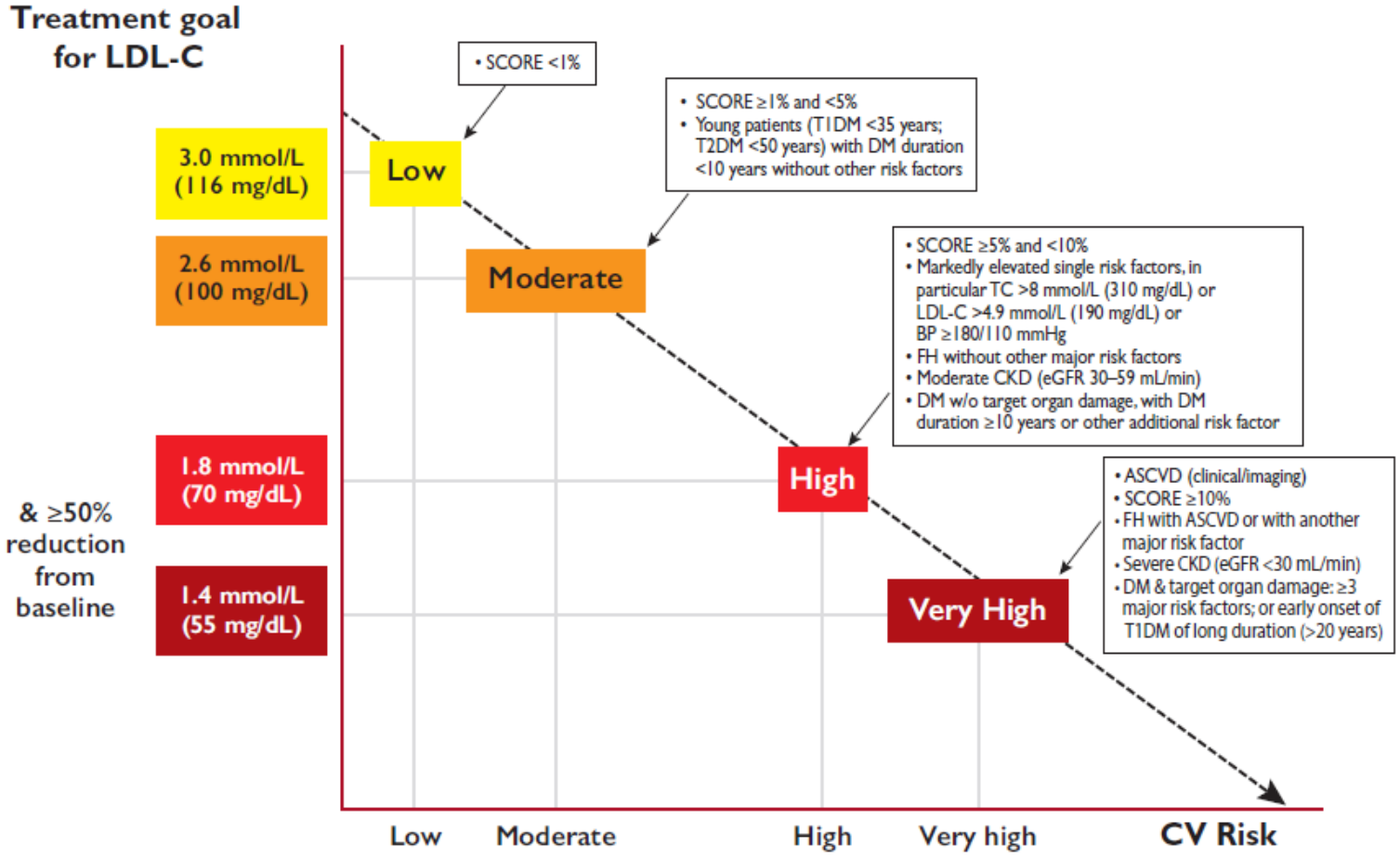


Ref.〉 1. Rosenson RS. Expert Opin Emerg Drugs. 2004;9(2):269-279. 2. LaRosa JC, et al. N Engl J Med. 2005;352(14):1425-1435. 3. Pedersen TR, et al. JAMA. 2005;294(19):2437-2445. 4. Nakamura H, et al. Lancet. 2006;368(9542):1155-1163. 5. Lancet Neurol 2009; 8: 453-63

2019 ESC/EAS guidelines : Cardiovascular Risk categories

Table 4 Cardiovascular risk categories

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. 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. DM with target organ damage,[a] 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.



<Ref.> Cosentino F, et al. Eur Heart J. 2020;41(2):255-323

2019 ESC/EAS guidelines

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1-78
doi:10.1093/eurheartj/ehz455
ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *Lipid modification to reduce cardiovascular risk*

- **Concept Change I: Start Early**
  - *Less "lipid-exposure" leads to prevention of lesion formation*
- **Concept Change II: Treat (Much More) Aggressively**
  - *From desirable target to "LDL-C elimination in the blood"*
- **Concept Change III: Use Combination Therapy**
  - *Statin + Ezetimibe (+/- PCSK9 Inhibitor) induced LDL-C lowering reduces CV risk*

2022 KSoLA guidelines : Recommendations for treatment goals

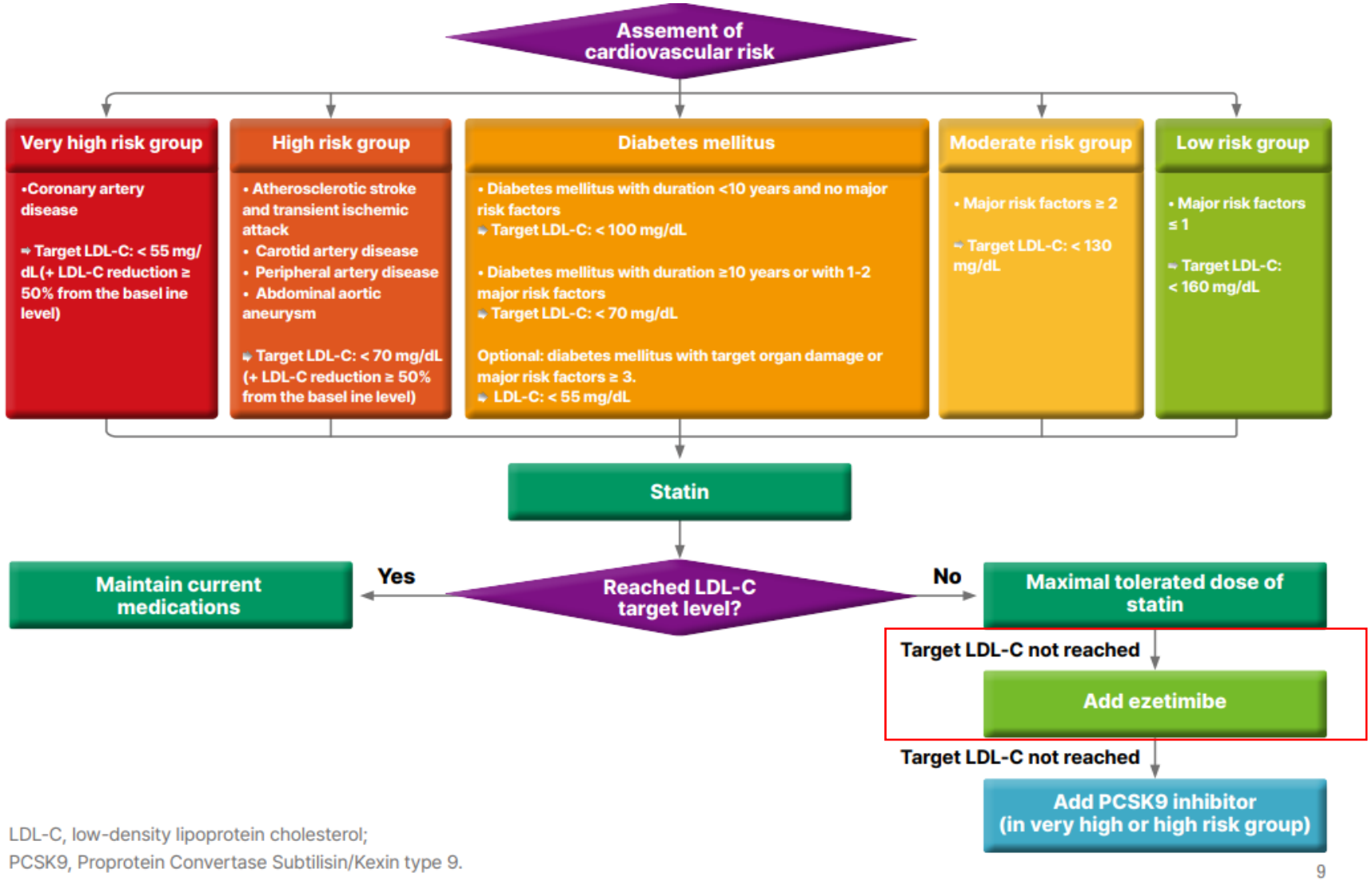
Risk category	LDL-C (mg/dL)	non-HDL-C (mg/dL)
Coronary artery disease[1)*]	< 55	< 85
Atherosclerotic stroke and transient ischemic attack* Carotid artery disease* Peripheral artery disease* Abdominal aortic aneurysm* Diabetes mellitus (duration ≥ 10 years or major risk factor† or target organ damage)[2)]	< 70	< 100
Diabetes mellitus (duration < 10 years and no major risk factors†)	< 100	< 130
Moderate risk (major risk factors† ≥ 2)	< 130	< 160
Low risk (major risk factors† ≤ 1)	< 160	< 190

*It is also recommended to reduce LDL-C by ≥ 50% from the baseline level.
†Age (men ≥ 45 years, women ≥ 55 years), family history of premature ASCVD, hypertension, smoking, and low HDL-C level (< 40 mg/dL).
1) In patient with acute myocardial infarction, statin is recommended irrespective of LDL-C level.
2) In diabetes mellitus with target organ damage (albuminuria, CKD [eGFR <60 mL/min/1.73m^2], retinopathy, neuropathy, left ventricular hypertrophy) or major risk factors† ≥ 3: target LDL-C < 55 mg/dL (optional)
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

5

<Ref.> Korean Guidelines for the Management of Dyslipidemia 5th

2022 KSoLA guidelines : Evidence-guided approach algorithm dyslipidemia treatment

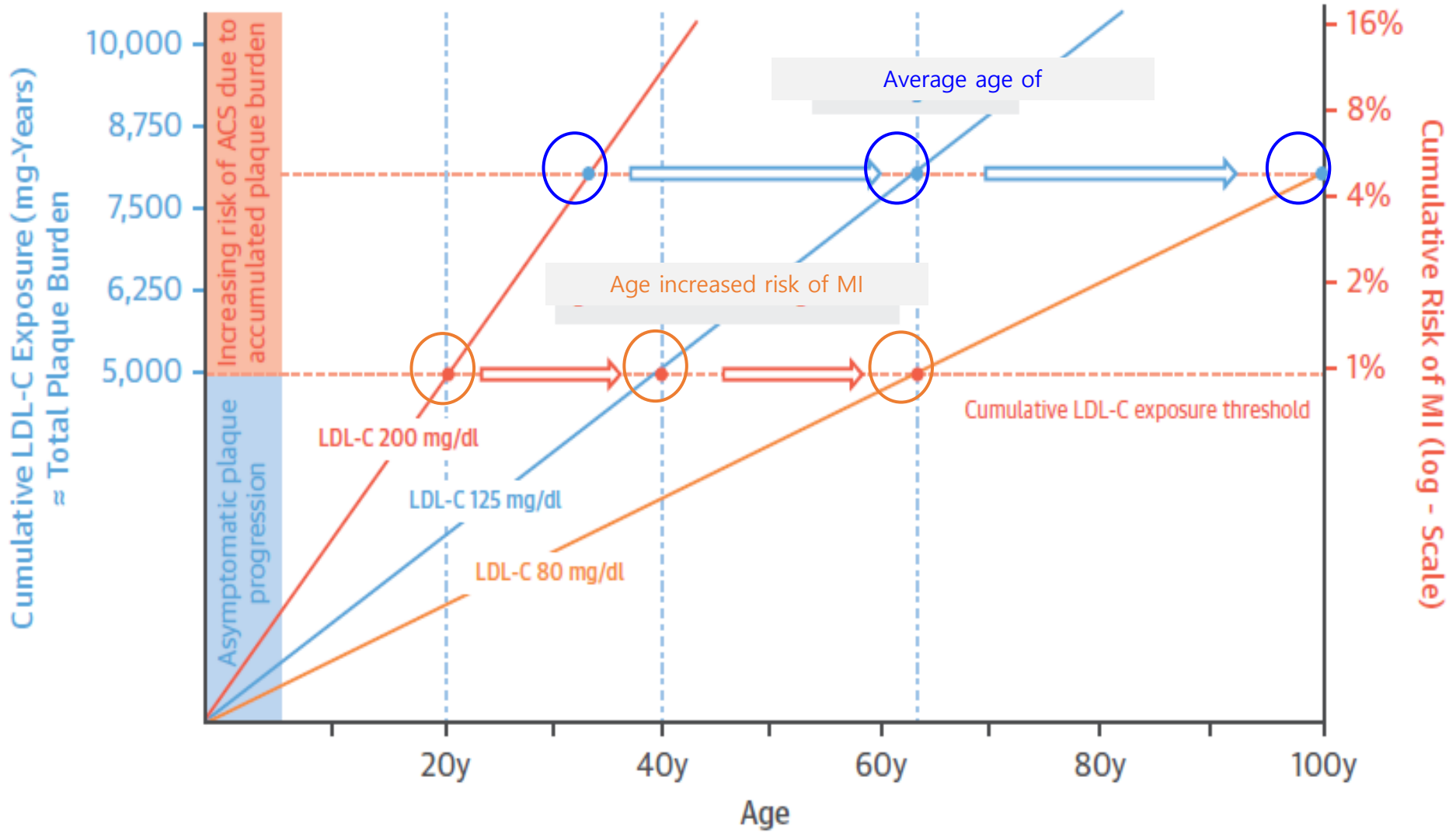


LDL-C, low-density lipoprotein cholesterol;
PCSK9, Proprotein Convertase Subtilisin/Kexin type 9.

9

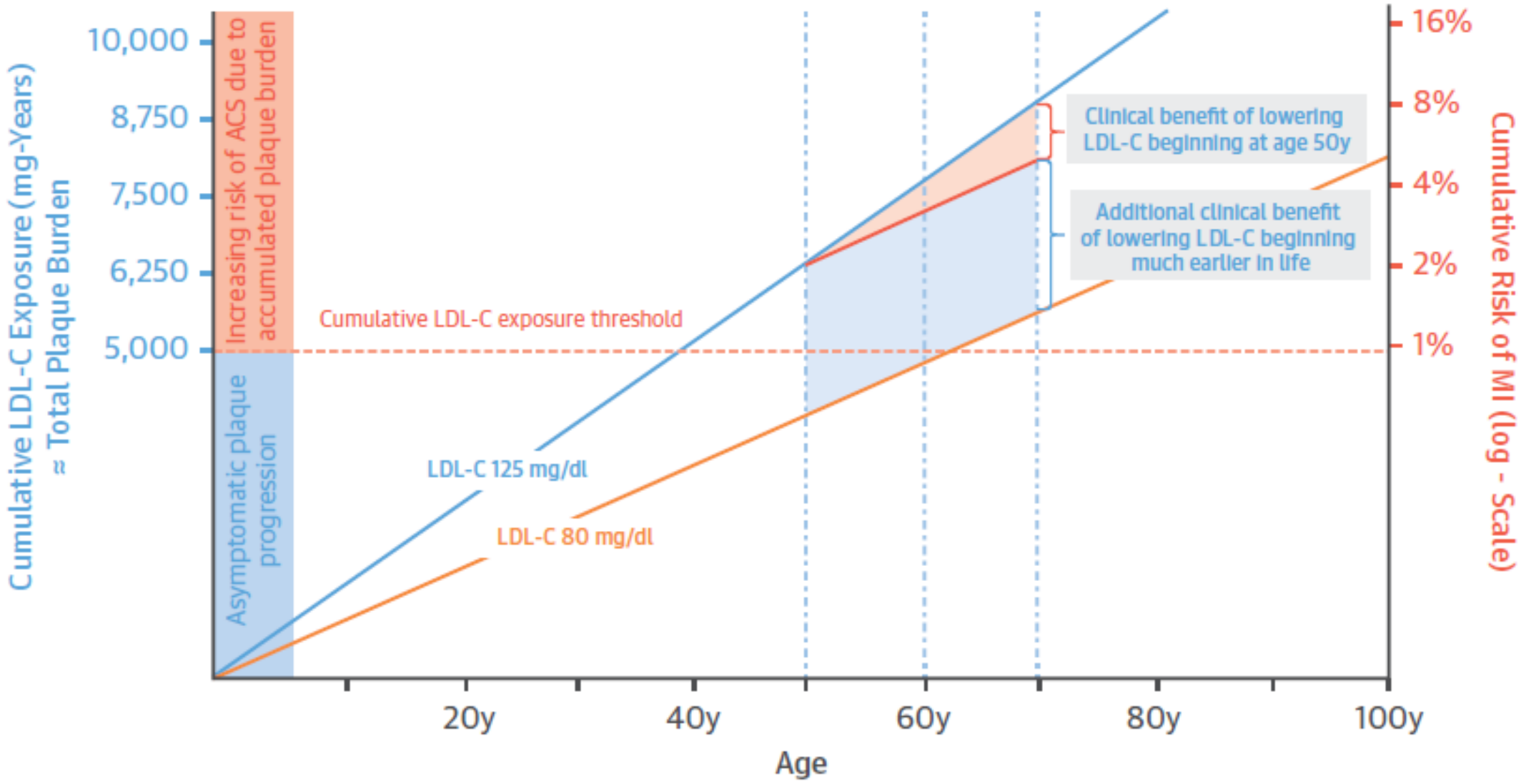
<Ref.> Korean Guidelines for the Management of Dyslipidemia 5th

Risk of ASCVD and Cumulative LDL-C exposure



Ref.> Ference BA, et al. J Am Coll Cardiol. 2018; 72(10):1141-1156.

Risk of ASCVD and Cumulative LDL-C exposure



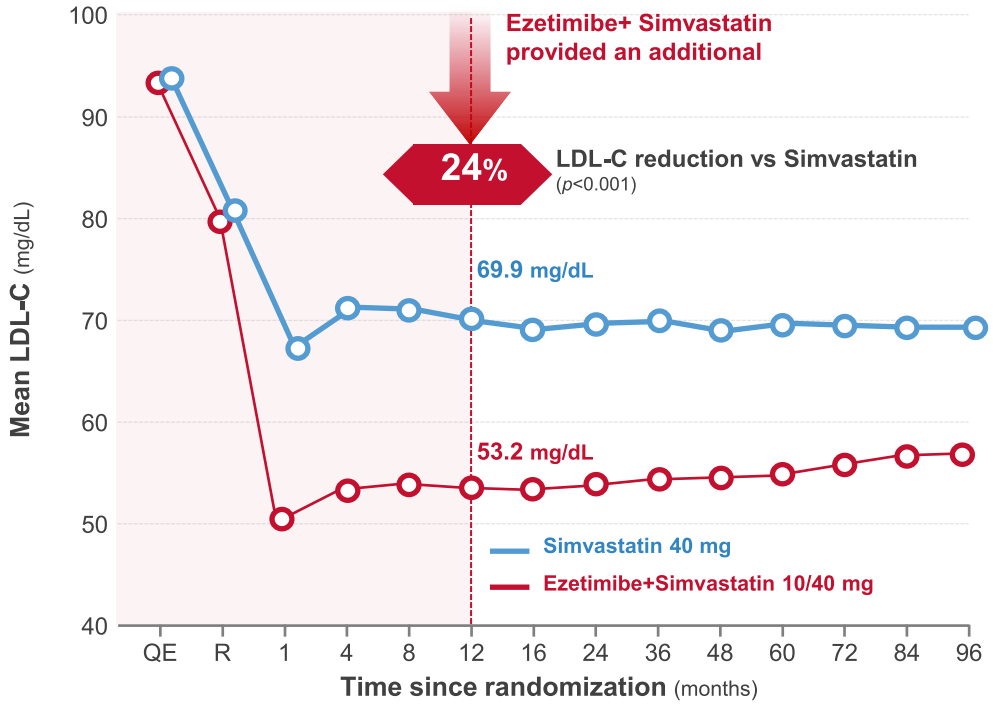
Ref.> Ference BA, et al. J Am Coll Cardiol. 2018; 72(10):1141-1156.

IMPROVE-IT Trial

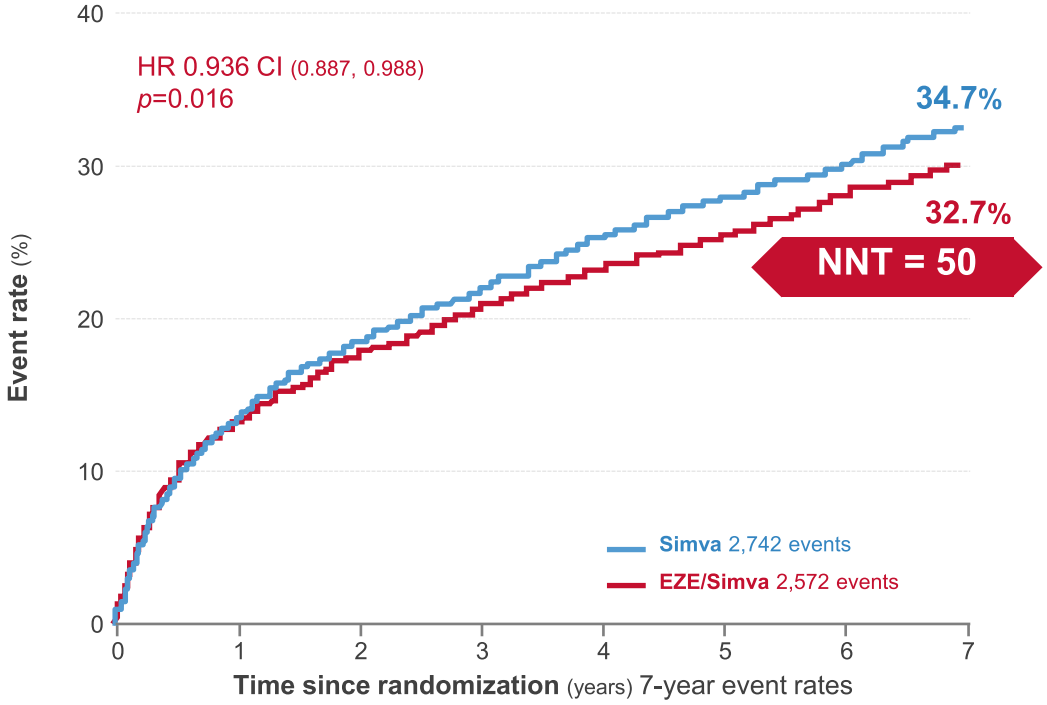
Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes (ACS)

Patient	18,144 patients with ACS
Intervention	Simvastatin 40mg + Ezetimibe 10mg (n=9,067)
Comparison	Simvastatin 40mg (n=9,077)
Outcomes	Composite of cardiovascular death, MI, stroke, hospitalization for UA or revascularization (median f/u 6 years)

LDL-C Lowering



Primary endpoint

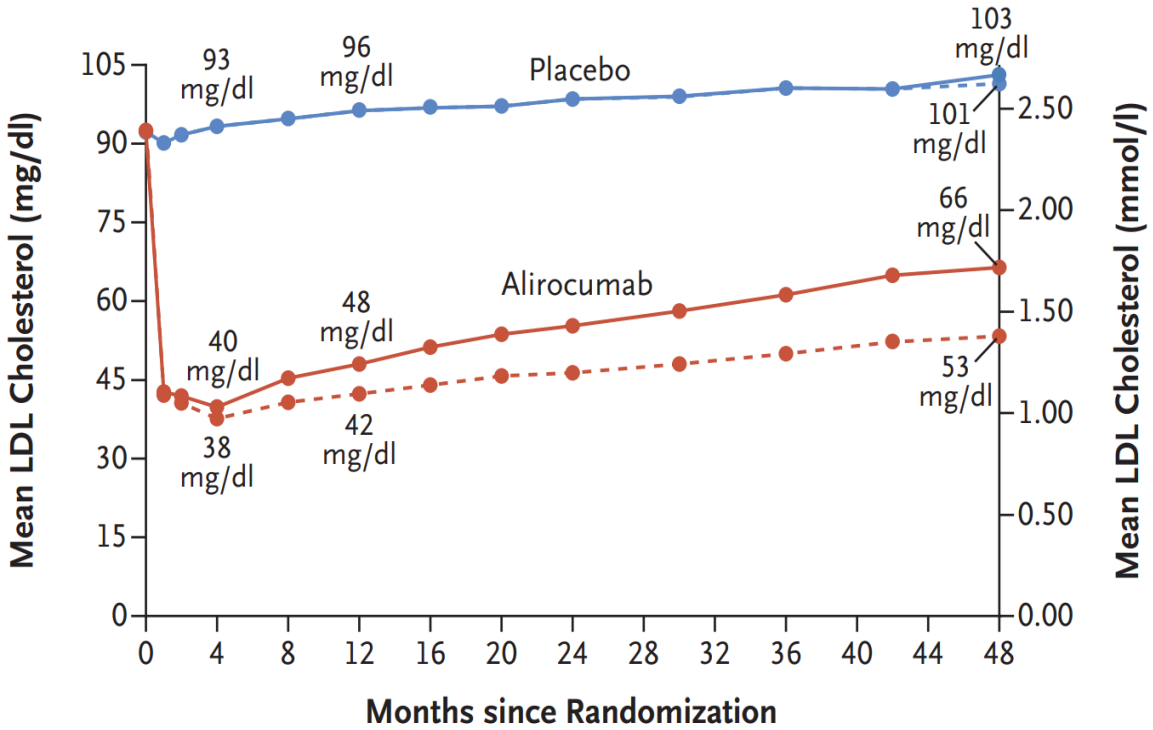


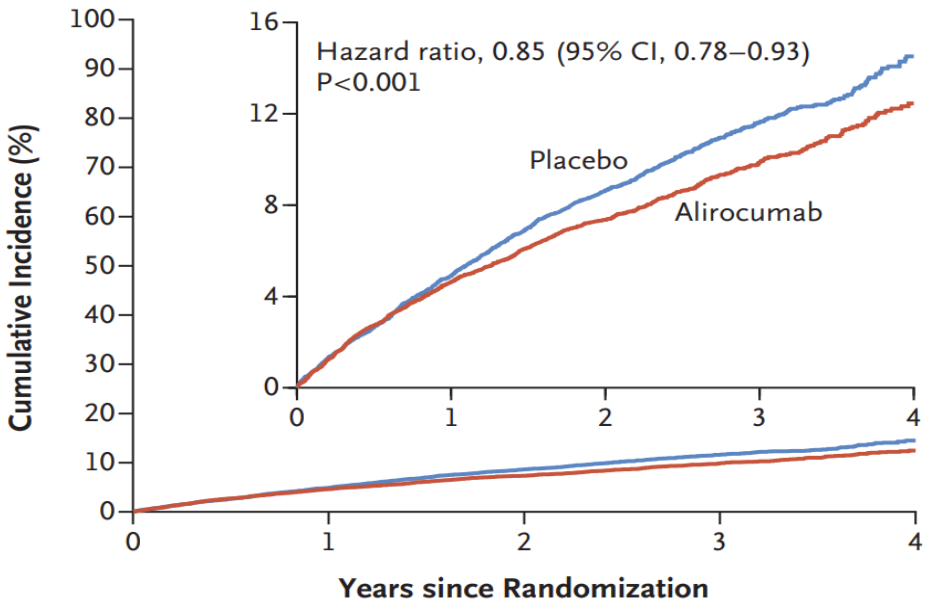
N Engl J Med. 2015;372;2387-97

ODEYSSEY OUTCOMES Trial

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

Patient	18,924 patients with ASCVD and LDL >70 mg/dL receiving statin
Intervention	Alirocumab (either 75mg or 150mg every 2 weeks) (n=9,462)
Comparison	Placebo (n=9,462)
Outcomes	Composite of cardiovascular death, MI, stroke, hospitalization for UA (median f/u 2.8 years)





No. at Risk

Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

N Engl J Med. 2018;379;2097-107

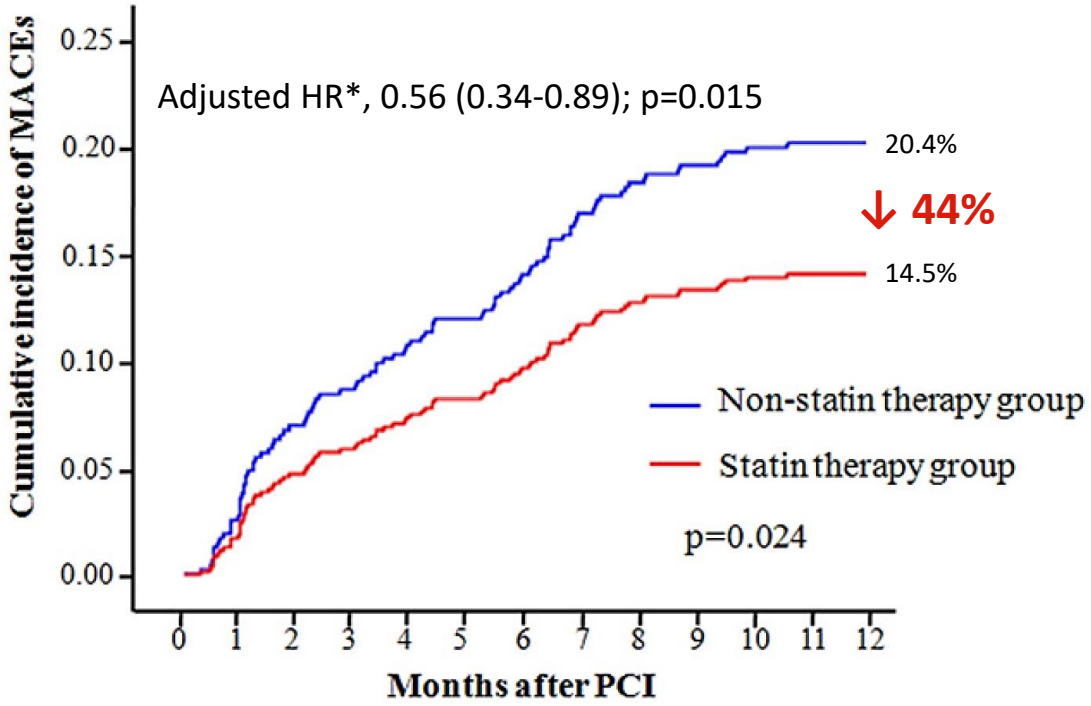
Benefits of statin with AMI who have extremely low LDL-C

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

1,054 patients with acute MI 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, target vessel revascularization, 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.

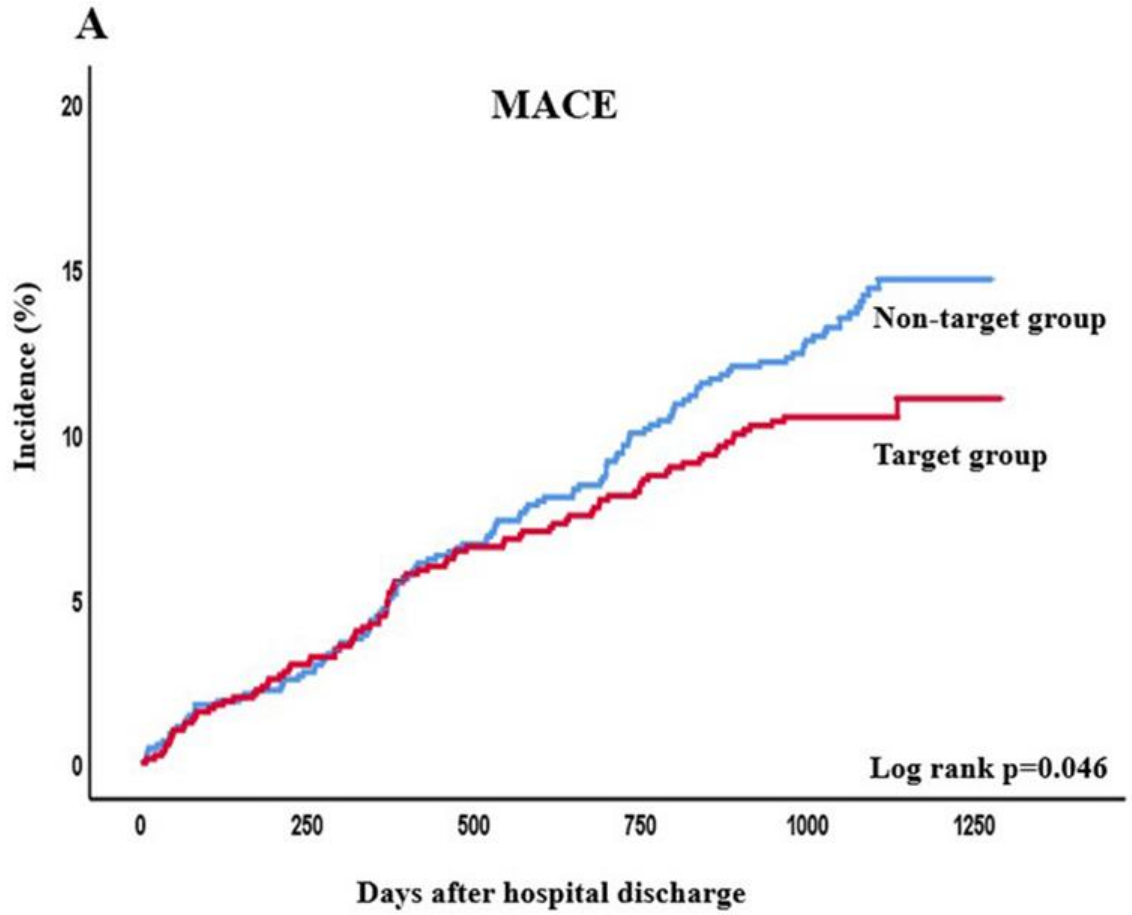
KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institutes of Health; **MACE**, major adverse cardiac event; **PCI**, percutaneous coronary intervention; **CABG**, coronary artery bypass grafting

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.

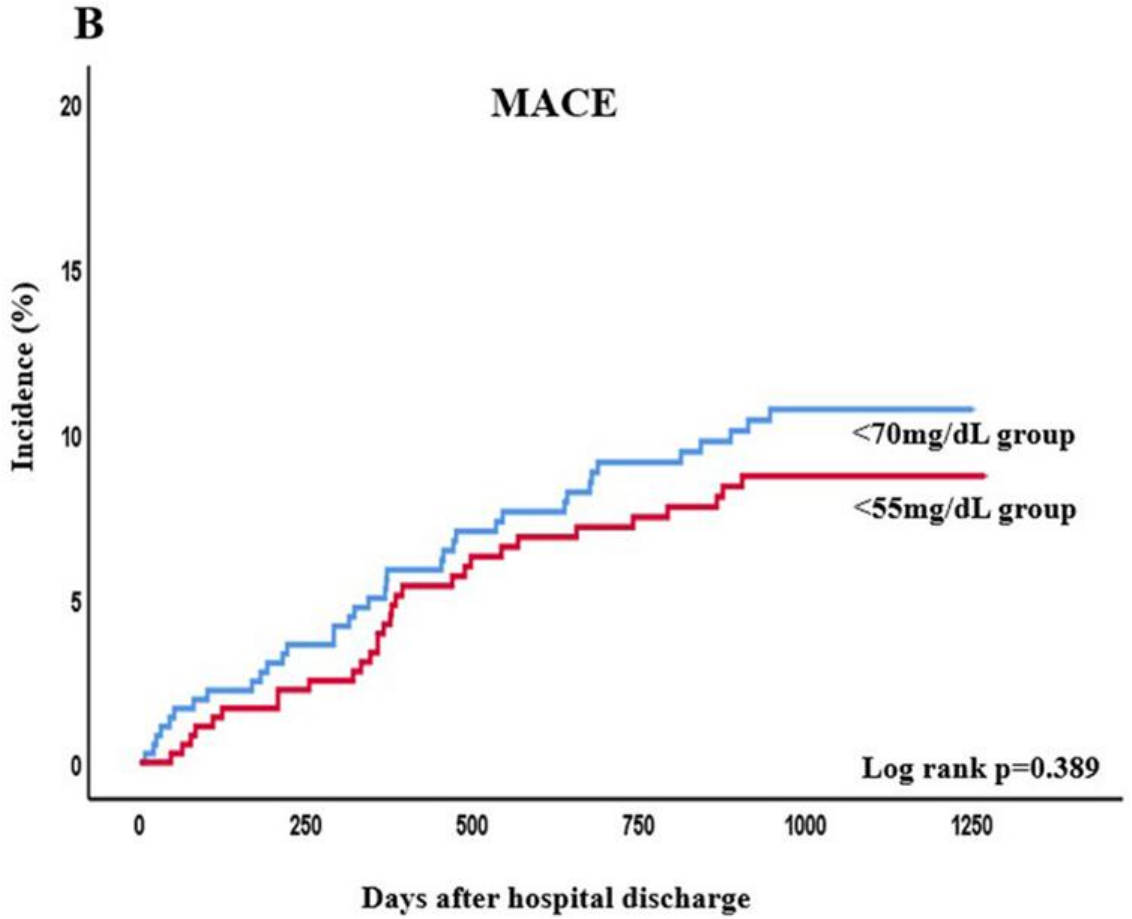
Is LDL-C < 55mg/dL beneficial ?? – Based on KAMIR

Optimal low-density lipoprotein cholesterol target level in Korea AMI patients (< 70 mg/dL vs. < 55 mg/dL)

Target vs. Non-target



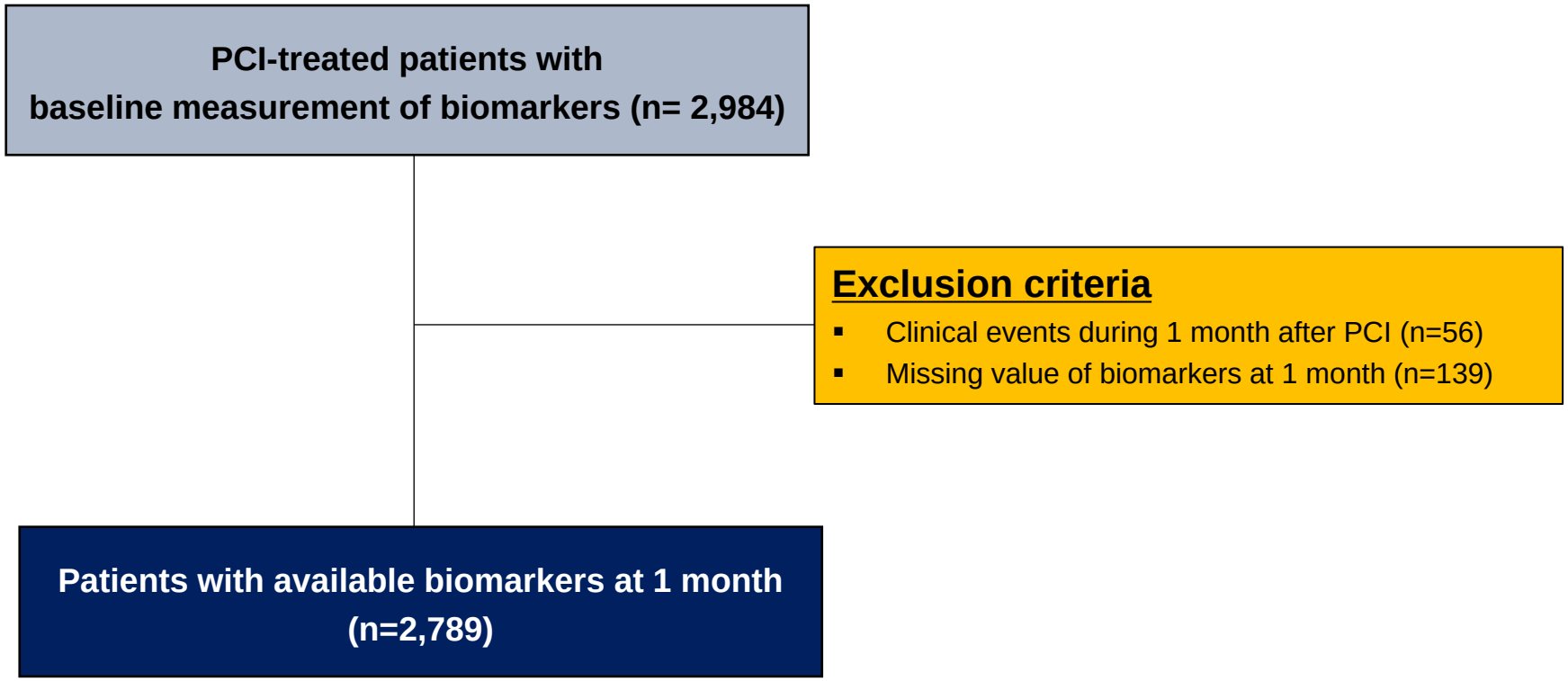
< 70 mg/dL vs. < 55 mg/dL



Target group : LDL-C < 70 mg/dL and ≥ 50% reduction from the baseline level
Non-target group : Failed to achieve LDL-C < 70 mg/dL and ≥ 50% reduction from the baseline level

Int J Cardiol. 2002 Mar 15:351:15-22

Long-term Prognostic Impacts of Residual Cardiovascular Risk after PCI

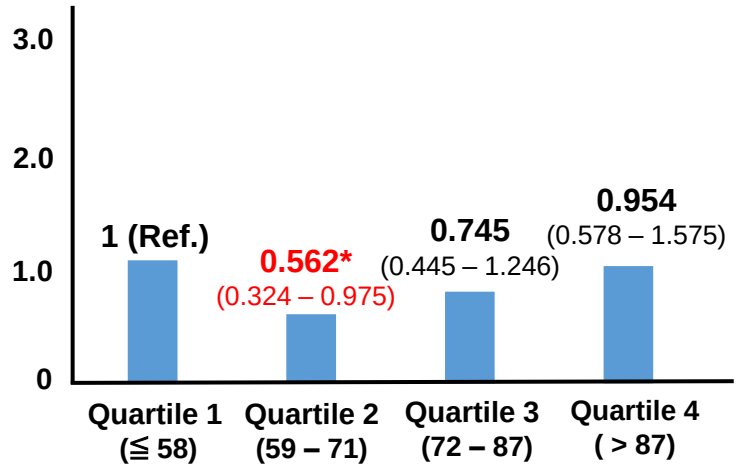


The primary endpoint : a composite of CV death, MI, or stroke up to 4 years

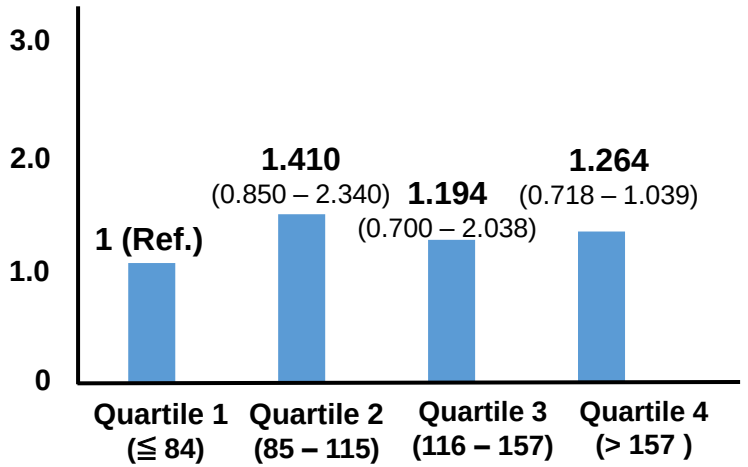
JH Cho, YH Jeong, Unpublished data

Long-term Prognostic Impacts of Residual Cardiovascular Risk after PCI

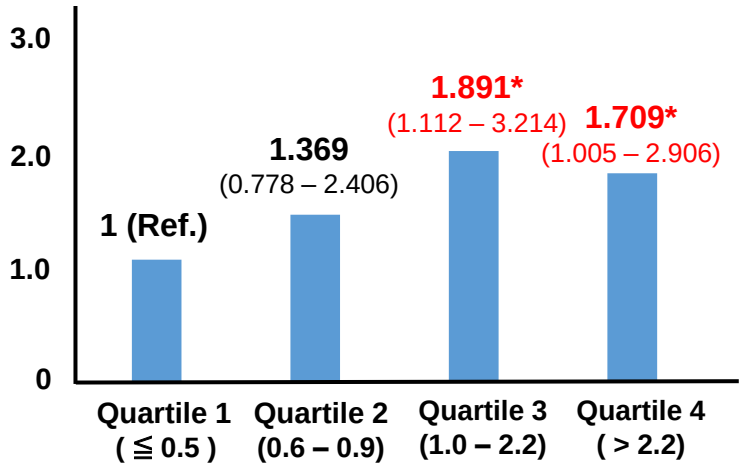
A. LDL (mg/dL)



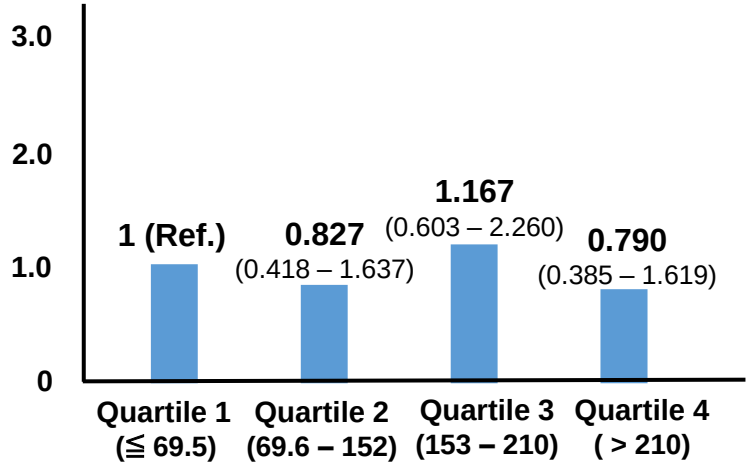
B. Triglyceride (mg/dL)



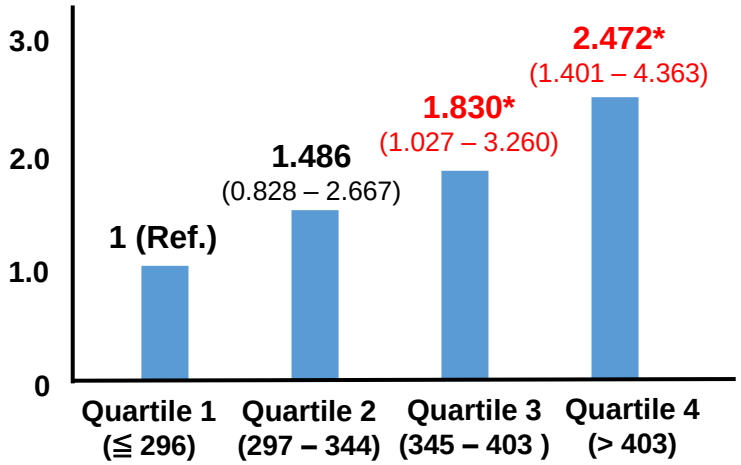
C. hs-CRP (mg/L)



D. PRU



E. Fibrinogen (mg/dL)



Adjusted with index AMI diagnosis, age, sex, BMI, HTN, DM, CKD, anemia, current smoker, multivessel disease, complex PCI, potent $P2Y_{12}$ inhibitor, BB, RASi, and statin

JH Cho, YH Jeong, Unpublished data

Ez-PAVE Trial

Effects of Ezetimibe Combination Therapy for Patients With Atherosclerotic Cardiovascular Disease; Randomized Comparison of LDL-cholesterol Targeting <70 Versus <55mg/dL; Ez-PAVE Trial

ClinicalTrials.gov ID NCT04626973

Sponsor Yonsei University

Information provided by Yonsei University (Responsible Party)

Last Update Posted 2021-06-11

Study Details | **Table View** | No Results Posted | Record History

On this page

- Trial Contacts
- Study Record Dates
- Outcome Measures
- Trial Description
- Recruitment Information

Trial Contacts

Contacts ICMJE

1. Contact: Byeong-Keuk Kim, MD, PhD
   Phone Number:
   82-2-2228-8465
   Email Address: KIMBK@yuhs.ac

LDL-C target goal attainment by CV risk group

A retrospective cohort study using the NHS-National Health Examination Cohort (NHIS-HEALS) database

National Health Insurance Service—National Health Screening Cohort enrollees (n=514,866)

↓

Patients who received health examination with LDL-C measurement between January 1, 2007, and December 31, 2011 (n=414,088)

↓

Patients without any missing values in major risk factors (n=312,622)

↓

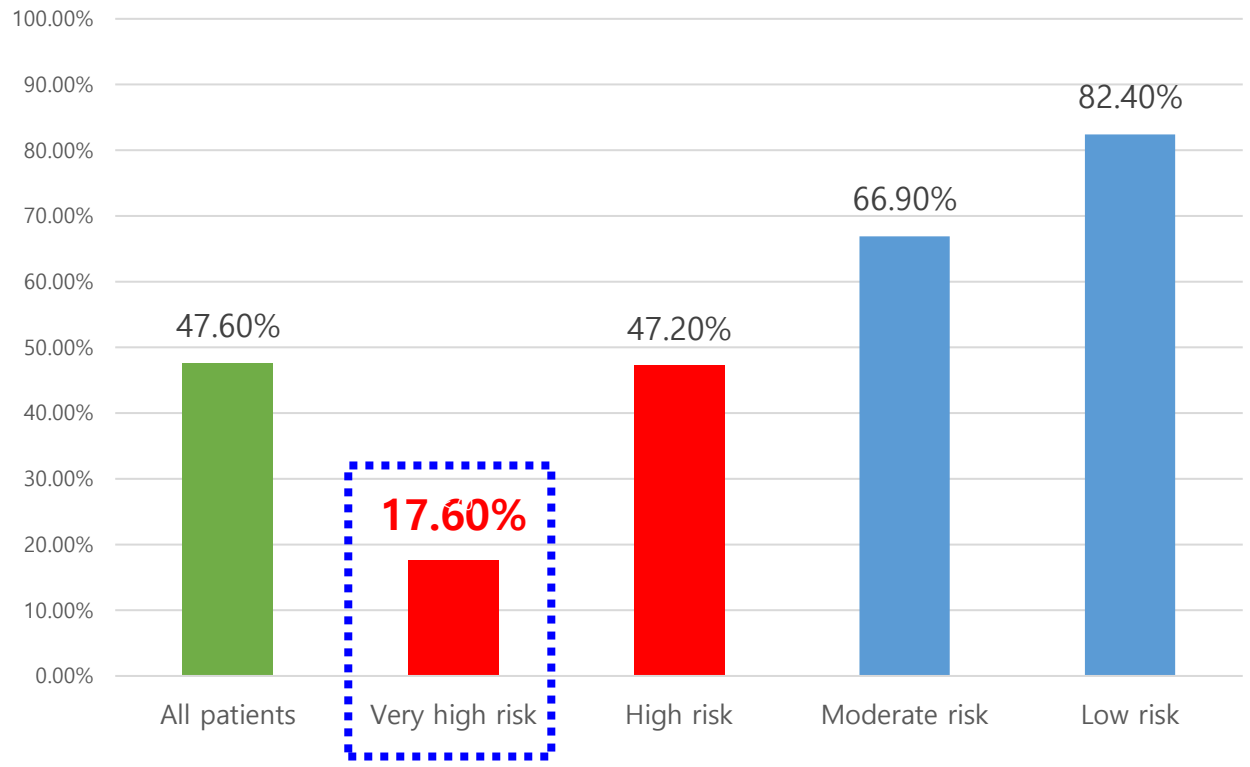
Patients with at least one diagnosis of dyslipidemia during the one year before the index date (n=69,942)

↓

Patients who achieved LDL-C goal (n=33,270)

Patients who did not achieve LDL-C goal (n=36,672)

LDL-C Target Achievement Rate



Patients (n=69,942), retrospective cohort study, using the National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS) database from 2006 to 2013.

Percentage of patients by risk group : Very high risk 36.7%, High risk 22.5%, Moderate risk 20.1%, Low risk 20.6%, as defined by the 2015 Korean guidelines

Ref.> Kim S. et al. PLoS One. 2020:15(1):e0228472

LDL-C goal attainment status and comparison of cardiovascular events

CV events	LDL-C goal achievers		LDL-C goal non-achievers		*P*-value[a]
	Number of events	Rates per 100 PYs	Number of events	Rates per 100 PYs	
Total CV events[b]	11,560	11.93	19,890	24.35	<0.0001
All-cause death	539	0.56	718	0.88	<0.0001
CV death	39	0.04	73	0.09	<0.0001
Acute coronary syndrome[c]	1,764	1.82	3,021	3.70	<0.0001
Ischemic stroke	1,686	1.74	3,584	4.39	<0.0001
Peripheral artery disease	7,571	7.81	12,567	15.38	<0.0001

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PY, person-year.

[a]*P*-values for differences between rates of LDL-C goal achievers and non-achievers.

[b]Total CV events included all-cause death, acute coronary syndrome, ischemic stroke, and peripheral artery disease.

[c]Acute coronary syndrome is a composite of myocardial infarction and unstable angina.

increasing risk by 2.5 times

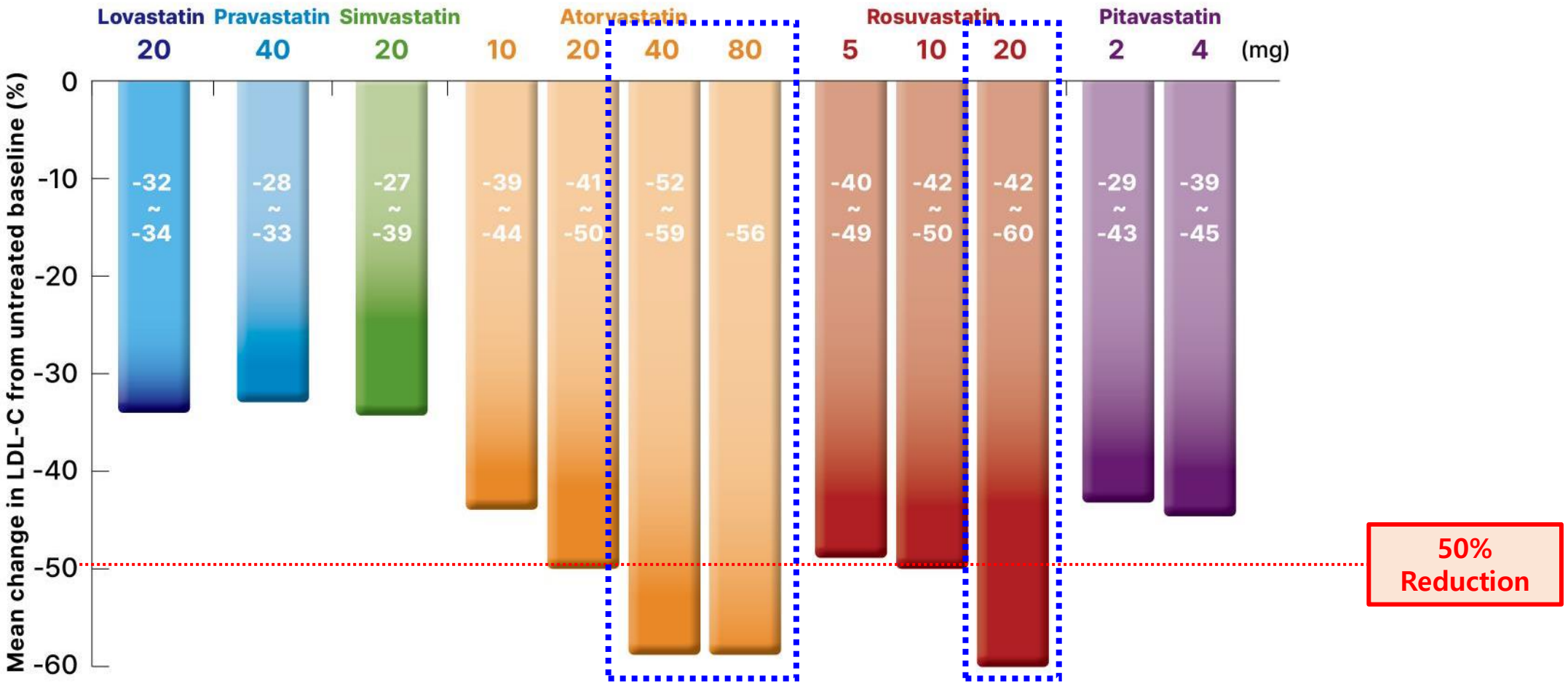
Patients (n=69,942), retrospective cohort study, using the National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS) database from 2006 to 2013.

Percentage of patients by risk group : Very high risk 36.7%, High risk 22.5%, Moderate risk 20.1%, Low risk 20.6%,

Ref.> Kim S. et al. PLoS One. 2020:15(1):e0228472

Limitations of Statin treatment (LDL-C lowering)

To achieve a reduction of 50% or more compared to baseline in high-risk/very-high-risk patients, high doses of ATV 40mg and RSV 20mg or more are recommended, as statin monotherapy has limitations in controlling LDL-C

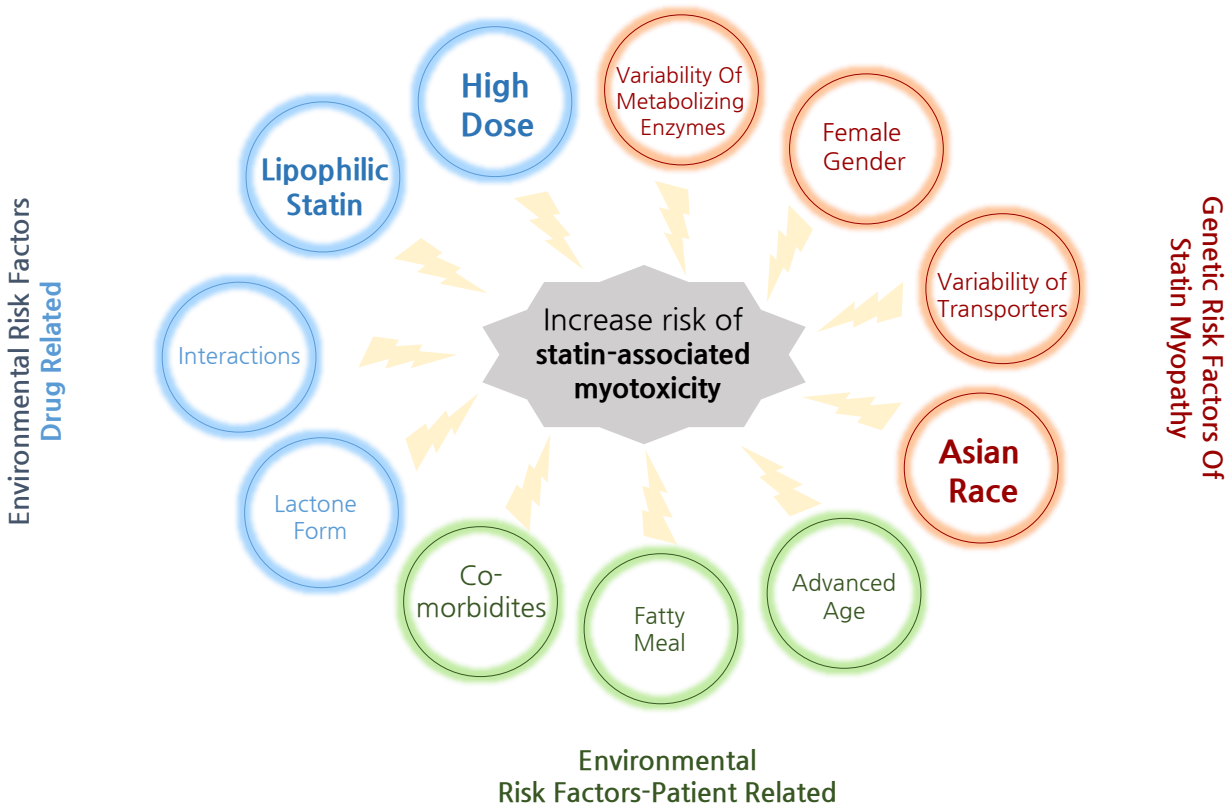


<Ref.> Korean Guidelines for the Management of Dyslipidemia 5th

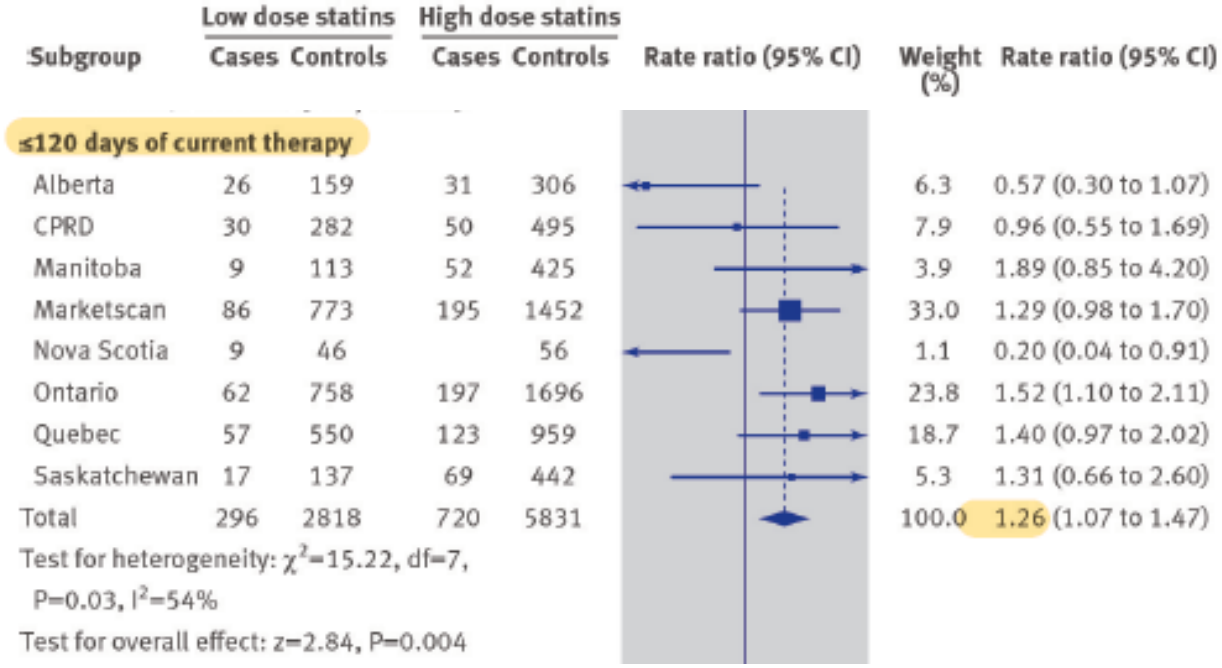
Limitations of Statin treatment (side effect)

Statin-related Muscle Symptoms (SAMS): Risk Factors

SAMS(Statin-Associated Muscle Symptoms): 스타틴 관련 근육 증상



New diabetes by High dose statin



Subgroup	Low dose statins Cases	Low dose statins Controls	High dose statins Cases	High dose statins Controls	Rate ratio (95% CI)	Weight (%)	Rate ratio (95% CI)
≤120 days of current therapy							
Alberta	26	159	31	306		6.3	0.57 (0.30 to 1.07)
CPRD	30	282	50	495		7.9	0.96 (0.55 to 1.69)
Manitoba	9	113	52	425		3.9	1.89 (0.85 to 4.20)
Marketscan	86	773	195	1452		33.0	1.29 (0.98 to 1.70)
Nova Scotia	9	46		56		1.1	0.20 (0.04 to 0.91)
Ontario	62	758	197	1696		23.8	1.52 (1.10 to 2.11)
Quebec	57	550	123	959		18.7	1.40 (0.97 to 2.02)
Saskatchewan	17	137	69	442		5.3	1.31 (0.66 to 2.60)
Total	296	2818	720	5831		100.0	1.26 (1.07 to 1.47)

Test for heterogeneity: χ^2=15.22, df=7, P=0.03, I^2=54%

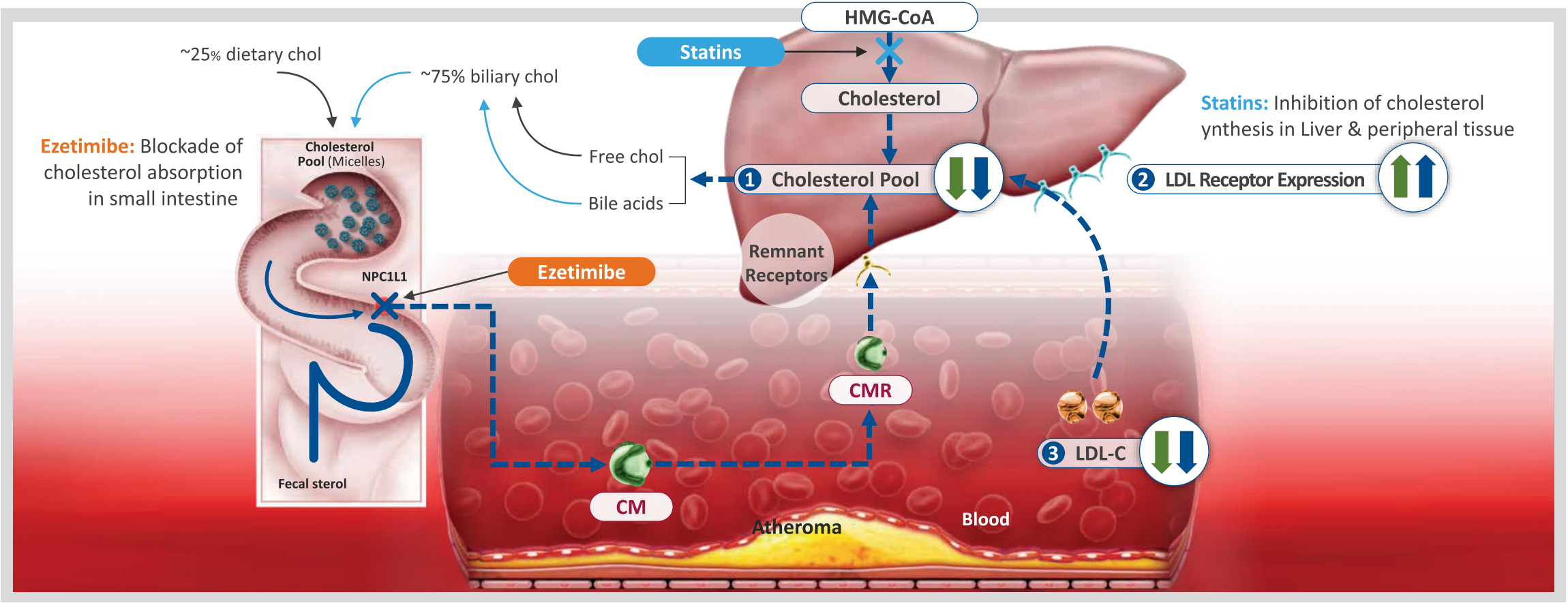
Test for overall effect: z=2.84, P=0.004

<Ref.> Taha DA, et al. Transl Res. 2014;164(2):85-109. / Dormuth CR, et al. BMJ. 2014;348:g3244.

Ezetimibe and Statins have complementary mechanisms of action

Together, Ezetimibe in combination with a statin provides:

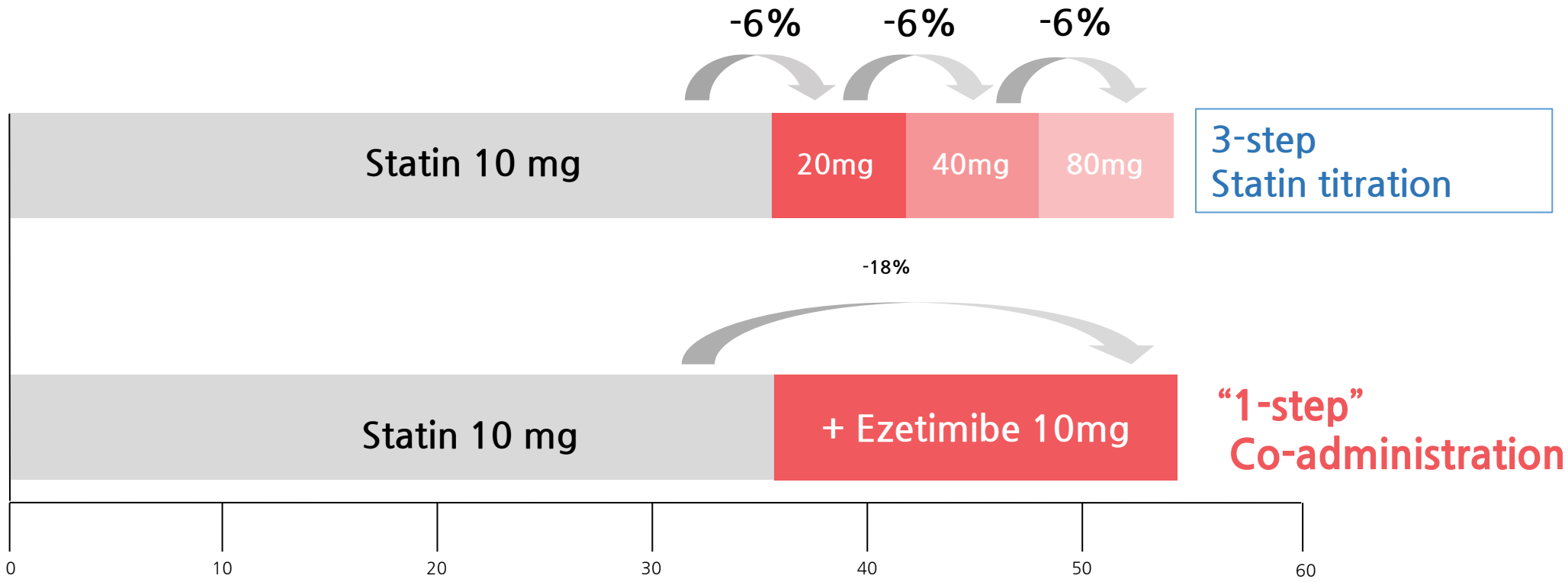
❶ Reduction of hepatic cholesterol ❷ Upregulation of hepatic LDL receptor expression ❸ Increased clearance of plasma LDL-C



NPC1L1=Niemann-Pick C1-like 1; HMG-CoA=3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

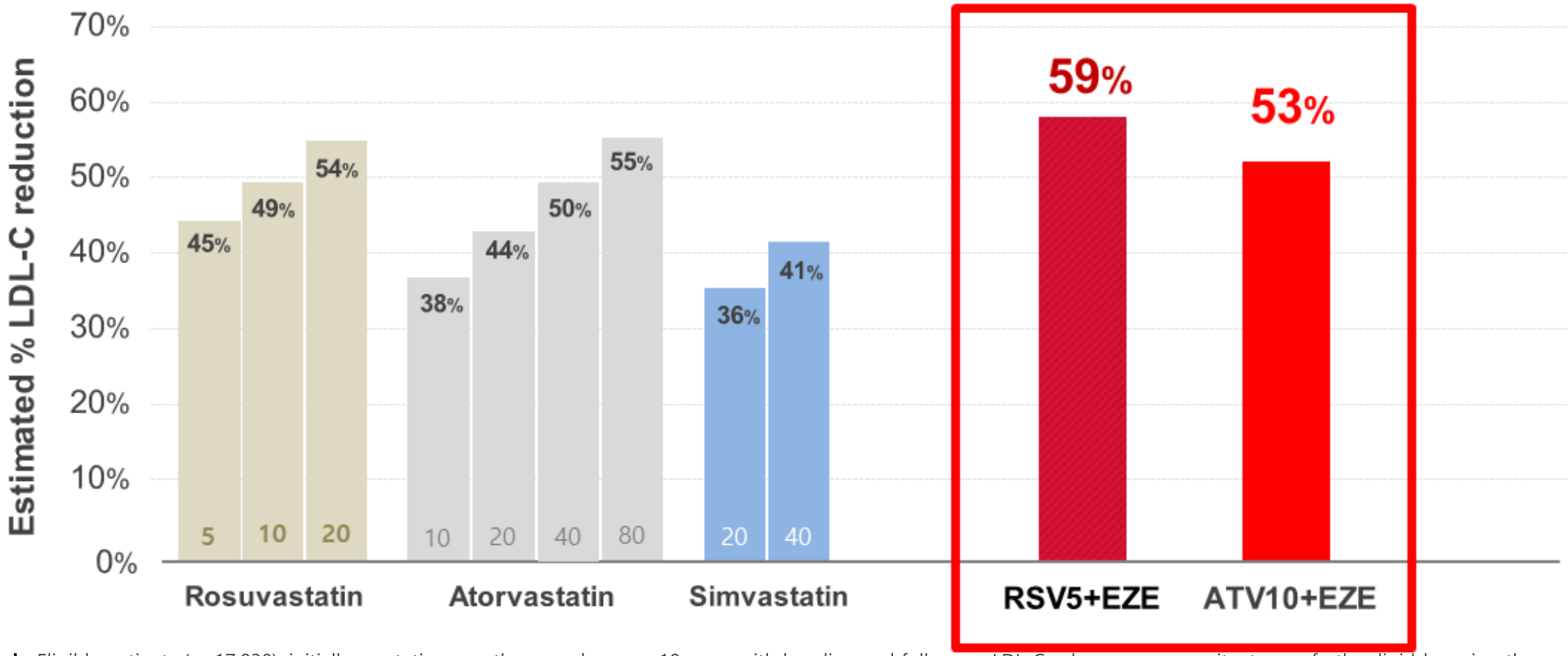
<Ref.> 1.Grigore L et al. Vas Health Risk Manag. 2008;4:267-278. 2. Bays HE, et al. Expert Rev Cardiovasc Ther. 2008;6(4):447-470.

LDL-C lowering : Statin up-titration vs Statin + Ezetimibe



<Ref.> Bays H, et al. Expert Opin Pharmacother. 2003;4(5):779-790.

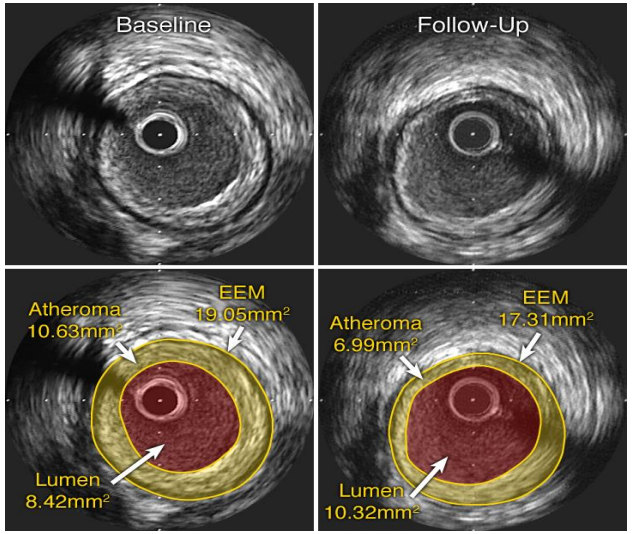
LDL-C lowering : Statin up-titration vs Statin + Ezetimibe



Method : Eligible patients (n=17,830), initially on statin monotherapy who were 18 years with baseline and follow-up LDL-C values, no concomitant use of other lipid-lowering therapy, and on lipid-lowering therapy for 42 days, were identified between November 1, 2002 and September 30, 2009. The percent change from baseline in LDL-C levels and the odds ratios for attainment of LDL-C,1.8 and 2.6 mmol/L (70 and 100 mg/dL) were estimated using an analysis of covariance and logistic regression, respectively, adjusted for various baseline factors.

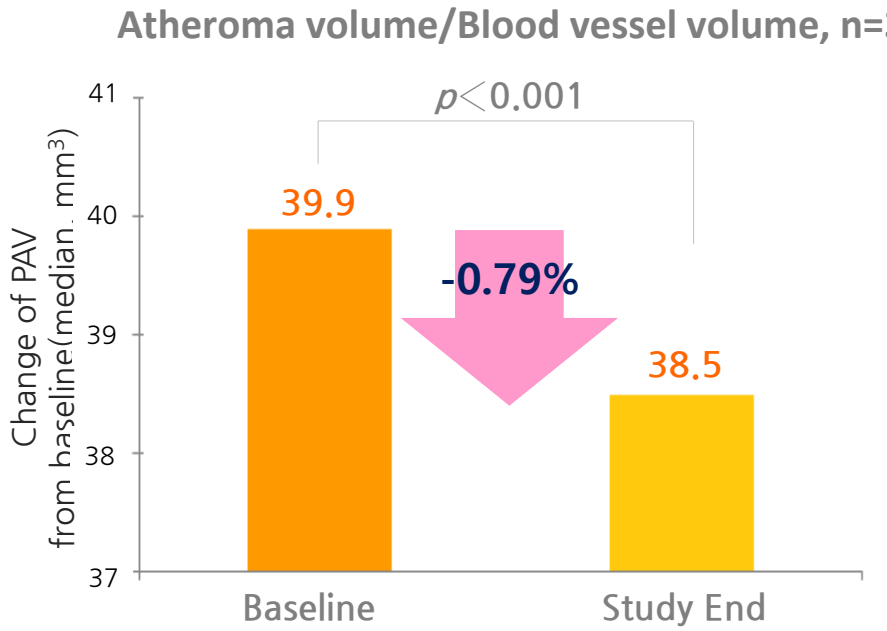
<Ref.> Foody JM, et al. Vasc Health Risk Manag 2013;9:719-727.

Patients Showing Plaque Regression (ASTEROID)

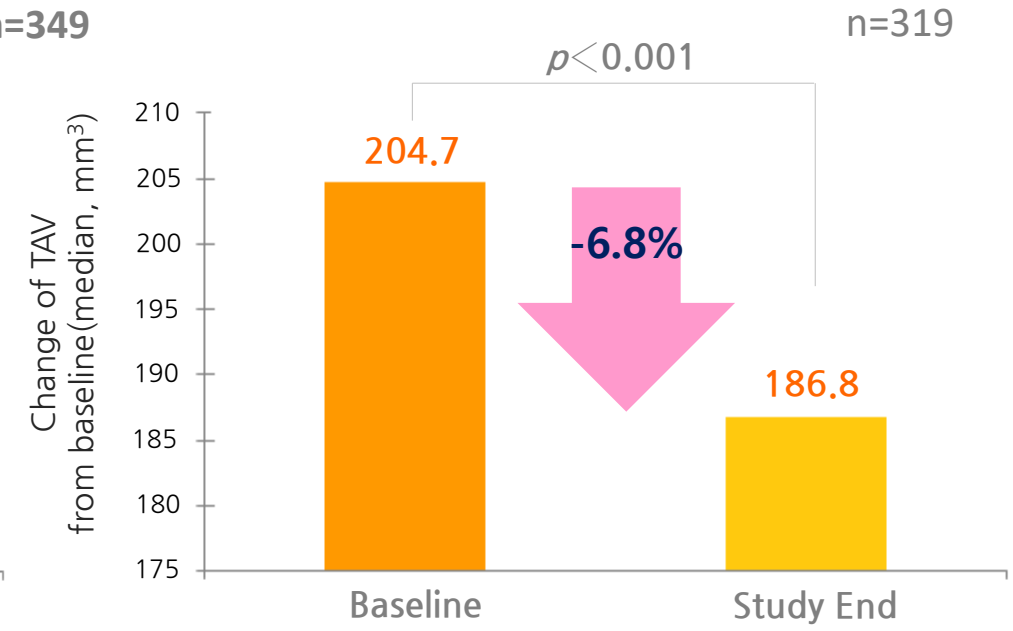


Regression of atheroma p<0.001

<Percent Atheroma Volume>



<Total Atheroma Volume>



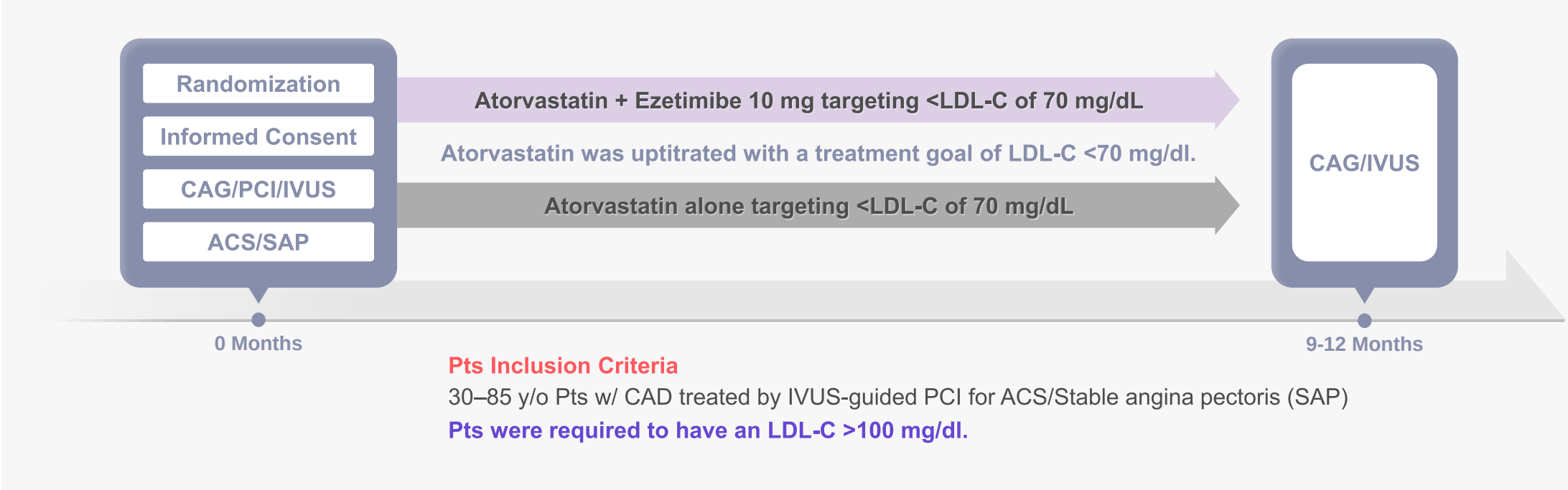
ASTEROID, A Study To Evaluate the Effect of ROsuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

- ✓ **Methods**: Prospective, open-label blinded end-points trial was performed at 53 community and tertiary care centers in the United States, Canada, Europe, and Australia. A motorized IVUS pullback was used to assess coronary atheroma burden at baseline and after 24 months of treatment. Each pair of baseline and follow-up IVUS assessments was analyzed in a blinded fashion. Between November 2002 and October 2003, 507 patients had a baseline IVUS examination and received at least 1 dose of study drug. After 24 months, 349 patients had evaluable serial IVUS examinations.
- ✓ **Result**:The mean (SD) baseline low-density lipoprotein cholesterol (LDL-C) level of **130.4 (34.3) mg/dL declined to 60.8 (20.0) mg/dL, a mean reduction of 53.2% (P<.001)**. Mean (SD) high-density lipoprotein cholesterol (HDL-C) level at baseline was 43.1 (11.1) mg/dL, increasing to 49.0 (12.6) mg/dL, an increase of 14.7% (P<.001). The mean (SD) change in PAV for the entire vessel was -0.98% (3.15%), with a median of -0.79% (97.5% CI, -1.21% to -0.53%) (P<.001 vs baseline). The mean (SD) change in atheroma volume in the most diseased 10-mm subsegment was -6.1 (10.1) mm3, with a median of -5.6 mm3 (97.5% CI, -6.8 to -4.0 mm3) (P<.001 vs baseline). Change in total atheroma volume showed a 6.8% median reduction; with a mean (SD) reduction of -14.7 (25.7) mm3, with a median of -12.5 mm3 (95% CI, -15.1 to -10.5 mm3) (P<.001 vs baseline). Adverse events were infrequent and similar to other statin trials.

Ref.> Nissen SE, et al. JAMA. 2006;295(13):1556-1565.

Regression of Coronary Atherosclerosis : PRECISE-IVUS Trial

- The aim of this study was to evaluate the effects of ezetimibe plus atorvastatin versus atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent PCI.



- Eligible pts who underwent PCI were randomly assigned to atorvastatin alone or atorvastatin + ezetimibe (10 mg) daily.

Randomization was stratified by
❶ gender, ❷ age, ❸ history of HTN, ❹ history of DM, ❺ history of PAD, ❻ serum LDL-C level,
❼ serum HDL-C level, ❽ serum TG level, and ❾ statin pretreatment prior to study enrollment.

Ref.> Tsujita, K. et al. J Am Coll Cardiol. 2015; 66: 495-507

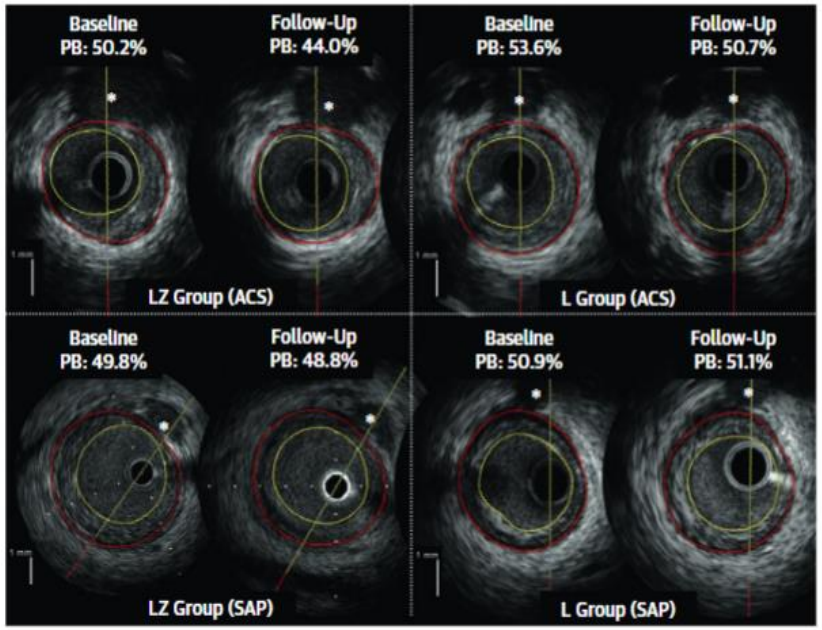
Regression of Coronary Atherosclerosis : PRECISE-IVUS Trial

TABLE 3 Demonstration of Coronary Plaque Progression/Regression

	Baseline			9-12 Months Follow-Up		
	LZ Group (n = 100)	L Group (n = 102)	p Value	LZ Group (n = 100)	L Group (n = 102)	p Value
Plaque volume, mm^3	72.6 (37.6 to 117.4)	76.3 (45.5 to 128.4)	0.5	69.6 (35.0 to 107.2)	77.3 (45.4 to 126.2)	0.2
Percent atheroma volume, %	51.3 ± 10.8	50.9 ± 11.4	0.8	49.3 ± 10.3	50.4 ± 11.6	0.5
TAV_{norm}, mm^3	89.6 (65.8 to 118.8)	84.8 (61.5 to 112.7)	0.7	85.4 (65.5 to 110.0)	87.2 (60.1 to 111.8)	0.6
Vessel volume, mm^3	144.4 (78.5 to 218.6)	159.8 (97.7 to 244.4)	0.3	141.8 (70.0 to 222.3)	155.7 (101.4 to 241.6)	0.2
Lumen volume, mm^3	70.4 (34.5 to 117.1)	79.4 (47.5 to 116.6)	0.3	65.8 (36.5 to 113.8)	79.1 (47.7 to 115.3)	0.2
Lesion length, mm	10.1 (5.6 to 14.6)	12.4 (7.5 to 16.0)	0.11	9.7 (5.8 to 14.5)	11.9 (7.2 to 15.9)	0.10

	Absolute Change				
	LZ Group (n = 100)	p Value Compared With Baseline	L Group (n = 102)	p Value Compared With Baseline	p Value Between Groups
Plaque volume, mm^3	-3.9 (-10.6 to 0.0)	<0.001	-1.0 (-6.8 to 5.7)	0.4	0.001
Percent atheroma volume, %	-1.4 (-3.4 to -0.1)	<0.001	-0.3 (-1.9 to 0.9)	0.03	0.001
ACS cohort	-2.3 (-3.7 to -0.5)	<0.001	-0.2 (-1.3 to 0.5)	0.2	<0.001
SAP cohort	-1.2 (-2.2 to -0.1)	0.001	-0.7 (-2.3 to 1.1)	0.08	0.2
TAV_{norm}, mm^3	-5.3 (-12.4 to 0.1)	<0.001	-1.2 (-5.7 to 3.3)	0.1	<0.001
Vessel volume, mm^3	-4.1 (-12.6 to 3.1)	0.001	-0.6 (-11.8 to 10.6)	0.9	0.04
Lumen volume, mm^3	-0.3 (-4.9 to 4.0)	0.4	0.8 (-5.6 to 6.9)	0.5	0.4

FIGURE 3 Plaque Progression/Regression



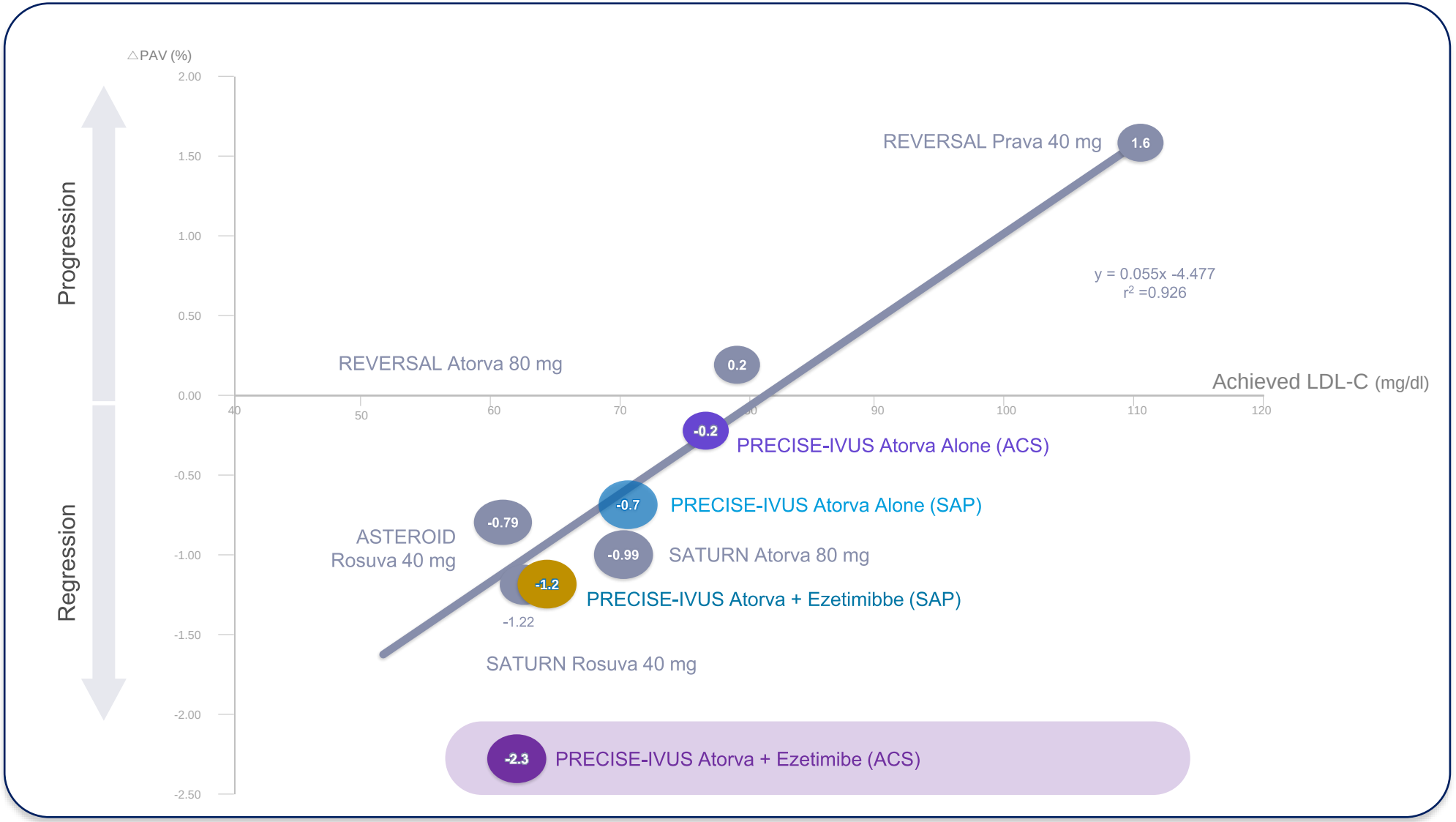
IVUS images of the same cross sections at baseline and follow-up show outlined leading edges of lumen **(yellow line)** and external elastic membrane **(red line)**. Note the substantial reduction in plaque area observed for the cross-sectional images, especially in the LZ group versus the L group.*Side branches show same position and shape. PB = plaque burden; other abbreviations as in Figures 1 and 2.

PRECISE-IVUS, Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound

✓ **Methods**: prospective, randomized, controlled, multicenter study. Eligible patients who underwent PCI were randomly assigned to atorvastatin alone or atorvastatin plus ezetimibe (10 mg) daily. Atorvastatin was uptitrated witha treatment goal of low-density lipoprotein cholesterol (LDL-C) <70 mg/dl. Serial volumetric intravascular ultrasound was performed at baseline and again at 9 to 12 months to quantify the coronary plaque response in 202 patients

Ref.> Tsujita, K. et al. J Am Coll Cardiol. 2015; 66: 495-507

Relationship between achieved LDL-C and Change in Atheroma volume

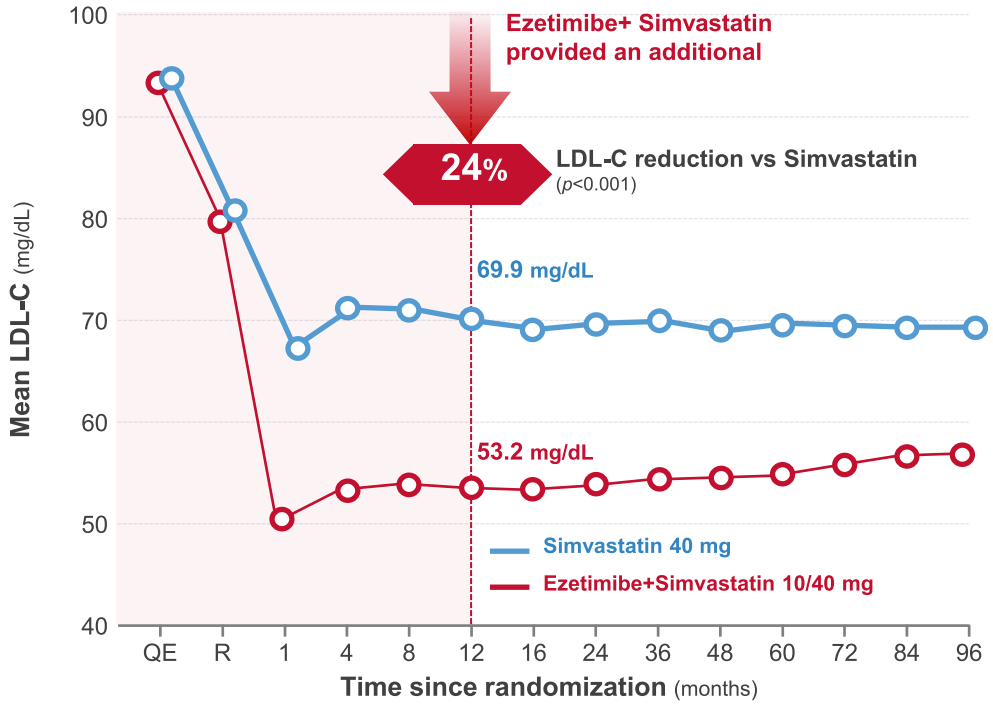


IMPROVE-IT Trial

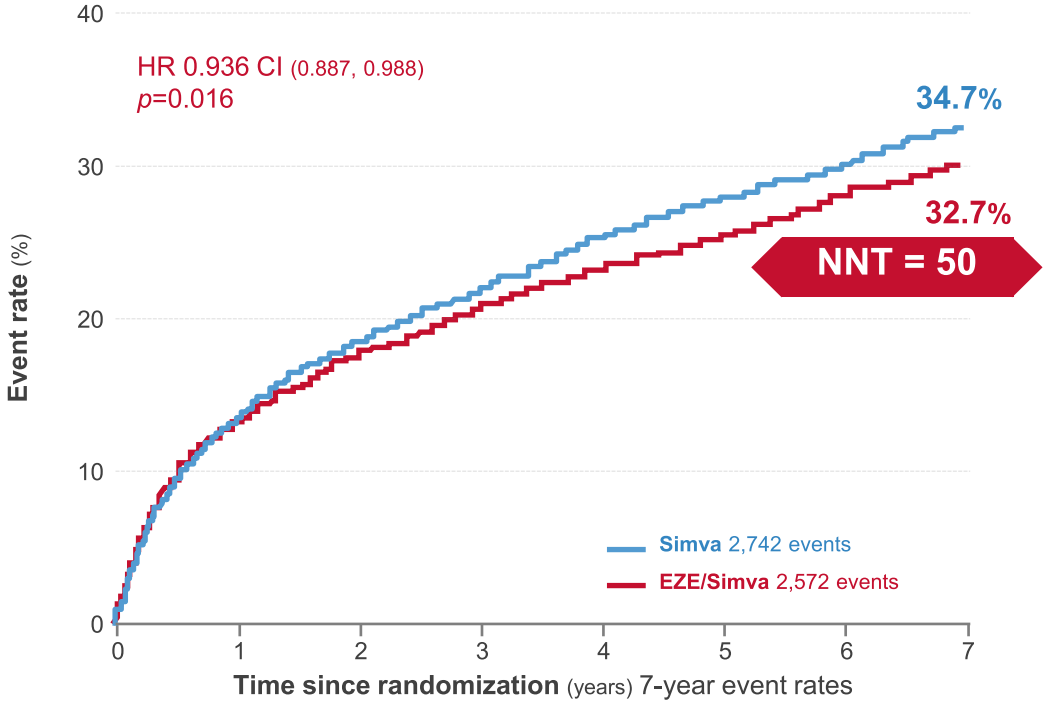
Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes (ACS)

Patient	18,144 patients with ACS
Intervention	Simvastatin 40mg + Ezetimibe 10mg (n=9,067)
Comparison	Simvastatin 40mg (n=9,077)
Outcomes	Composite of cardiovascular death, MI, stroke, hospitalization for UA or revascularization (median f/u 6 years)

LDL-C 수치 감소



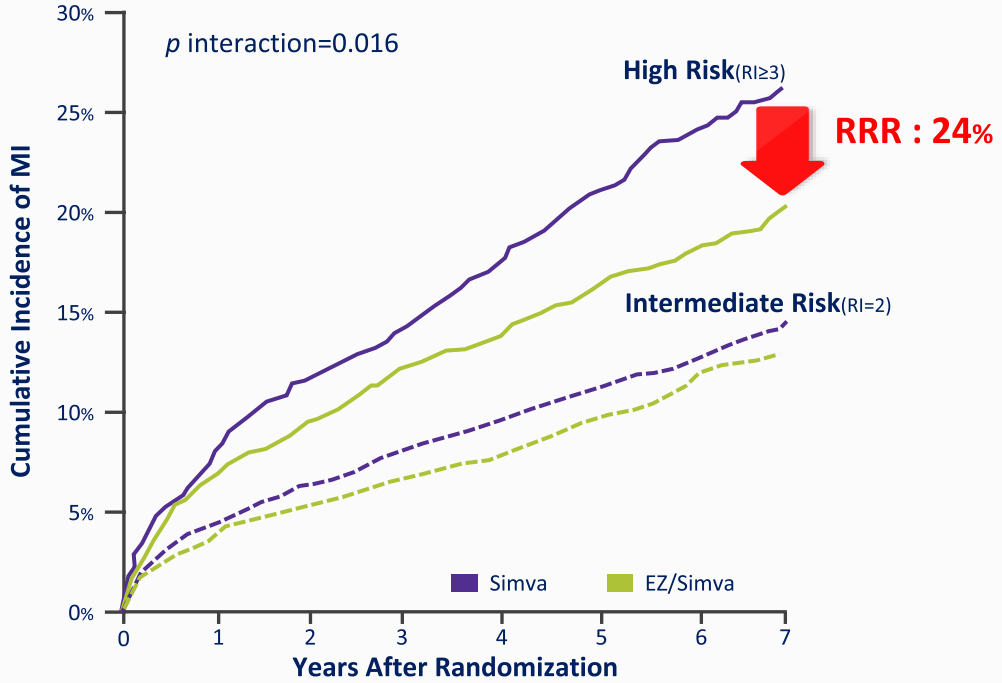
Primary endpoint



N Engl J Med. 2015;372;2387-97

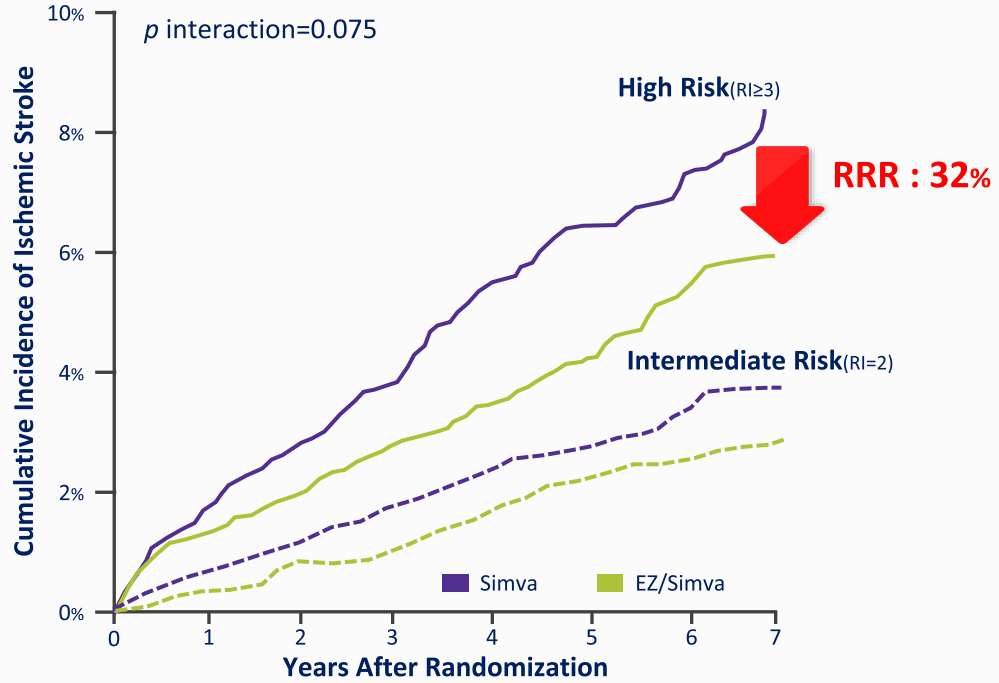
Ezetimibe demonstrated 24% In MI & 32% in Ischemic Stroke when added to statin therapy in high risk patients

Outcomes by Risk Category and Randomized Treatment : MI*



		7yr KM	ARR	HR
High risk	Simva	26.2%	5.9% (2.9, 9.1)	0.76 (0.66, 0.88)
	Ez/Simva	20.3%		
Intermediate risk	Simva	14.4%	1.5% (-0.5, 3.7)	0.87 (0.74, 1.02)
	Ez/Simva	12.9%		

Outcomes by Risk Category and Randomized Treatment : Ischemic stroke**



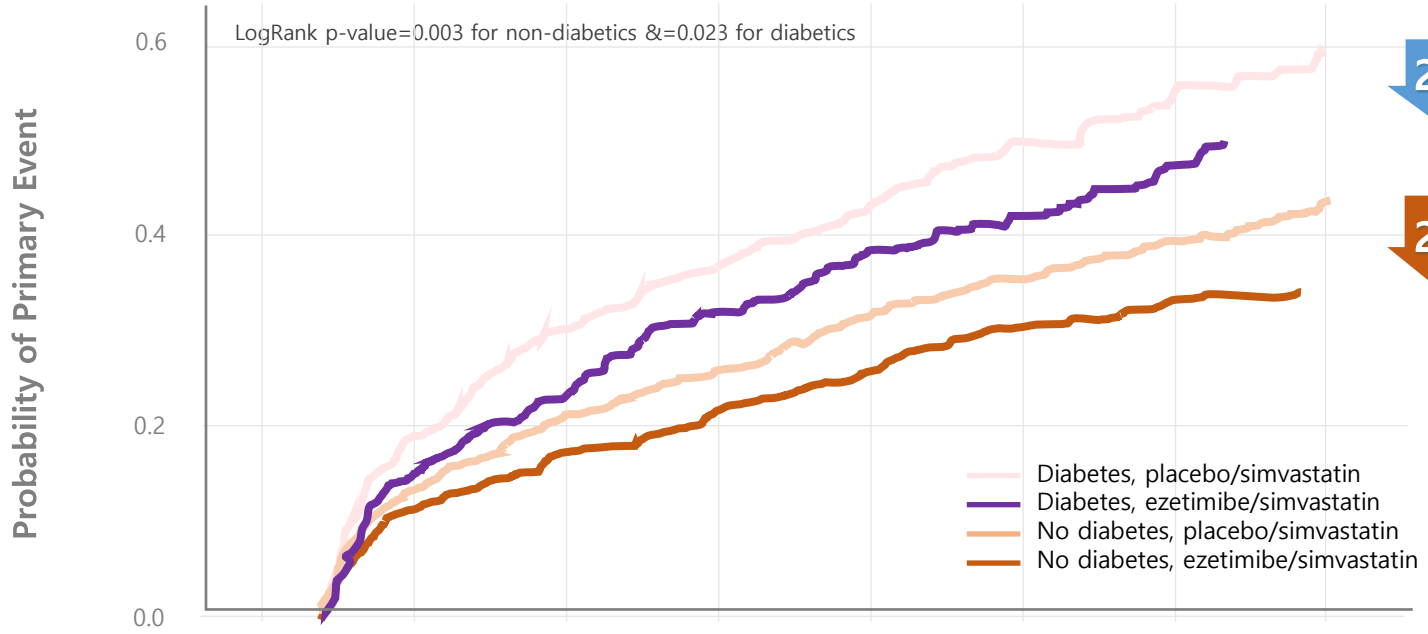
		7yr KM	ARR	HR
High risk	Simva	8.4%	2.4% (0.4, 4.4)	0.68 (0.52, 0.88)
	Ez/Simva	6.0%		
Intermediate risk	Simva	3.8%	1.0% (-0.2, 2.1)	0.75 (0.54, 1.05)
	Ez/Simva	2.8%		

Ref > 1. Bohula EA, *et al.* Atherothrombotic risk stratification and Ezetimibe for secondary prevention. *Journal of the american college of cardiology.* 2017;69(8):911-921

[IMROVE-IT subgroup]

The CV benefit of Ezetimibe add-on therapy in elderly patients ≥75 years old with DM or non-DM

KM curves for the primary efficacy endpoint* in subjects with age ≥75years of age stratified by DM status[1]



20% HR 0.80 (95% CI, 0.65-0.99) *p*=0.039

21% HR 0.79 (95% CI, 0.68-0.92) *p*=0.003

	0	1	2	3	4	5	6	7
Diabetes, placebo/simvastatin	968	778	706	645	572	394	296	177
Diabetes, ezetimibe/simvastatin	**1009**	**784**	**698**	**639**	**551**	**397**	**283**	**159**
No diabetes, placebo/simvastatin	402	300	258	228	200	133	93	48
No diabetes, ezetimibe/simvastatin	**418**	**300**	**248**	**213**	**178**	**114**	**66**	**31**

Time (year) **post-randomization**

Ref> Giugliano RP,et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes: Results from IMPROVE-IT. Circulation. 2018;137:1571–1582.

[IMPROVE-IT : Long-term Safety]

Simva/Eze vs. Simva after ACS Among Patients ≥75 Years Starting EZE/ATV Combo

Table 2. Safety End Points According to Age at Randomization and Treatment

	Patient Age Group by Treatment, No. (%)					
	<65 y		65-74 y		≥75 y	
	Simvastatin Monotherapy (n = 5129)	Simvastatin-Ezetimibe (n = 5044)	Simvastatin Monotherapy (n = 2520)	Simvastatin-Ezetimibe (n = 2653)	Simvastatin Monotherapy (n = 1428)	Simvastatin/Ezetimibe (n = 1370)
Liver-related events						
ALT or AST level or both ≥3 × ULN	108 (2.1)	128 (2.5)	51 (2.0)	60 (2.3)	49 (3.4)	36 (2.6)
Gallbladder-related adverse events	169 (3.3)	138 (2.7)	105 (4.2)	100 (3.8)	47 (3.3)	44 (3.2)
Muscle-related events						
Rhabdomyolysis	6 (0.1)	5 (0.1)	9 (0.4)	5 (0.2)	3 (0.2)	3 (0.2)
Myopathy	4 (0.1)	7 (0.1)	5 (0.2)	7 (0.3)	1 (0.1)	1 (0.1)
Myalgia	52 (1.0)	53 (1.1)	34 (1.3)	25 (0.9)	16 (1.1)	11 (0.8)
Myalgia with CK	17 (0.3)	16 (0.3)	9 (0.4)	5 (0.2)	5 (0.4)	5 (0.4)
Myopathy/rhabdomyolysis/myalgia with CK	27 (0.5)	28 (0.6)	22 (0.9)	16 (0.6)	9 (0.6)	9 (0.7)
Any cancer	368 (7.2)	378 (7.5)	335 (13.3)	339 (12.8)	212 (14.8)	192 (14.0)
Cataracts	106 (2.1)	116 (2.3)	134 (5.3)	151 (5.7)	85 (6.0)	81 (5.9)
Cognitive impairment	110 (2.1)	107 (2.1)	61 (2.4)	72 (2.7)	68 (4.8)	64 (4.7)

Ref> Bach RG, et al. JAMA Cardiol. doi:10.1001/jamacardio.2019.2306

[RACING] Long-term efficacy and Safety :
Moderate intensity statin with Ezetimibe vs High intensity statin


THE LANCET

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ARTICLES | VOLUME 400, ISSUE 10349, P380-390, JULY 30, 2022

Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial

Prof Byeong-Keuk Kim, MD * · Sung-Jin Hong, MD * · Yong-Joon Lee, MD · Soon Jun Hong, MD · Prof Kyeong Ho Yun, MD · Prof Bum-Kee Hong, MD · et al. Show all authors · Show footnotes

Published: July 18, 2022 · DOI: https://doi.org/10.1016/S0140-6736(22)00916-3 · Check for updates

- **Objective**

: this RACING trial sought to compare 3-year clinical efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients who are at very high risk for cardiovascular diseases. We sought to establish that adding ezetimibe to moderate-intensity statin could be an effective treatment for lowering cholesterol.

prospective, multicenter, open, randomized study, phase 4 clinical trial

Clinical CVD, Age 19-80 (n=3,780)

Moderate Intensity Statin + Ezetimibe
(ROS/EZE10/10mg) (N=1,890)

High Intensity Statin (Rosuvastatin 20mg) (N=1,890)

Non inferior

Regular clinical visits

Day 0 | 2 months | 6 months | 12 months | 24 months | 36 months

Randomization

Laboratory study

Primary Endpoint

Composite of CV death, major CV events* or nonfatal stroke within 3 years

*Any revascularization and hospitalization for CV events

Secondary Endpoint

- **Proportion of patients with LDL-C <70 mg/dL at 1, 2, and 3 years**
- **Composite of all death, major CV event, or nonfatal stroke**
- **Discontinuation or dose-reduction of study drug by intolerance**
- **Clinical adverse events**

LDL-C, low density lipoprotein cholesterol; CV, cardiovascular; CVD, cardiovascular disease.

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

[RACING] Long-term efficacy and Safety :
Moderate intensity statin with Ezetimibe vs High intensity statin

The primary endpoint occurred in **172 patients (9·1%) in the combination therapy** group and **186 patients (9·9%) in the high-intensity statin monotherapy** group (absolute difference −0·78%; 90% CI −2·39 to 0·83)

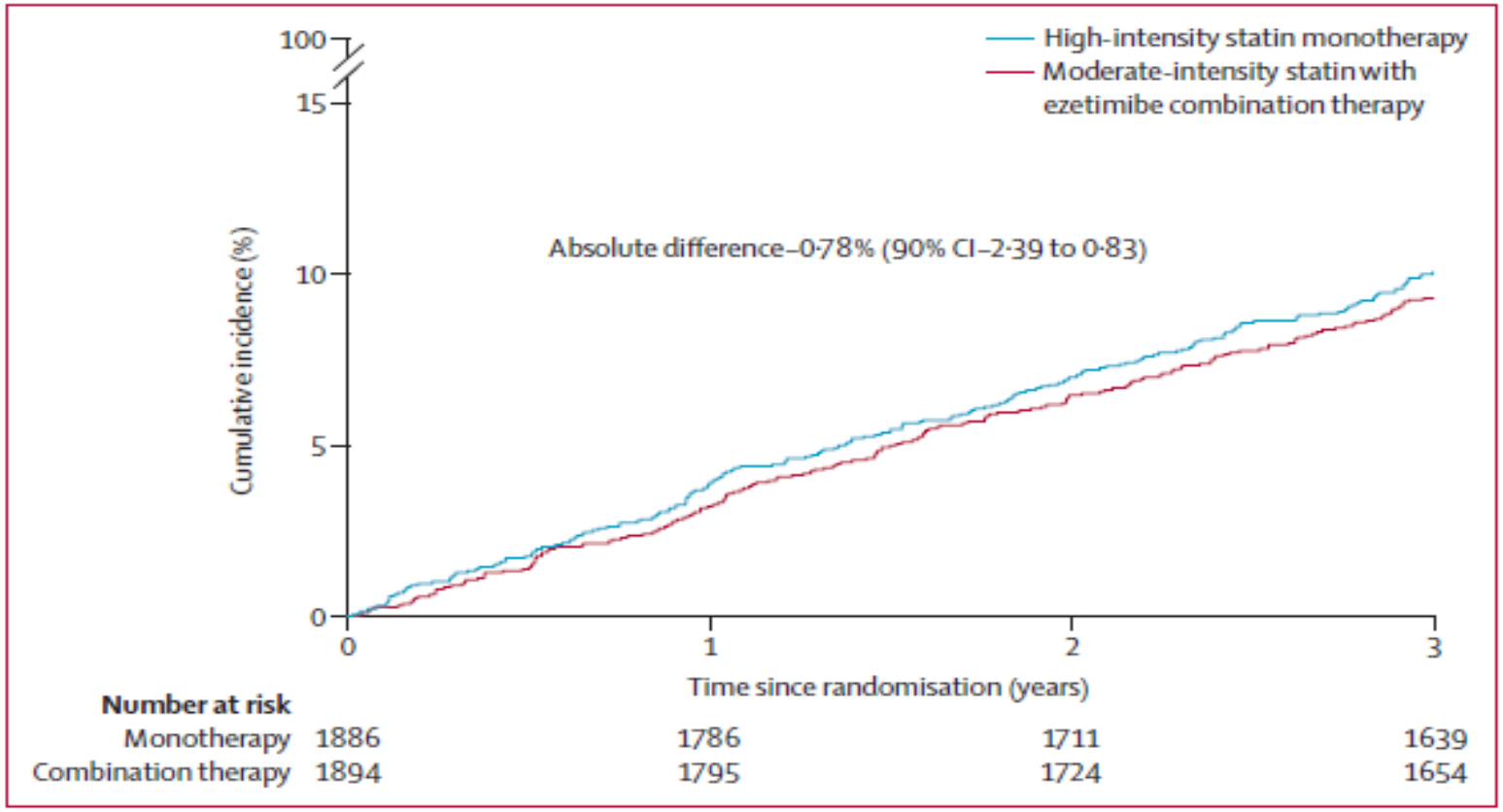


Figure 2: **Kaplan-Meier curves of the primary endpoint of the intention-to-treat population**

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

[RACING] Long-term efficacy and Safety :
Moderate intensity statin with Ezetimibe vs High intensity statin

Moderate intensity statin with Ezetimibe has a higher proportion of patients who achieved LDL cholesterol concentration of less than 70 mg/dL

	Moderate-intensity statin with ezetimibe combination therapy	High-intensity statin monotherapy	Absolute differences in proportions, % (95% CI)
1 year			
Number of patients	1675	1673	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1217 (73%)	923 (55%)	17·5 (14·2 to 20·7)
LDL cholesterol concentration (mg/dL)	58 (47–71)	67 (55–80)	..
2 years			
Number of patients	1558	1539	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1168 (75%)	924 (60%)	14·9 (11·6 to 18·2)
LDL cholesterol concentration (mg/dL)	57 (45–70)	65 (53–79)	..
3 years			
Number of patients	1349	1315	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	978 (72%)	759 (58%)	14·8 (11·1 to 18·4)
LDL cholesterol concentration (mg/dL)	58 (47–71)	66 (54–80)	..

Data are number of patients (%) or median (IQR).

Table 3: **Proportions of the patients with LDL cholesterol concentrations <70 mg/dL in the intention-to-treat population**

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

[RACING] Long-term efficacy and Safety :
Moderate intensity statin with Ezetimibe vs High intensity statin

	Moderate-intensity statin with ezetimibe combination therapy (n=1846)	High-intensity statin monotherapy (n=1832)	Absolute difference (95% CI)
Serious adverse events			
Death	26 (1·4%)	22 (1·2%)	0·21 (−5·88 to 1·01)
Adverse events			
Discontinuation or dose reduction of study drug due to intolerance	88 (4·8%)	150 (8·2%)	−3·42 (−5·07 to −1·80)
Reported symptoms			
Dizziness or general weakness	10	21	..
Chest discomfort or headache	7	12	..
Gastrointestinal symptoms	4	9	..
Urticaria or itching sensation	6	7	..
Myalgia	7	22	..
Other	5	3	..
Physician discretion			
Liver enzyme elevation	15	32	..
Creatine kinase elevation	25	33	..
Fasting glucose concentration elevation	5	6	..
Other	4	5	..
New-onset diabetes	145 (7·9%)	159 (8·7%)	−0·82 (−2·65 to 1·00)
New-onset diabetes with anti-diabetic medication initiation	95 (5·1%)	107 (5·8%)	..
Muscle-related adverse events	21 (1·1%)	34 (1·9%)	0·69 (−2·22 to 0·82)
Myalgia	17 (0·9%)	29 (1·6%)	0·66 (−1·46 to 1·06)
Myopathy	2 (0·1%)	4 (0·2%)	−0·11 (−0·50 to 0·25)
Myonecrosis*	11 (0·6%)	13 (0·7%)	0·11 (−0·72 to 0·48)
Mild	8	9	..
Moderate	2	3	..
Severe including rhabdomyolysis	1	1	..
Gallbladder-related adverse events	13 (0·7%)	7 (0·4%)	0·32 (−0·22 to 0·89)
Major bleeding	17 (0·9%)	13 (0·7%)	0·21 (−0·44 to 0·87)
Cancer diagnosis	37 (2·0%)	28 (1·5%)	0·48 (−0·43 to 0·14)
New-onset neurocognitive disorder	4 (0·2%)	2 (0·1%)	0·11 (−0·25 to 0·50)
Cataract surgery	19 (1·0%)	21 (1·1%)	−0·12 (−0·86 to 0·62)

Data are n (%). These events were adverse events of special interest in this study. ULN=upper limit of normal. *Severity of myonecrosis was classified by an elevation of creatine kinase concentration compared with either baseline concentration or the ULN: mild >3 times ULN; moderate ≥10 times ULN; severe ≥50 times ULN.

Table 4: **Secondary safety endpoint of the safety population**

Discontinuation or dose reduction of study medication owing to adverse events or intolerance occurred in **88 patients (4·8%) in the combination therapy** group and **150 patients (8·2%) in the high-intensity statin monotherapy group (p<0·0001).**

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

[LOADSTAR] Long-term efficacy and Safety :
Treat-to-Target or High-Intensity Statin in Patients with CAD

QUESTION Is treatment to a goal low-density lipoprotein cholesterol (LDL-C) level between 50 and 70 mg/dL noninferior to a strategy using high-intensity statin therapy among patients with coronary artery disease?

CONCLUSION This randomized clinical trial found that the treat-to-target LDL-C strategy was noninferior to the high-intensity statin strategy for major clinical outcomes.

POPULATION

3172 Men
1228 Women

Adults with clinically diagnosed coronary artery disease (ie, stable ischemic heart disease or acute coronary syndrome)

Mean age: 65.1 years

LOCATIONS

12
Centers in South Korea

INTERVENTION

Treat to target
Titrated-intensity statin therapy, with an LDL-C level between 50 and 70 mg/dL as the target

High-intensity statin
Rosuvastatin, 20 mg, or atorvastatin, 40 mg, once daily

PRIMARY OUTCOME

3-Year composite of death, myocardial infarction, stroke, or coronary revascularization with a noninferiority margin of 3.0 percentage points

FINDINGS

Primary end point

Treat to target
8.1% (177 of 2200 patients)

High-intensity statin
8.7% (190 of 2200 patients)

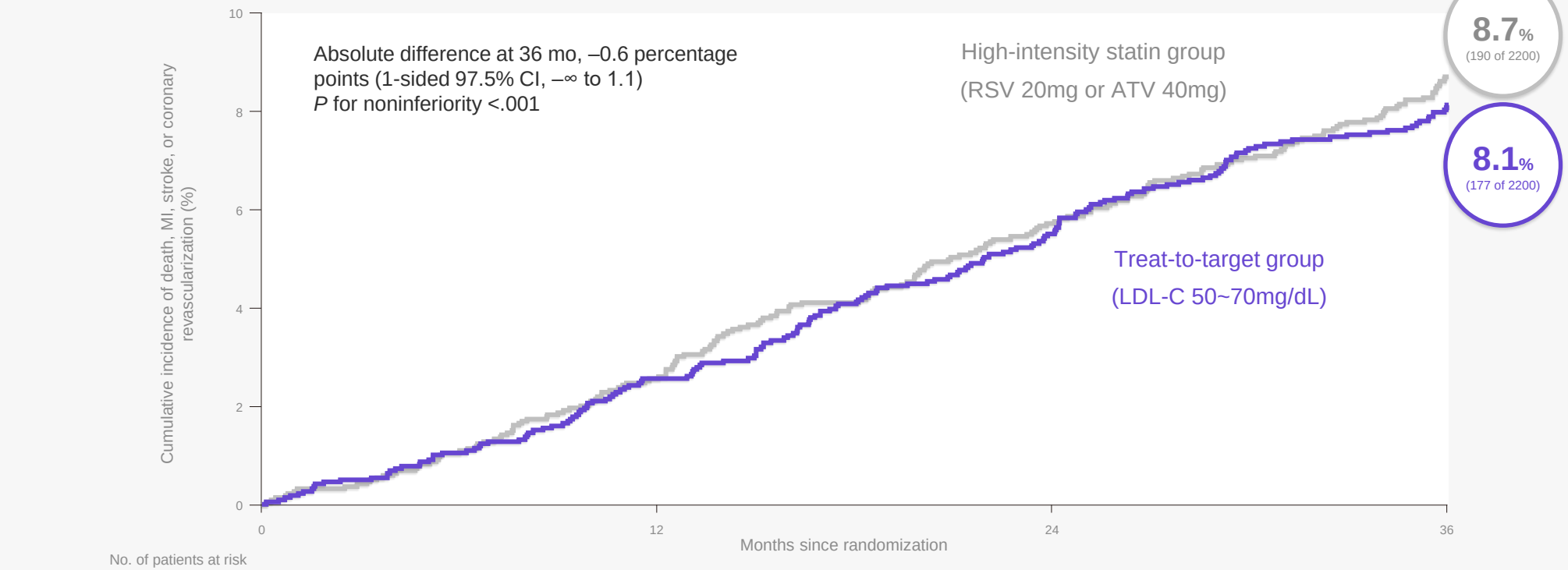
Treat-to-target LDL-C strategy was noninferior to high-intensity statin strategy:

Absolute difference,
−0.6 percentage points
(1-sided 97.5% CI, −∞ to 1.1)

Hong SJ, Lee YJ, Lee SJ, et al; LODESTAR Investigators. Treat-to-target or high-intensity statin in patients with coronary artery disease: a randomized clinical trial. *JAMA*. Published March 6, 2023. doi:10.1001/jama.2023.2487

[LOADSTAR] Long-term efficacy and Safety :
Treat-to-Target or High-Intensity Statin in Patients with CAD

Cumulative incidence of the primary end point



No. of patients at risk

High-intensity statin group	2200	2127	2056	1985
Treat-to-target group	2200	2123	2054	1989

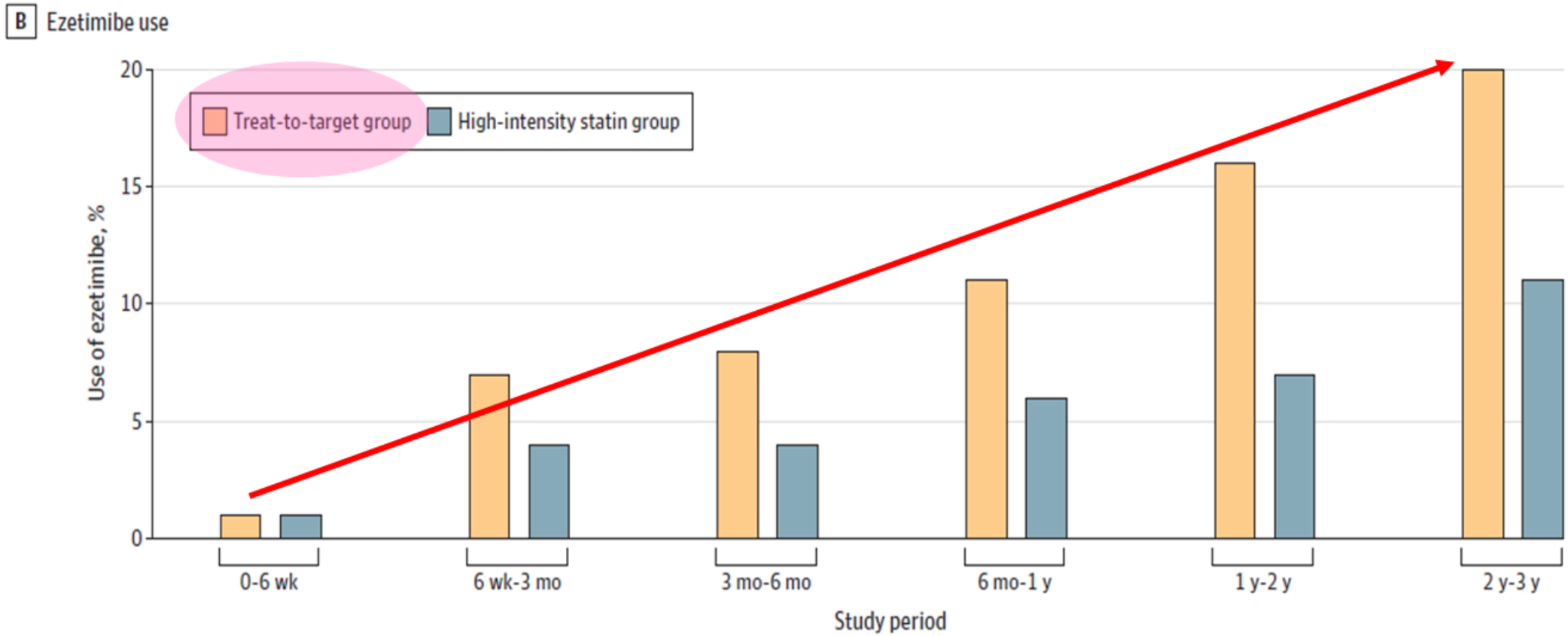
Adapted from Hong SJ, *et al.*

LODESTAR : Low-Density Lipoprotein Cholesterol-Targeting Statin Therapy Versus Intensity-Based Statin Therapy in Patients With Coronary Artery Disease, **MI :** Myocardial infarction, **CI :** Confidence interval, **mo :** Month, **CAD :** Coronary artery disease, **MACE :** Major adverse cardiovascular events

Study design a. This randomized, multi center, noninferiority study was to assess whether a treat-to-target strategy is noninferior to a strategy of high-intensity statins for long-term clinical outcomes in patients with coronary artery disease. Eligible patients (N=4,400) were randomized in a 1:1 manner to receive a statin using either the targeted strategy of titrated-intensity statin therapy (treat-to-target) (n=2,200) or the strategy of high-intensity statin therapy (n=2,200). The patients were stratified by baseline LDL-C levels of 100 mg/dL or greater, acute coronary syndrome, and the presence of diabetes. Primary end point was a 3-year composite of death, myocardial infarction, stroke, or coronary revascularization with a noninferiority margin of 3.0 percentage points.

1. Hong SJ, *et al*. Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease: A Randomized Clinical Trial. *JAMA*. 2023 Apr 4;329(13):1078-1087.

[LOADSTAR] Use of Ezetimibe
Treat-to-Target or High-Intensity Statin in Patients with CAD



[LOADSTAR] Long-term efficacy and Safety :
Treat-to-Target or High-Intensity Statin in Patients with CAD

크레젯 리토바젯

Secondary end points at 3 years after randomization

Outcome	Patients, No. (%) Treat-to-target group (n = 2200)	Patients, No. (%) High-intensity statin group (n = 2200)	Absolute difference, % (95% CI)*	*P* value
Composite of new-onset diabetes, aminotransferase or creatine kinase elevation, or end-stage kidney disease (post hoc)	**132 (6.1)**	**177 (8.2)**	**−2.1 (−3.6 to −0.5)**	**.009**
New-onset diabetes	121 (5.6)	150 (7.0)	−1.3 (−2.8 to 0.1)	.07
Initiation of antidiabetic medication	73	105		
Cataract operation	43 (2.0)	42 (1.9)	0.1 (−0.8 to 0.9)	.90
Discontinuation of statin therapy	31 (1.5)	46 (2.2)	−0.7 (−1.5 to 0.1)	.09
Composite of laboratory abnormalities**	18 (0.8)	30 (1.3)	−0.5 (−1.1 to 0.1)	.11
Aminotransferase elevation	8	12		
Creatine kinase elevation	3	8		
Creatinine elevation	7	11		
Peripheral artery revascularization	12 (0.6)	17 (0.8)	−0.2 (−0.8 to 0.3)	.35
Hospitalization due to heart failure	13 (0.6)	7 (0.3)	0.3 (−0.1 to 0.7)	.17
End-stage kidney disease	3 (0.1)	10 (0.5)	−0.3 (−0.7 to 0.0)	.05

Daewoong Pharmaceutical’s Product information

DAEWOONG

Litorvazet (Ezetimibe/Atorvastatin)

▣제품정보

1.제품명 : **리토바젯 정(Litorvazet Tab.)**

2.성분명 : 에제티미브 / 아토르바스타틴 (Ezetimibe/Atorvastatin)

10/5mg(6월 출시 예정), 10/10mg, 10/20mg, 10/40mg

3.적응증 : 원발성 고콜레스테롤혈증, 동형접합 가족형 고콜레스테롤혈증(HoFH)

4.용법용량 : 식사와 관계없이 1일 1회 투약(하루 중 아무 때나)

10/5mg	10/10mg	10/20mg	10/40mg
	A | 10	A | 20	A | 40
11.6 x 5.6 x 4.6 mm	12 x 5.4 x 4 mm	13.6 x 5.8 x 4.4 mm	16.2 x 6.5 x 5 mm
636원(예정)	637원	808원	1,203원

※ 약물의 실제 크기와 다르며 사이즈는 장축x단축x두께로 나타냄

Crezet (Ezetimibe/Rosuvastatin)

▣제품정보

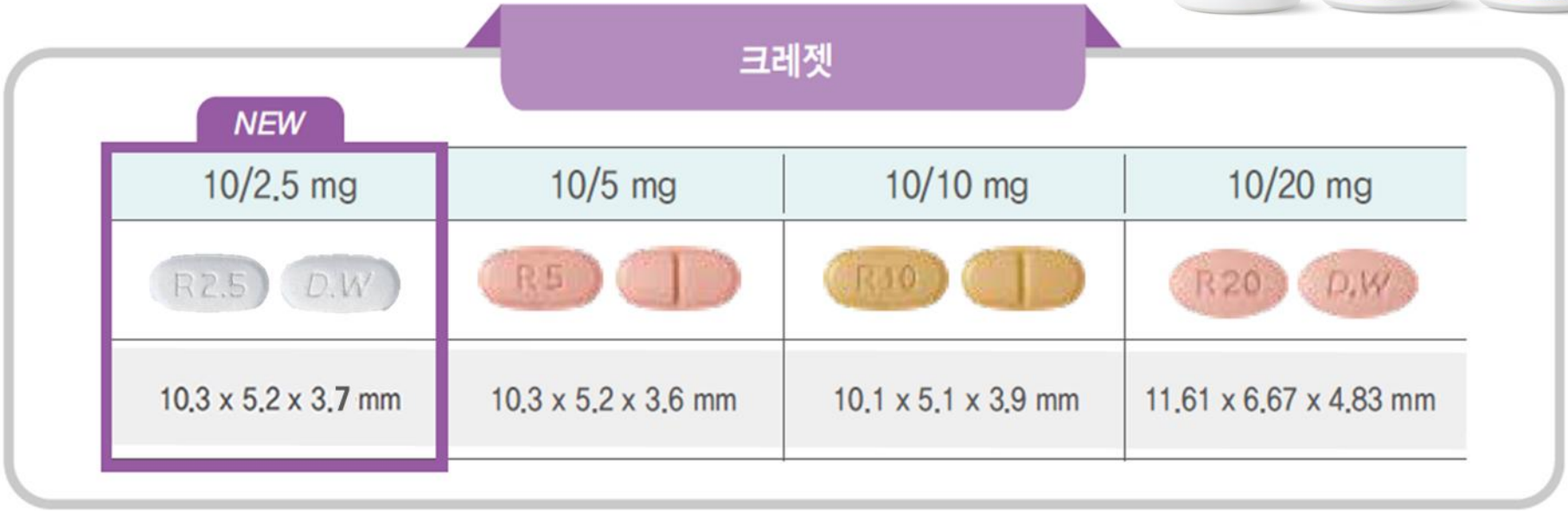
1.제품명 : **크레젯 정(CREZET Tab.)**

2.성분명 : 에제티미브 / 로수바스타틴 (Ezetimibe / Rosuvastatin)

10/2.5mg, 10/5mg, 10/10mg, 10/20mg

3.적응증 : 원발성 고콜레스테롤혈증

4.용법용량 : 식사와 관계없이 1일 1회 투약(하루 중 아무 때나)



※ 약물의 실제 크기와 다르며 사이즈는 장축x단축x두께로 나타냄

Conclusion

- **LDL-C** is a **major risk factor for Coronary Artery Disease** and requires aggressive management
- Guidelines suggest **earlier and more aggressive control of LDL cholesterol** in CAD patients
- **Statins** are recommended as **a first-line treatment for CAD patients**, as they have been shown to reduce LDL-C levels, have pleiotropic effects, and have demonstrated cardiovascular disease prevention effects. However, **statins have limitations** in **achieving LDL-C target levels** in CAD patients, and **the risk of side effects** may increase with the use of high doses to achieve target levels.
- **Combination therapy of statins and ezetimibe** has demonstrated **superior LDL-C-lowering** efficacy compared to statin monotherapy, with **higher LDL-C target attainment rates** and additional **CVD prevention** effects in CAD patients. Moreover, the **medication adherence** rate was even improved.