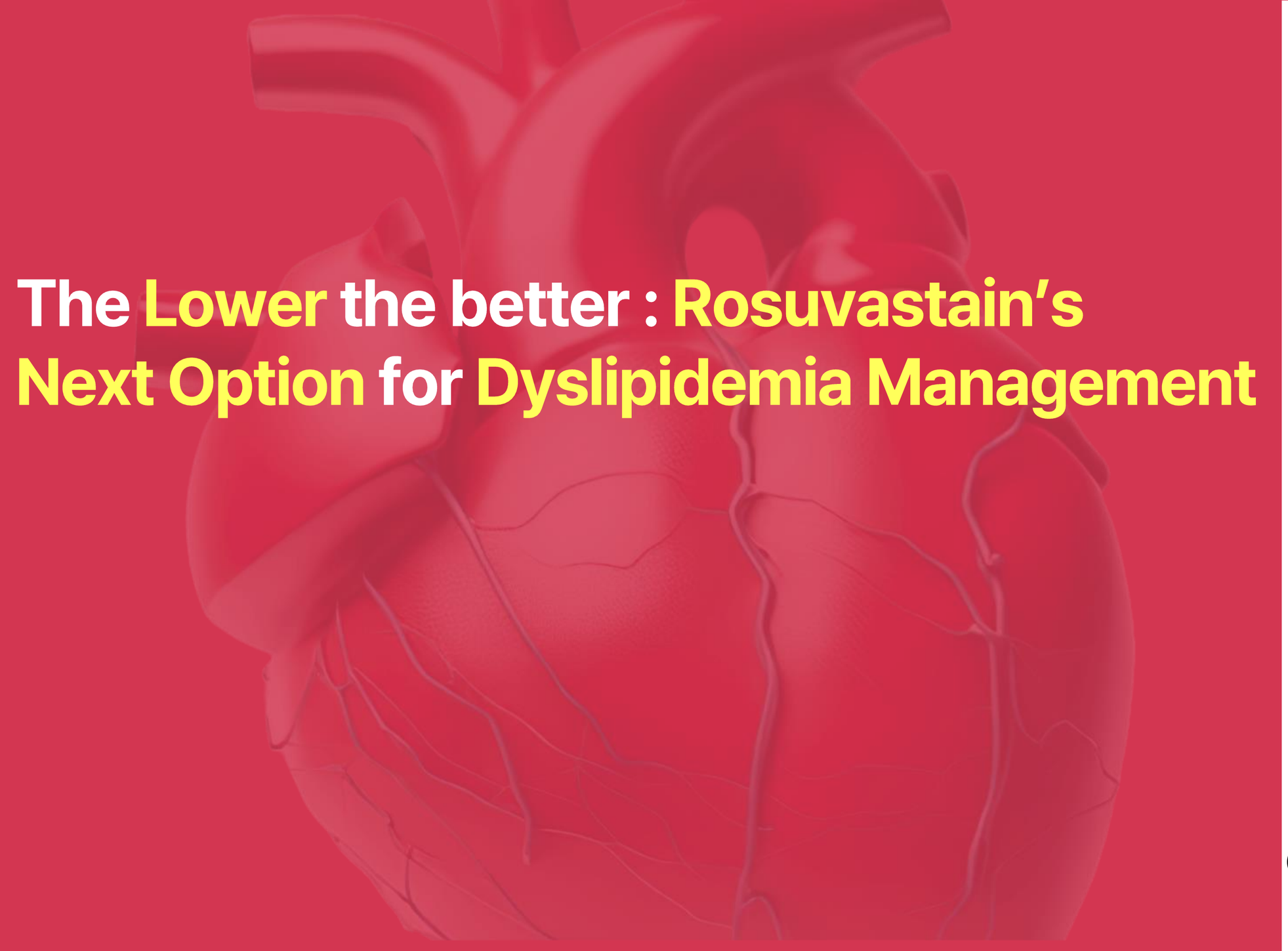


The Lower the better : Rosuvastain's Next Option for Dyslipidemia Management

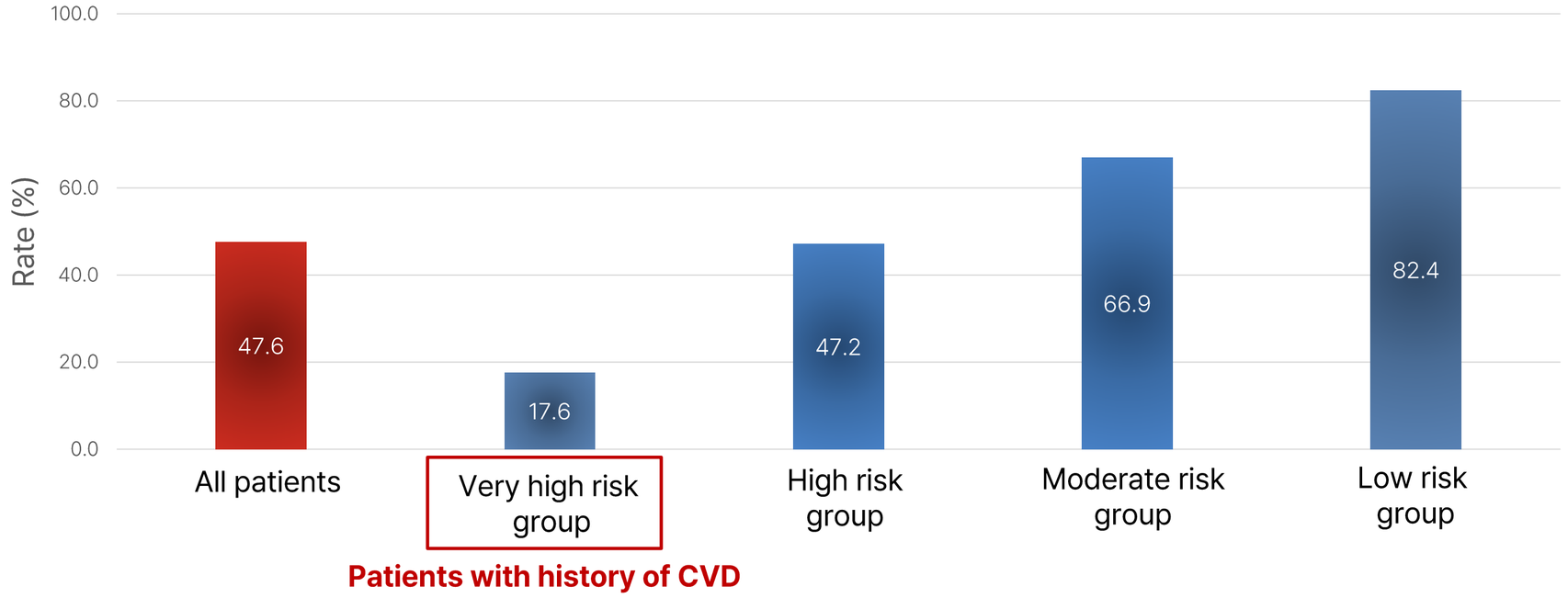
Lecture : **Doyeon Hwang**

(Seoul National University Hospital, Korea (Republic of)

Contents

Only 17.6% of very high risk patients for ASCVD have achieved their LDL-C goal in Korea

LDL-C goal achievement of 69,942 patients with dyslipidemia in the NHIS-HEALS database (2006-2013)



Study Design

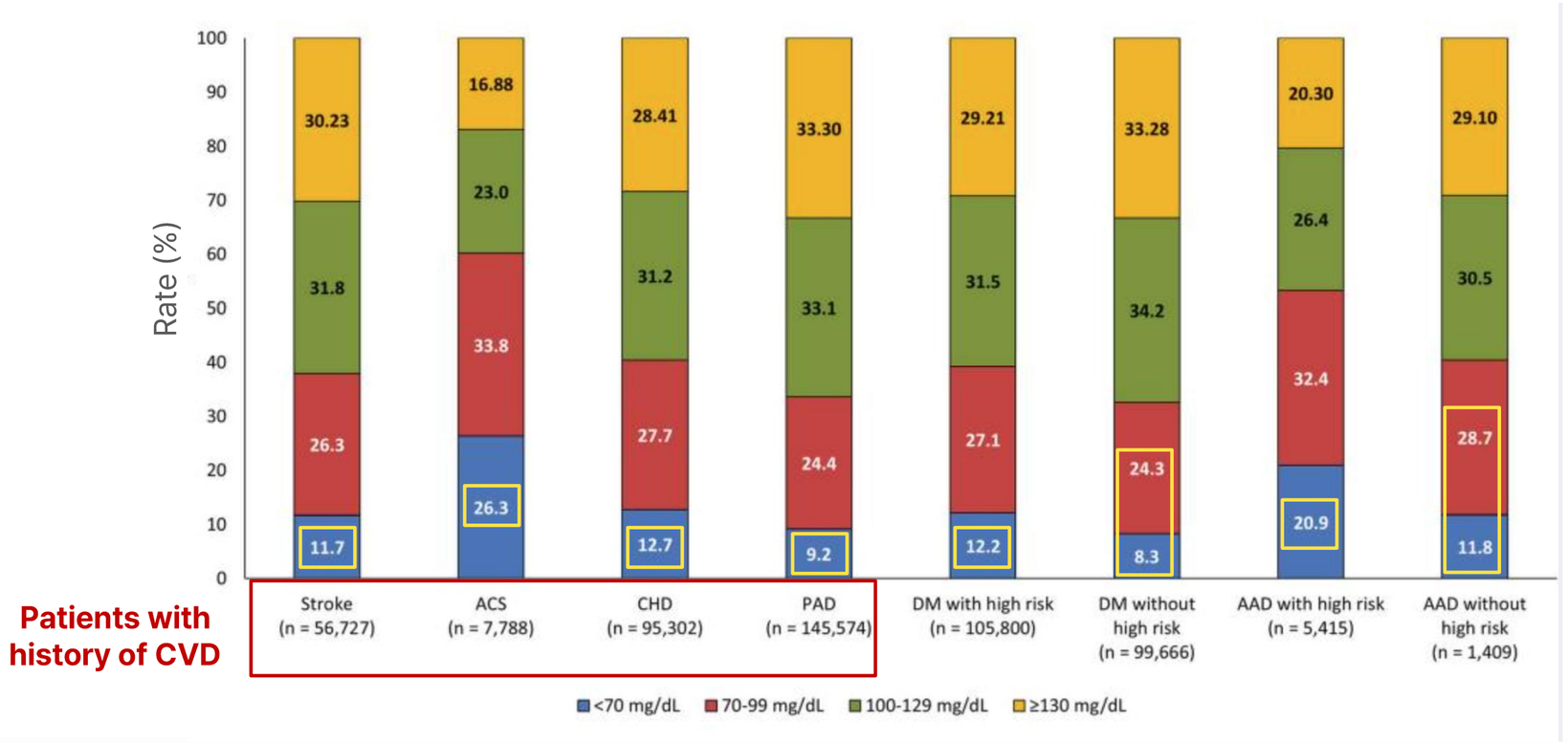
Retrospective cohort study using the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) database from 2006 to 2013. Patients who had a health examination with LDL-C measurement between January 1, 2007, and December 31, 2011 were identified. The 2015 Korean guidelines were used to measure LDL-C goal achievement based on the CV risk level. Crude CV event rates were calculated for total and individual CV events as the number of events divided by person-years (PYs) during the follow-up period.

Abbreviation ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL-C, low density lipoprotein-cholesterol;

Reference Kim S et al. Achievement of the low-density lipoprotein cholesterol goal among patients with dyslipidemia in South Korea. *PLoS One.* 2020;15(1):e0228472. Published 2020 Jan 30.

Under 50% high risk patients in Korea achieve the outlined LDL-C goal

Rate of LDL-C goal in all high-risk (known + newly defined high-risk patients) by target LDL-C level



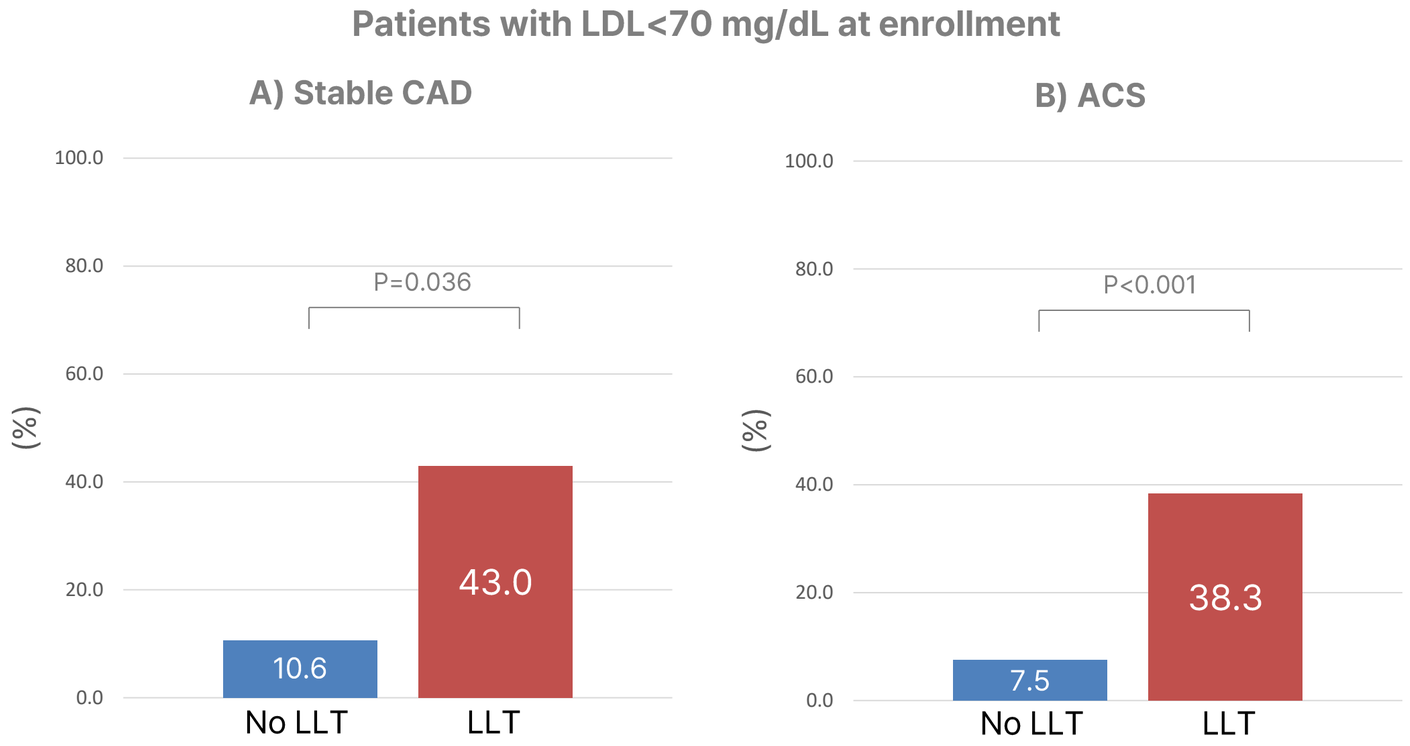
Study Design

Retrospective cohort study of 514,866 subjects from the National Health Insurance Service-National Health Screening Cohort database in Korea. Participants were followed up from 2002 to 2015. Subjects with a high-risk of CVD prior to LDL-C measurement and subjects who were newly-diagnosed for high-risk of CVD following LDL-C measurement were defined as known high-risk patients (*n* = 224,837) and newly defined high-risk patients (*n* = 127,559), respectively.

Abbreviation AAA, atherosclerotic artery disease; ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low density lipoprotein-cholesterol; PAD, peripheral artery disease;

Reference Yang YS et al. Low-density lipoprotein cholesterol goal attainment rates in high-risk patients with cardiovascular diseases and diabetes mellitus in Korea: a retrospective cohort study. *Lipids Health Dis.* 2020;19(1):5. Published 2020 Jan 11.

Minority of stable CAD or ACS patients achieved the LDL-C target due to insufficient statin monotherapy dosage



Statin monotherapy was the predominant LLT in both groups
- **81.2% in stable CAD**
- **84.6% in ACS**

Mean ATV-equivalent dose was 17mg/day

Study Design

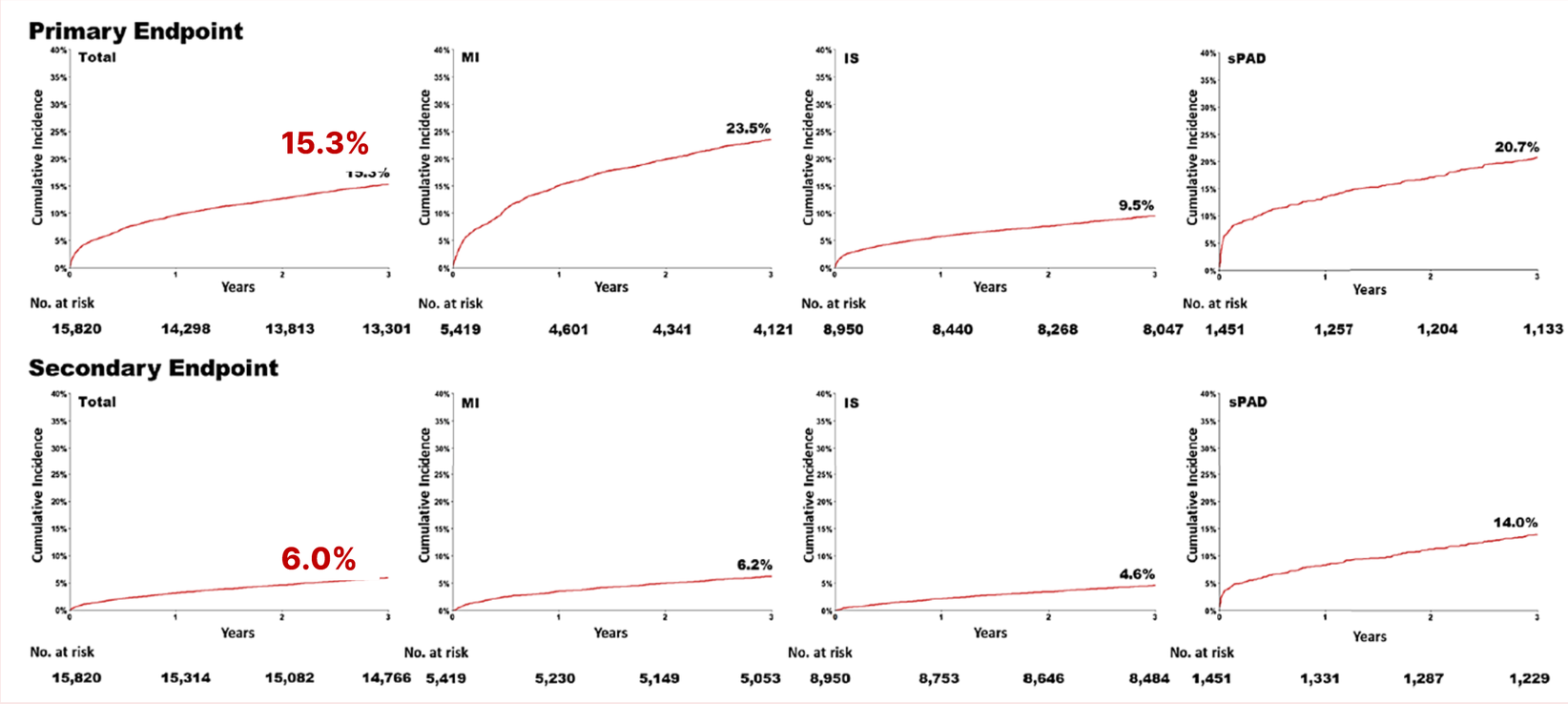
Observational, cross-sectional study to assess the rate of under-target LDL-C in Korean patients with stable CAD or ACS. 808 Patients were enrolled in Korea. Data were collected at outpatient visits for stable CAD and at hospital admission and 4-month follow-up for ACS. Lipid profiles and the use of lipid lowering therapy (LLT) were documented. Rates of LDL-C under target (<70mg/dL) were evaluated.

Abbreviation ACS, acute coronary syndrome; CAD, coronary artery disease; LDL-C, low density lipoprotein-cholesterol; LLT, lipid lowering therapy;

Reference Lee SH et al. Dyslipidemia and Rate of Under-Target Low-Density Lipoprotein-Cholesterol in Patients with Coronary Artery Disease in Korea. J Lipid Atheroscler. 2019;8(2):242-251.

Patients with very high-risk ASCVD were at substantial risk of further cardiovascular events in 3 years.

Three-year cumulative incidences of the primary and secondary endpoints in AMC Heart Registry



- MI
- Stroke
- Hospitalization for UA
- Revascularization
- All-cause mortality

- MI
- Stroke
- All-cause mortality

Study Design

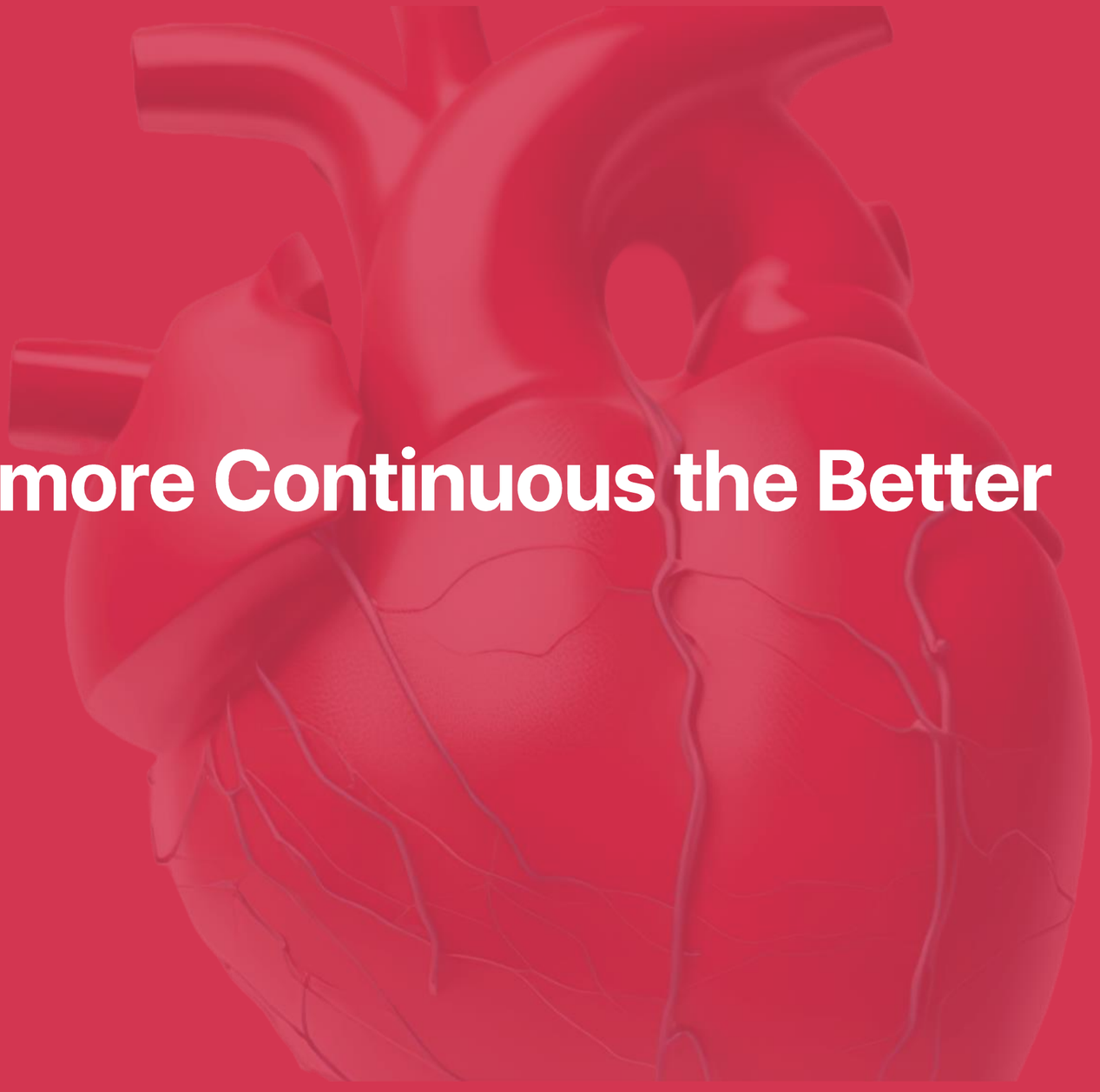
Retrospective cohort study of 514,866 subjects from the National Health Insurance Service-National Health Screening Cohort database in Korea. Participants were followed up from 2002 to 2015. Subjects with a high-risk of CVD prior to LDL-C measurement and subjects who were newly-diagnosed for high-risk of CVD following LDL-C measurement were defined as known high-risk patients (n = 224,837) and newly defined high-risk patients (n = 127,559), respectively.

Abbreviation AAA, atherosclerotic artery disease; ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low density lipoprotein-cholesterol; PAD, peripheral artery disease;

Reference Yang YS et al. Low-density lipoprotein cholesterol goal attainment rates in high-risk patients with cardiovascular diseases and diabetes mellitus in Korea: a retrospective cohort study. *Lipids Health Dis.* 2020;19(1):5. Published 2020 Jan 11.

02 *LDL-Cholesterol*

Lower, Earlier, and more Continuous the Better



2018 AHA/ACC Guideline

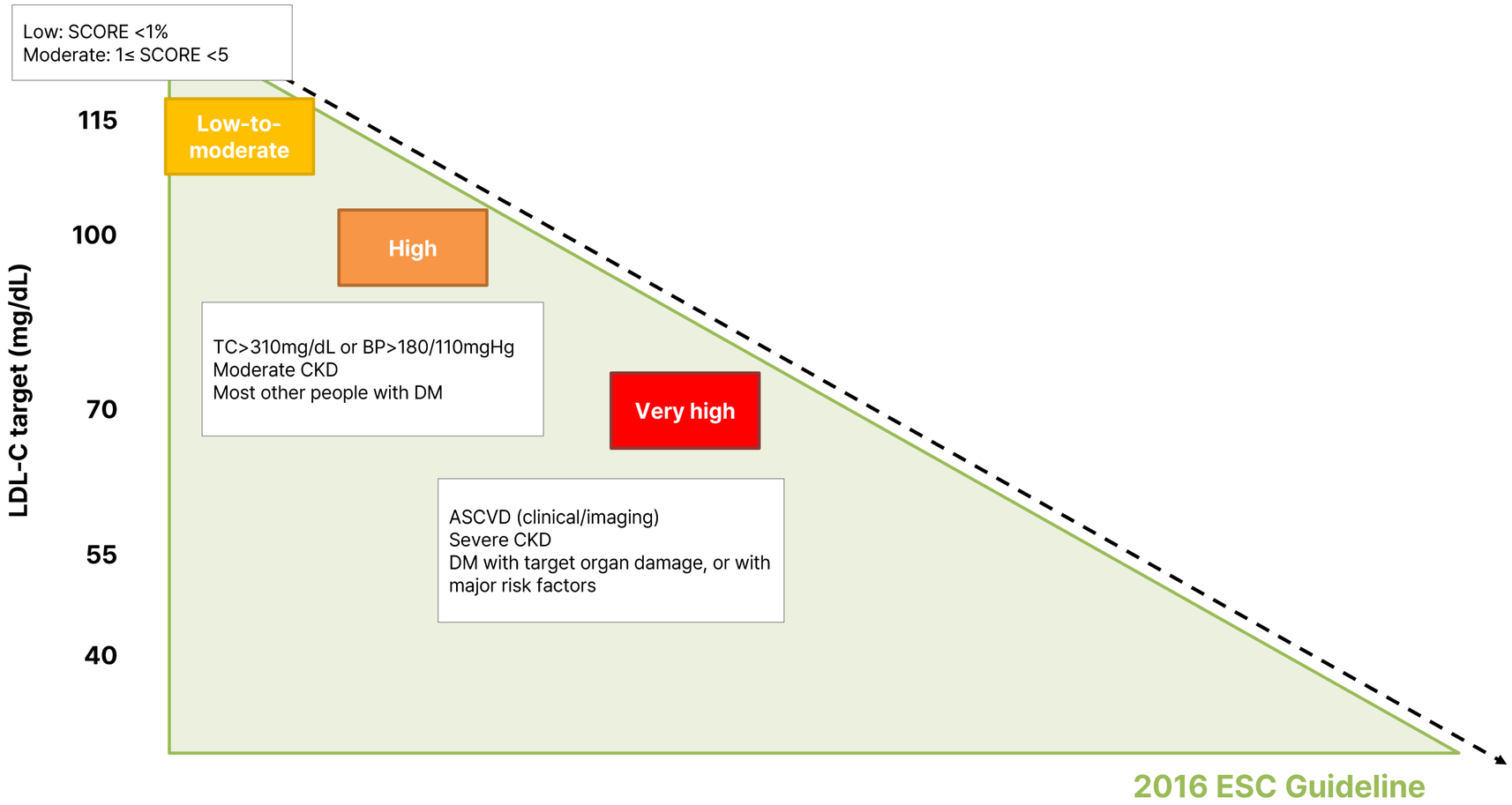
2018 AHA/ACC Guidelines		
	Risk category	**LDL-Cholesterol (mg/dL)**
Very high risk	• History of multiple major ASCVD events[a] • 1 Major ASCVD event and multiple high-risk conditions	<70
High risk	• Age ≥ 65 years • HeFH • History of prior CABG/PCI outside of the major ASCVD event(s) • DM • Hypertension • CKD (eGFR 15-59 mL/min/1.73m^2) • Persistently elevated LDL-C (≥ 100mg/dL) despite maximally tolerated statin therapy and ezetimibe • History of congestive heart failure	<70

[a]Major ASCVD events include recent ACS within the past 12 months, a history of MI other than the recent ACS, a history of ischemic stroke, and symptomatic PAD. High-risk conditions include age of ≥65 years, heterozygous familial hypercholesterolemia, prior PCI/CABG, diabetes mellitus, hypertension, CKD, current, smoking, history of heart failure, and LDL-C level of 100 mg/dL or higher while receiving maximal statin plus ezetimibe.

Abbreviation ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, Atherosclerotic cardiovascular disease; CABG, Coronary artery bypass graft; CKD, Chronic kidney disease; DM, Diabetes mellitus; HeFH, Heterozygous familial hypercholesterolemia; PCI, Percutaneous coronary intervention;

Reference Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol. 2019 Jun 25;73(24):3234-3237]. J Am Coll Cardiol. 2019;73(24):3168-3209.

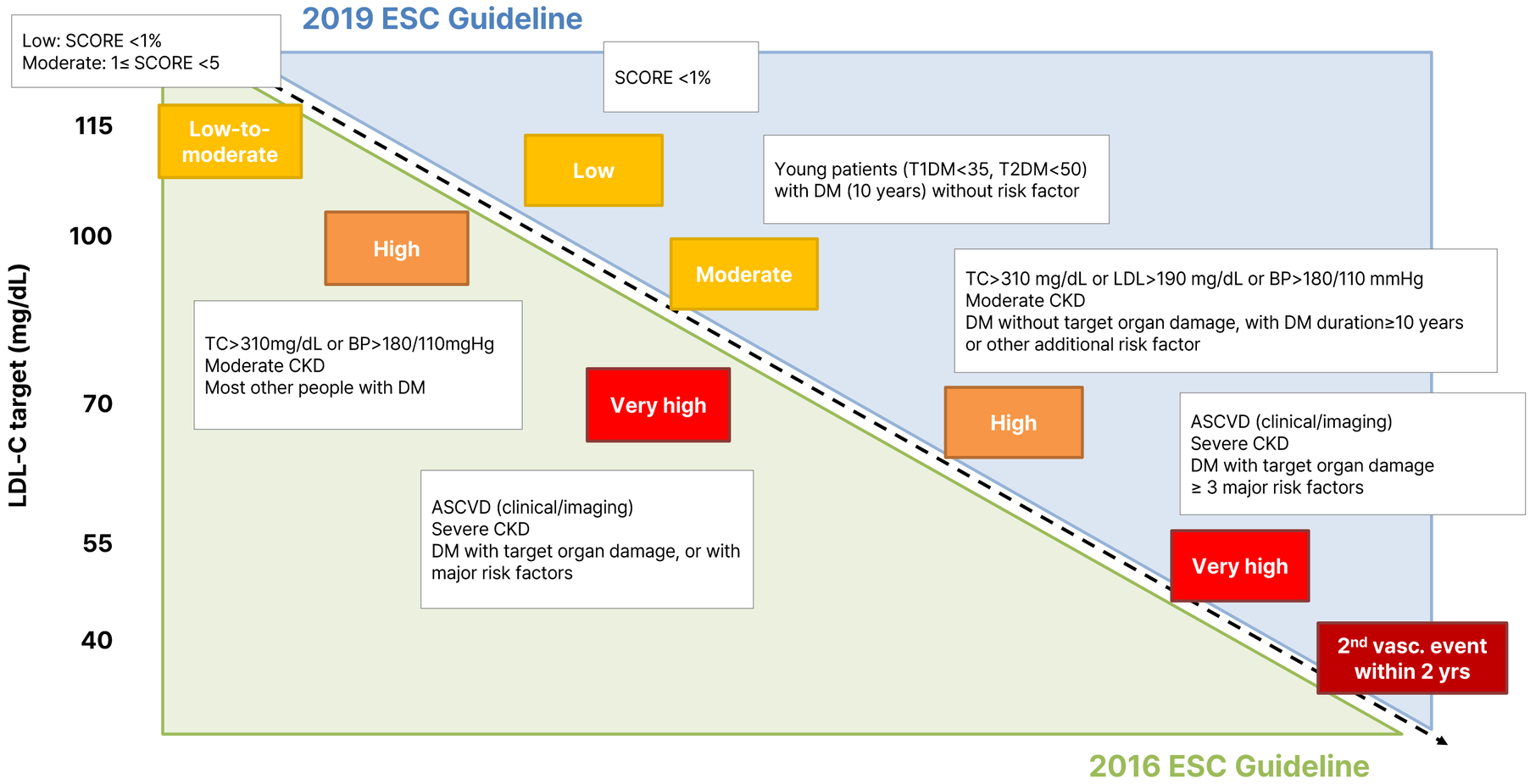
2016 ESC/EAS Guideline



Abbreviation ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; BP, blood pressure; CKD, chronic kidney disease; CT, computed tomography; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterolSCORE, Systematic Coronary Risk Estimation; T1DM, type 1 DM; TC, total cholesterol;

Reference 1. Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation. 2019 Jun 18;139(25):e1182-e1186] [published correction appears in Circulation. 2023 Aug 15;148(7):e5]. *Circulation.* 2019;139(25):e1082-e1143.

2019 ESC/EAS Guideline



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Reference 1. Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation. 2019 Jun 18;139(25):e1182-e1186] [published correction appears in Circulation. 2023 Aug 15;148(7):e5]. *Circulation.* 2019;139(25):e1082-e1143. 2. Mach F et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41(1):111-188.

2019 ESC/EAS Guideline

2019 ESC/EAS Guideline		
	Risk category	**LDL-Cholesterol (mg/dL)**
Very high risk	• ACS patients who experience a second vascular event within 2 years while taking maximally tolerated statin therapy	<40 *may be considered*
	• Documented ASCVD, either clinical or unequivocal on imaging[a] • DM with established ASCVD and/or severe target organ damage[b], 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) • FH with ASCVD or with another major risk factor	<55 and ≥50% reduction from baseline
High risk	• Markedly elevated single risk factors, in particular TC >310 mg/dL, LDL-C > 190 mg/dL, or BP ≥ 180/110 mmHg • FH without other major risk factors • DM without established ASCVD and/or severe target organ damage • Moderate CKD (eGFR 30-59 mL/min/1.73m^2)	<70 and ≥50% reduction from baseline
Moderate Risk	• Young patients (T1DM <35 yrs; T2DM <50 yrs) with DM duration <10 yrs, without other risk factors.	<130
Low Risk		<160

[a]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 artery 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. [b]Target organ damange is defined as microalbuminuria, retinopathy, or neuropathy.

Abbreviation ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; BP, blood pressure; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 DM; T2DM, type 2 DM; TC, total cholesterol; TIA, transient ischaemic attack.

Reference Mach F et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188.

2022 KSoLA Guideline

2022 KSoLA Guideline		
	Risk category	**LDL-Cholesterol (mg/dL)**
Very high risk	관상동맥질환[1]*	<55
High risk	• 죽상경화성 허혈뇌졸중 및 일과성 뇌허혈발작* • 경동맥질환* • 말초동맥질환* • 복부대동맥류* • 당뇨병(유병기간 10년 이상 또는 주요 심혈관질환 위험인자† 또는 표적장기손상을 동반한 경우)[2]	<70
Diabetes Mellitus	당뇨병 (유병기간 10년 미만, 주요 심혈관질환 위험인자†가 없는 경우)	<100
Moderate Risk	주요 심혈관질환 위험인자† 2개 이상	<130
Low Risk	주요 심혈관질환 위험인자† 1개 이하	<160

***LDL 콜레스테롤 기저치 대비 50% 이상 감소 시키는 것을 동시에 권고**

†연령 (남자 ≥ 45세, 여자 ≥ 55세), 조기 심혈관 질환 발생 가족력, 고혈압, 흡연, 낮은 HDL 콜레스테롤 수치 (<40 mg/dL)

1) 급성심근경색증은 기저치 LDL 콜레스테롤 농도와 상관없이 스타틴을 투약

2) 표적장기손상(알부민뇨, 만성콩팥병[추정사구체여과율 60 mL/min/1.73m^2 미만], 망막병증, 신경병증, 좌심실비대) 또는 3개 이상의 주요 심혈관질환 위험인자† 를 동반한 당뇨병의 경우: LDL 콜레스테롤 목표치 < 55 mg/dL 선택적 고려

Abbreviation HDL, High density lipoprotein; LDL, Low density lipoprotein;
Reference 한국지질동맥경화학회 이상지질혈증 진료지침 제5판 2022.

Treatment Guideline for Very High Risk Patients

	ACC/AHA 2018[1]	EAS/ESC 2019[2]	KSoLA 2022[3]
LDL-C Target (mg/dL)	**<70** and **≥50%↓** from baseline	**<55** and **≥50%↓** from baseline **<40** if 2nd vascular event within 2 years while taking maximally tolerated statin	**<55** and **≥50%↓** from baseline
1st line treatment	High intensity or maximal statin	High intensity statin	스타틴 목표 LDL-C 도달하지 못하는 경우 최대 가용 용량으로 증량
Addition of non-statin therapy	If LDL-C remains ≥70 mg/dL on maximally tolerated statin, **first consider adding ezetimibe**; if LDL-C remains ≥70 mg/ dL (or non–HDL-C ≥100 mg/dL), consider adding PCSK9 Inhibitor	If LDL-C remains ≥55 mg/dL on maximally tolerated statin, **first add ezetimibe**; if LDL-C remains ≥55 mg/dL, a combination with a PCSK9 inhibitor is recommended	최대 가용 용량의 스타틴을 사용하더라도 목표 LDL-C 도달하지 못하는 경우 **에제티미브 병용 권고**, 그럼에도 도달하지 않는 경우 PCSK9 억제제 병용 고려

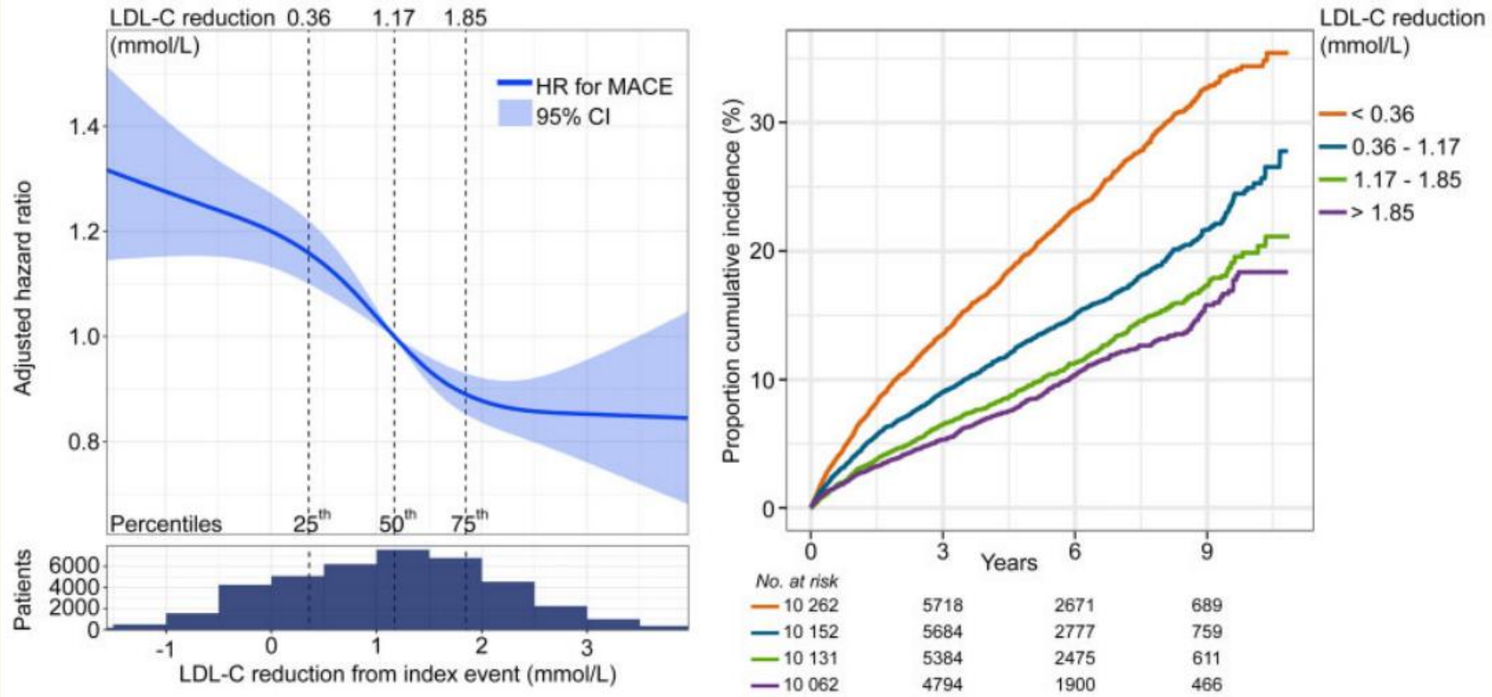
Abbreviation HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, Proprotein convertase subtilisin/kexin type 9;

Reference 1. Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol. 2019 Jun 25;73(24):3234-3237]. J Am Coll Cardiol. 2019;73(24):3168-3209. 2, Mach F et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188. 3. 한국지질동맥경화학회 이상지질혈증 진료지침 제5판 2022.

Earlier the Better

Early and aggressive LDL-C lowering after MI reduces the risk of major CV outcomes and mortality

Adjusted HR and incidence rates for MACE by change in LDL-C 6-10 weeks after MI



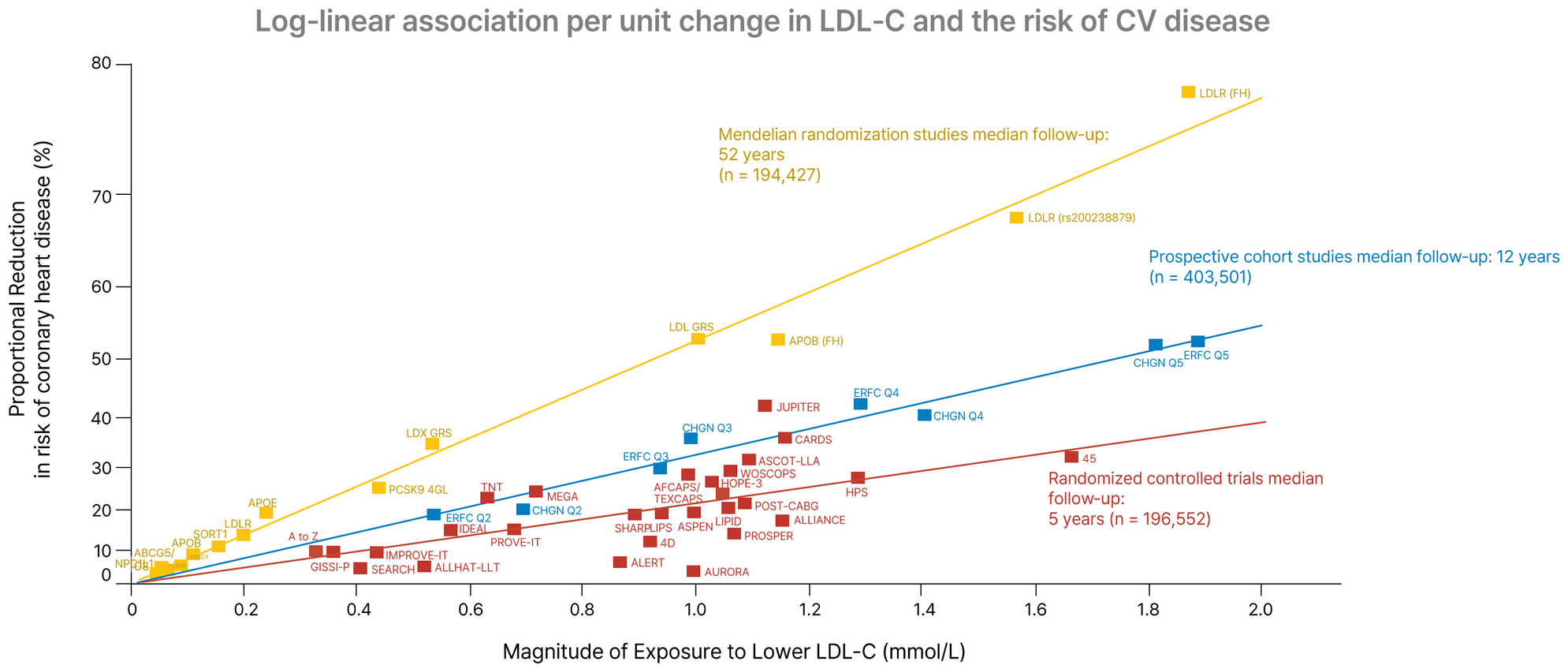
- Compared to patients with 0.36 mmol/L reduction (25th percentile), those with a 1.85 mmol/L reduction (75th percentile) had significantly lower hazard ratios for:
  - MACE (CV death, MI, stroke)
  - All-case mortality
  - MI
  - Ischemic stroke
  - Heart failure hospitalization
  - Coronary revascularization
- Every 1 mmol/L LDL-C reduction was associated with a 25% relative reduction in major vascular events

Study Design

Observational, cohort study of the Swedish nationwide SWEDEHEART registry to investigate the association between early LDL-C lowering and statin intensity after MI with long-term CV outcomes. 40.607 patients aged 30-<75 years admitted with MI were followed for a median of 3.78 years. Patients were categorised by quartiles of LDL-C change between the MI and a 6-10 week follow-up visit. Associations between LDL-C changes, statin intensity, and outcomes were assessed.

Abbreviation CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MACE, major cardiovascular events; MI, myocardial infarction;
Reference Schubert J et al. Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study. *Eur Heart J.* 2021;42(3):243-252.

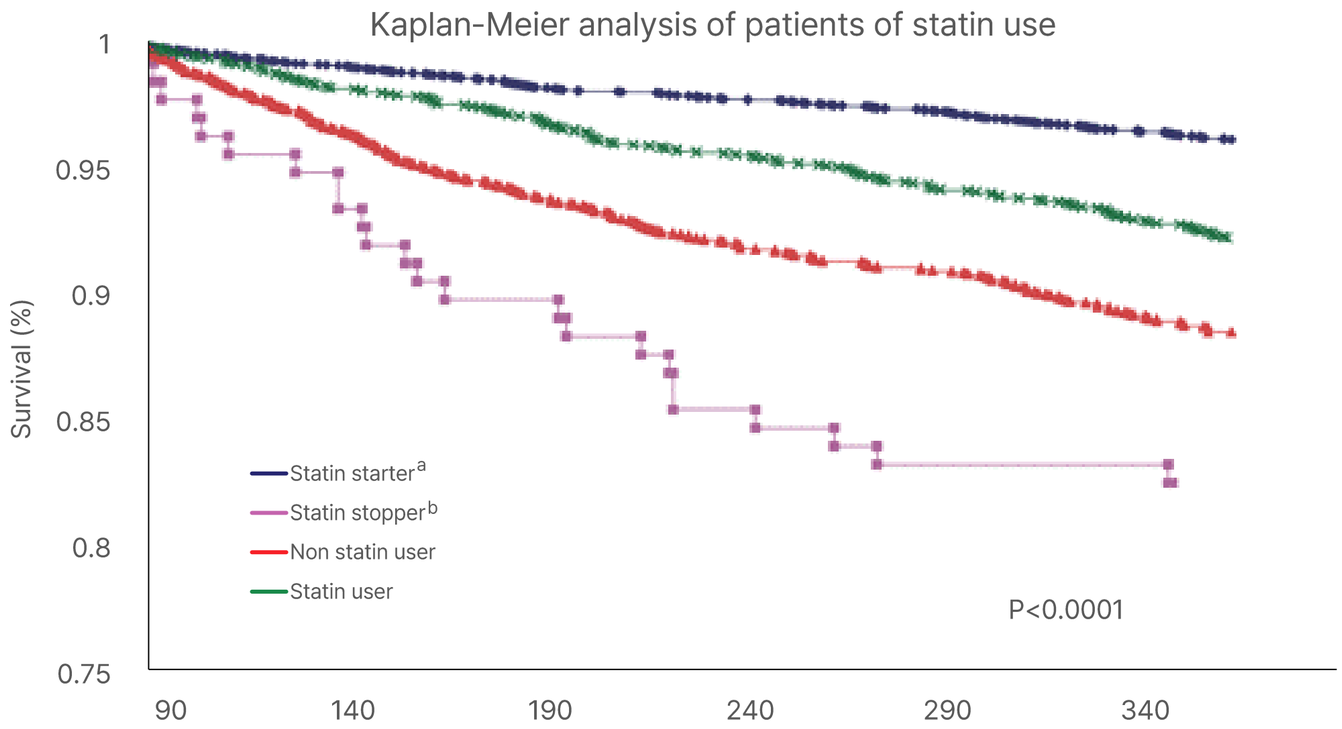
Statin-induced reduction in the risk of CV disease depends on both magnitude and duration of exposure



Abbreviation CV, cardiovascular; LDL-C, low density lipoprotein-cholesterol;

Reference 1. Ference BA et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J.* 2017;38(32):2459-2472.

Discontinuation of statin after AMI was associated with significantly higher mortality compared to non-users



- Compared to non-used, Adjusted HR for 1-year all-cause mortality were:
  - Users 0.84 (95% CI 0.66-1.09)
  - Starters 0.74 (95% CI 0.57-0.90)
  - Stoppers 1.88 (95% CI 1.13-3.07)
- Discontinuing statins after AMI was associated with significantly higher mortality compared to non-users (HR 1.88, P<0.05)

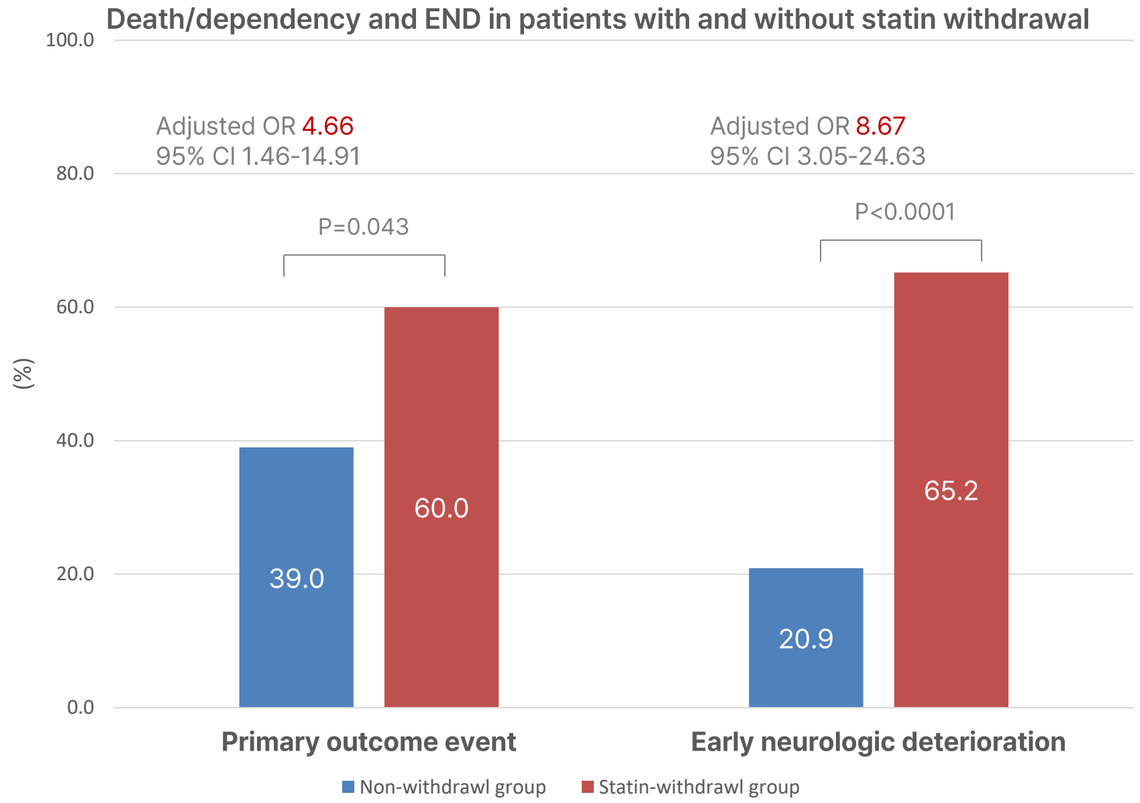
[a]Did not receive statins before AMI, but started after it
[b]Stopped statin therapy after AMI

Study Design

Population-based, cohort study of patients who survived a first AMI. According to the pattern of statin used: (i) non-users, patients who did not receive statin before or after AMI; (ii) non-users, patients not receiving statins before or after AMI; (iii) users, patients receiving statins before and continuing after; (iv) stoppers, consisting of patients who stopped statin therapy after AMI; Outcome of the study was all-cause mortality between 90 days and 1 year after the AMi.

Abbreviation AMI, acute myocardial infarction;
Reference Daskalopoulou SS et al. Discontinuation of statin therapy following an acute myocardial infarction: a population-based study. *Eur Heart J.* 2008;29(17):2083-2091.

Statin withdrawal after stroke onset is associated with increased risk of death *or* dependency and early neurologic deterioration



- After adjusting for age and baseline stroke severity, statin withdrawal was associated with:
  - 4.66-fold increase in the risk of death or dependency
  - 8.67-fold increase in the risk of early neurologic deterioration
  - 37.63 mL increase in mean infarct volume (SE 10.01; P<0.001)

Study Design

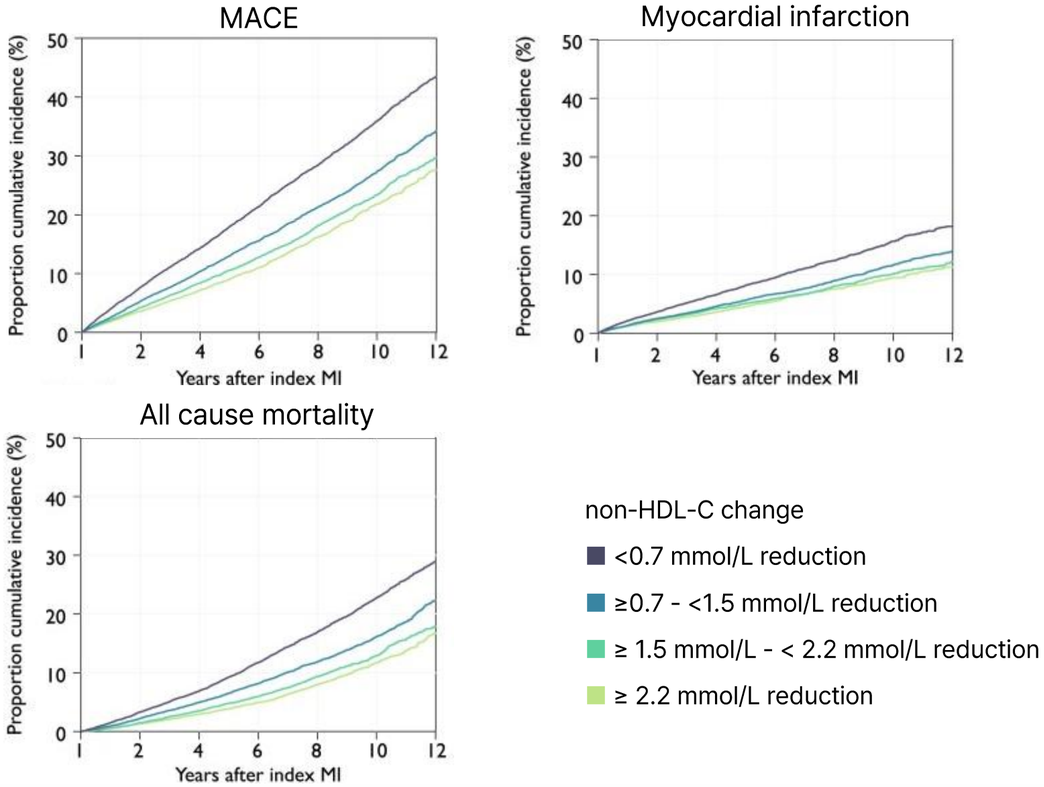
Randomised, controlled study. 89 Ischemic stroke patients on chronic statin treatment prior to stroke were randomized to either statin withdrawl for the first 3 days after admission or to immediately receive atorvastatin 20mg/day. Primary outcome was death or dependency (mRS score ≥2) at 3 months. Secondary outcomes were early neurologic deterioration (END) and infarct volume.

Abbreviation END, early neurological deterioration; mRS, modified Rankin Scale.

Reference Blanco M et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology. 2007;69(9):904-910.

Intensive lowering of non-HDL-C after MI was associated with better outcome

Cumulative incidence rates by outcome and change in non-HDL-C at 1 year after MI



- Cumulative incidence rate of outcomes by quartile of non–HDL-C reduction from 1-year follow-up:
  - Consistent curve separation with the largest reduction in non–HDL-C (≥2.2 mmol/L) associated with the lowest rates of events

Study Design

Observational study. From the SWEDEHEART registry, 56 262 patients with MI were included. Outcomes were major adverse cardiovascular event (MACE: death, MI, and ischaemic stroke), death, and non-fatal MI. Non–HDL-C was assessed at admission, 2 months, and 1 year. Target achievement (<2.2 mmol/L) of non–HDL-C, timing thereof, and outcomes were assessed.

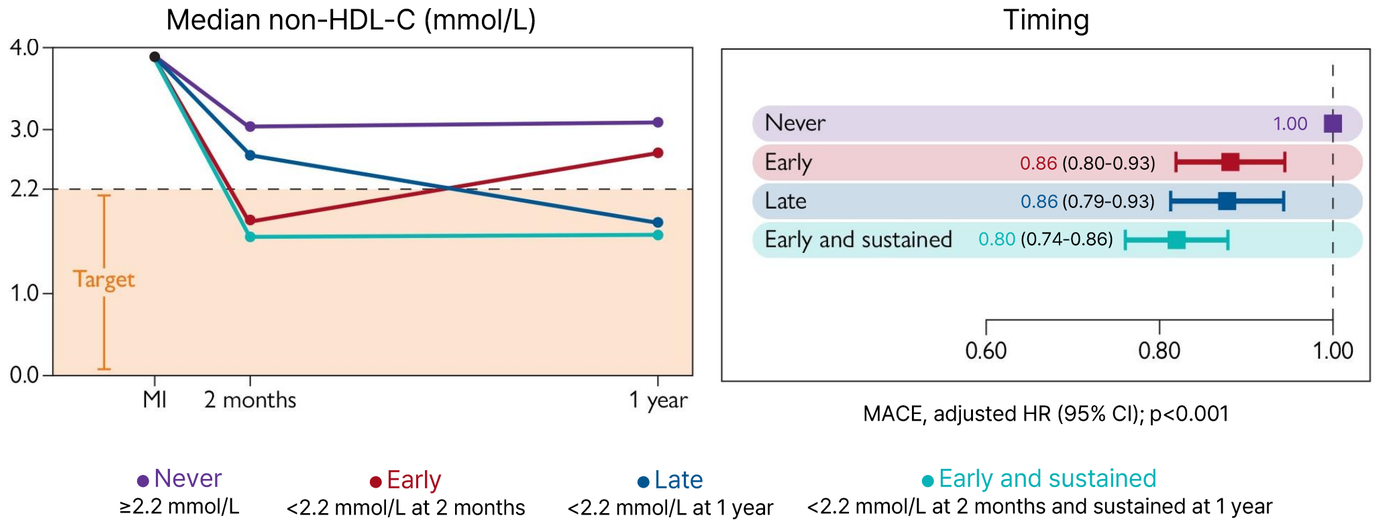
Abbreviation MACE, major adverse cardiovascular event; MI, myocardial infarction; non–HDL-C, non–high-density lipoprotein cholesterol; CI, confidence interval

Reference Schubert J et al. Intensive early and sustained lowering of non-high-density lipoprotein cholesterol after myocardial infarction and prognosis: the SWEDEHEART registry. Eur Heart J. 2024 Oct 14;45(39):4204-4215.

Early and sustained lowering of non-HDL-C after MI was associated with better outcome

Timing of reaching and duration of staying at non-HDL-C target

46,518 patients with MI and 7,407 MACE (all-cause mortality, MI, or stroke)



- Risk of MACE after 1-year follow-up:
  - Lowest for patients achieving the non-HDL-C target **early and maintaining** it (HR 0.80, 95% CI 0.74–0.86).
  - Similar if only achieving target early (HR 0.86, 95% CI 0.80-0.93) or late (HR 0.86, 95% CI 0.79-0.93)

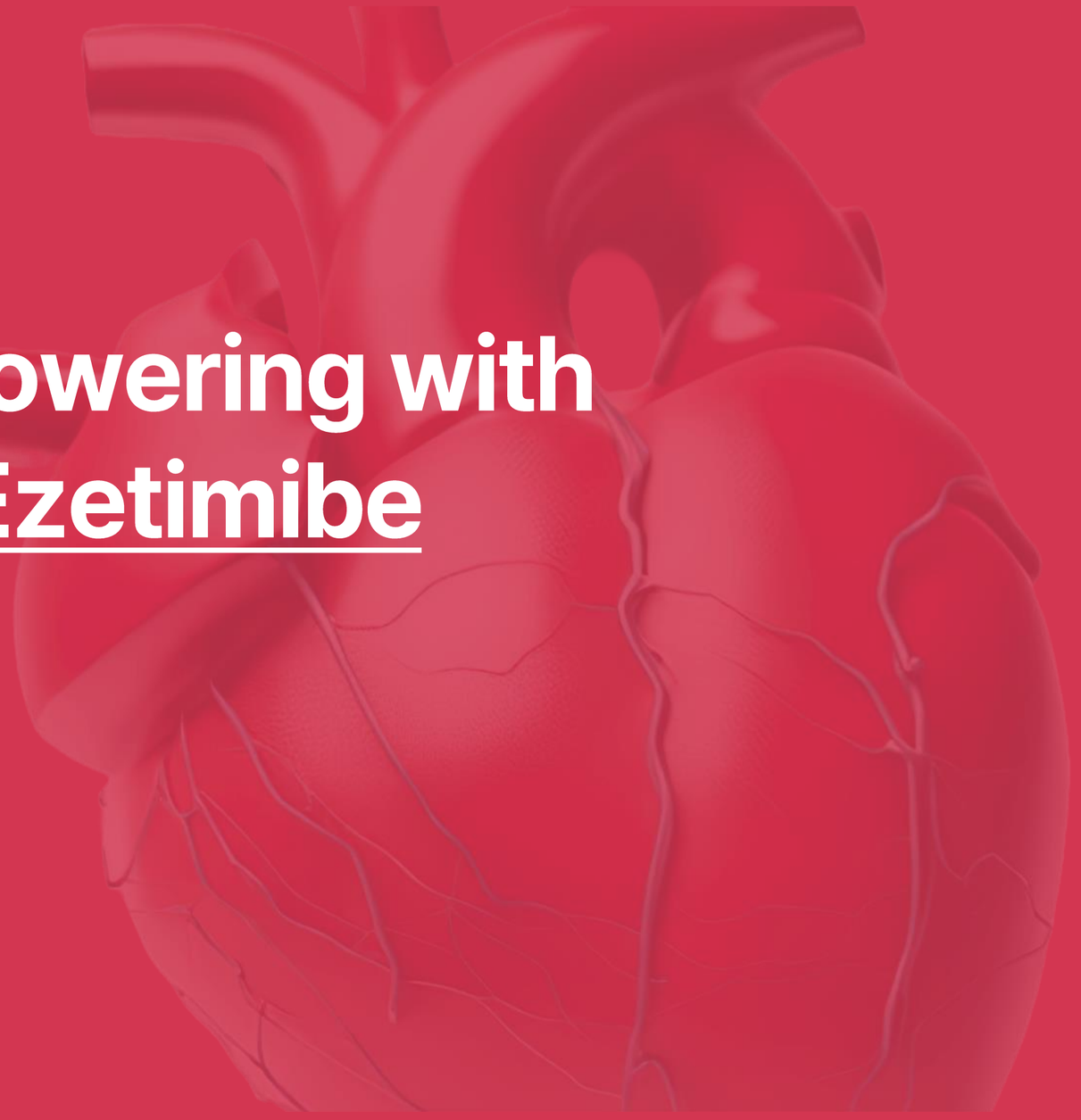
Study Design

Observational study. From the SWEDEHEART registry, 56 262 patients with MI were included. Outcomes were major adverse cardiovascular event (MACE: death, MI, and ischaemic stroke), death, and non-fatal MI. Non–HDL-C was assessed at admission, 2 months, and 1 year. Target achievement (<2.2 mmol/L) of non–HDL-C, timing thereof, and outcomes were assessed.

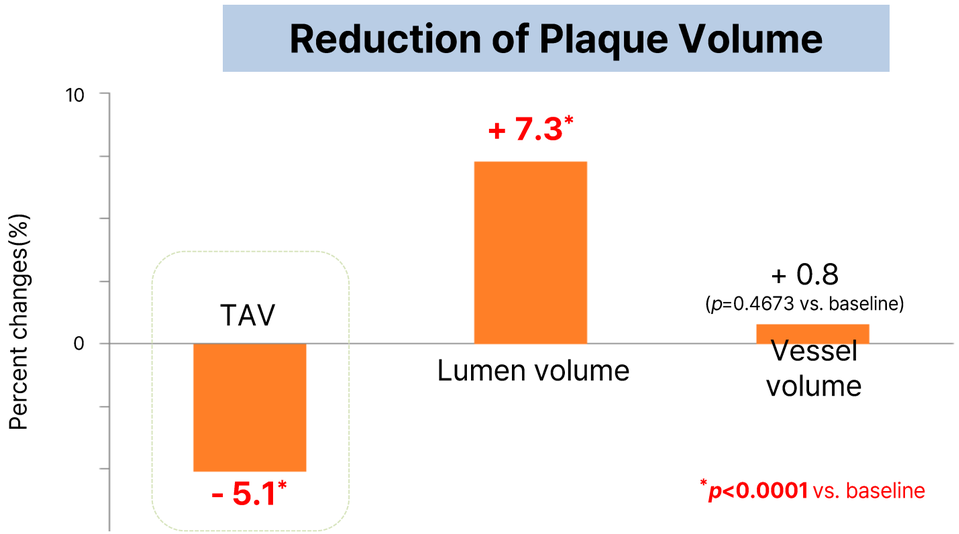
Abbreviation MACE, major adverse cardiovascular event; MI, myocardial infarction; non–HDL-C, non–high-density lipoprotein cholesterol; CI, confidence interval

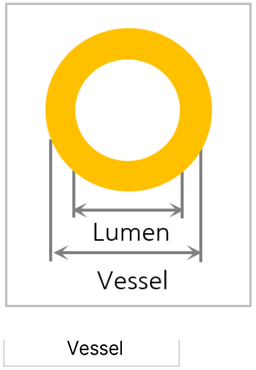
Reference Schubert J et al. Intensive early and sustained lowering of non-high-density lipoprotein cholesterol after myocardial infarction and prognosis: the SWEDEHEART registry. Eur Heart J. 2024 Oct 14;45(39):4204-4215.

03 Optimal LDL-C Lowering with Rosuvastatin + Ezetimibe



Patients Showing Plaque Regression (COSMOS)





- The **mean dosage** of rosuvastatin at follow-up IVUS was **16.9±5.3mg/day.**
- Among the patients who completed the trial, **72.2% received** the maximum dosage(**20mg/day**)

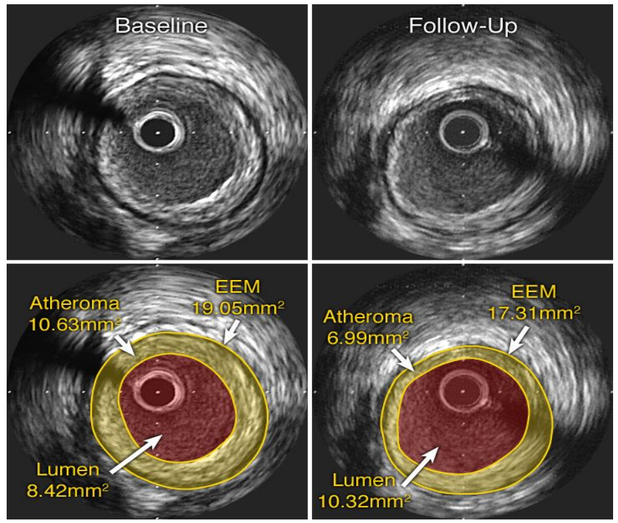
COSMOS(=**CO**ronary atherosclerosis **S**tudy **M**easuring effects **O**f rosuvastatin using intravascular ultrasound in Japanese **S**ubjects) **study**

Study Design

- ✓ **Methods**: A 76-week open-label trial was performed at 37 centers in Japan. Eligible patients began treatment with rosuvastatin 2.5 mg/day, which could be increased at 4-week intervals to <or=20 mg/day. A total of 214 patients underwent intravascular ultrasound (IVUS) at baseline; 126 patients had analyzable IVUS images at the end of the study.
- ✓ **Result**: The change in the serum low-density lipoprotein-cholesterol level from baseline to end of follow-up was -38.6 +/-16.9%, whereas that of high-density lipoprotein-cholesterol was +19.8 +/-22.9% (both P<0.0001). Percent change of plaque volume, the primary endpoint, was -5.1 +/-14.1% (P<0.0001).
- ✓ **Conclusions**: Rosuvastatin exerted significant regression of coronary plaque volume in Japanese patients with stable CAD, including those who had previously used other lipid-lowering drugs. Rosuvastatin might be useful in the setting of secondary prevention in patients with stable CAD.

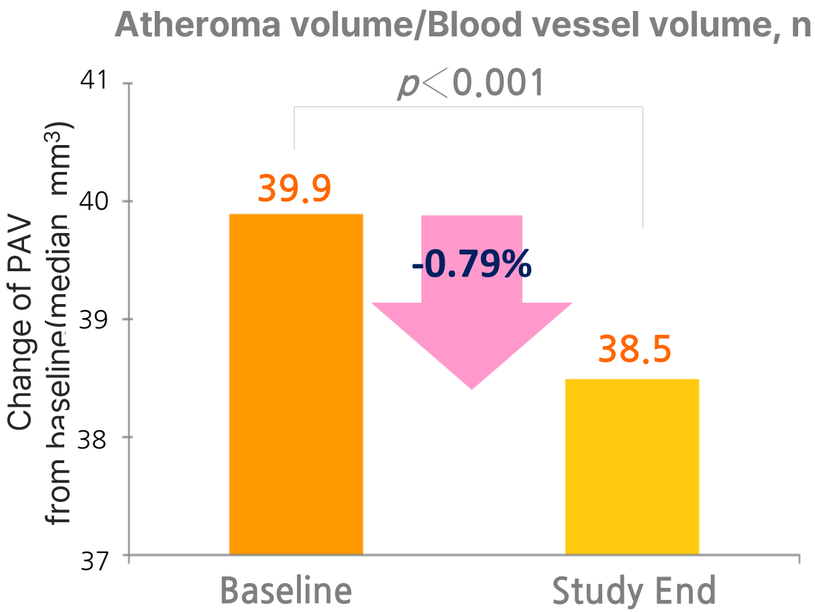
Ref.> Takayama T, et al. Circ J. 2009;73:2110-2117.

Patients Showing Plaque Regression (ASTEROID)

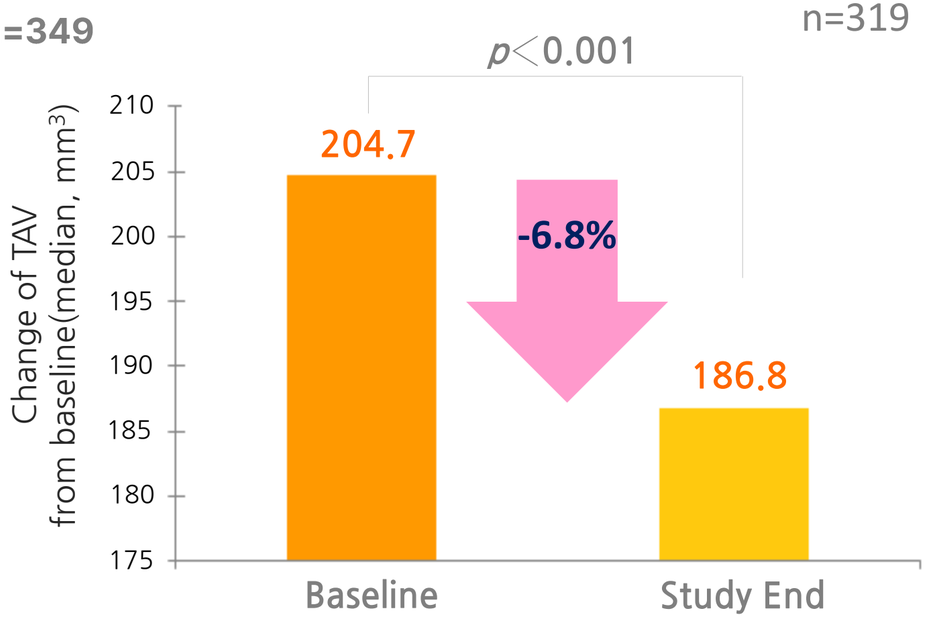


Regression of atheroma p<0.001

<Percent Atheroma Volume>



<Total Atheroma Volume>

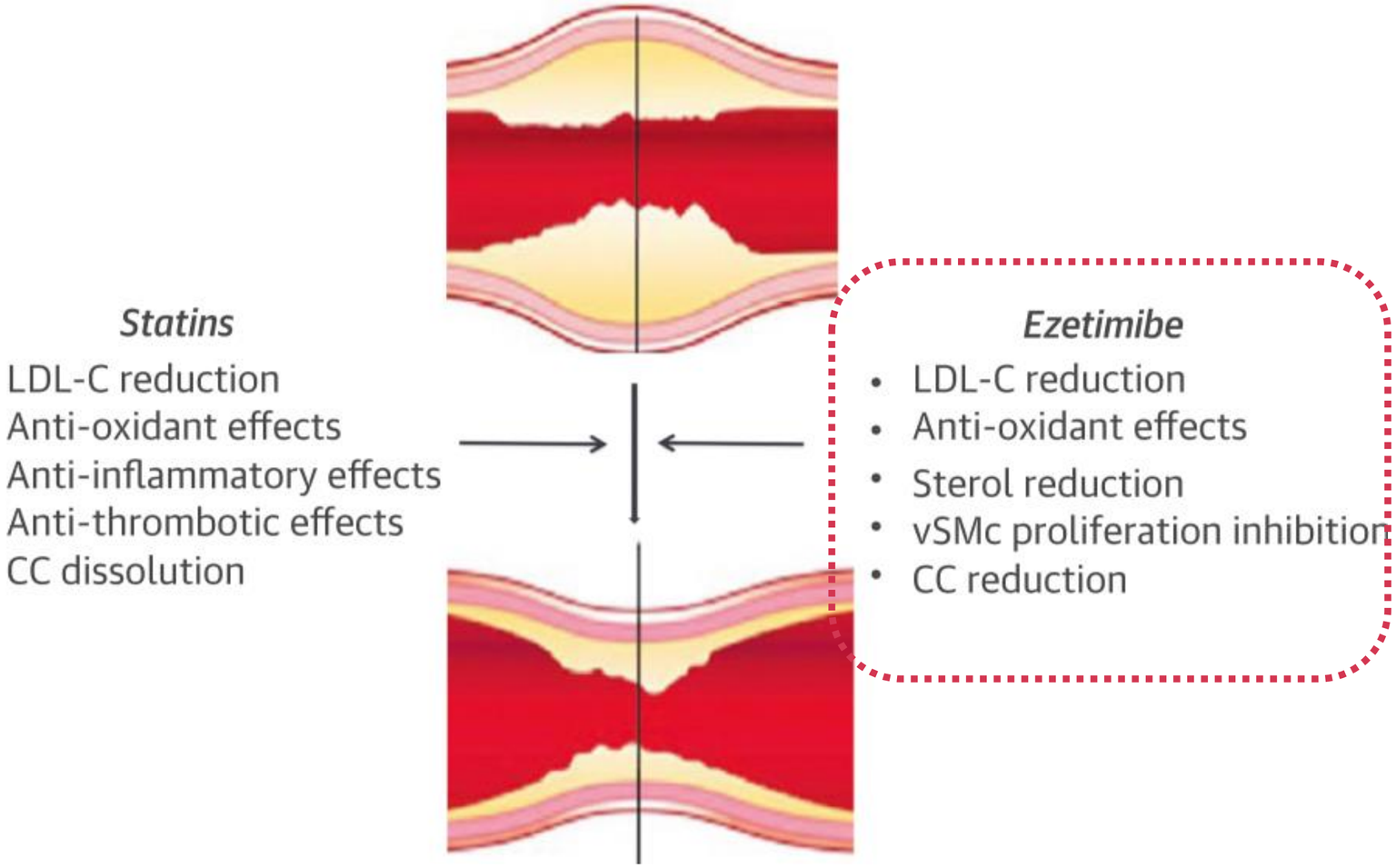


ASTEROID, A Study To Evaluate the Effect of ROsuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

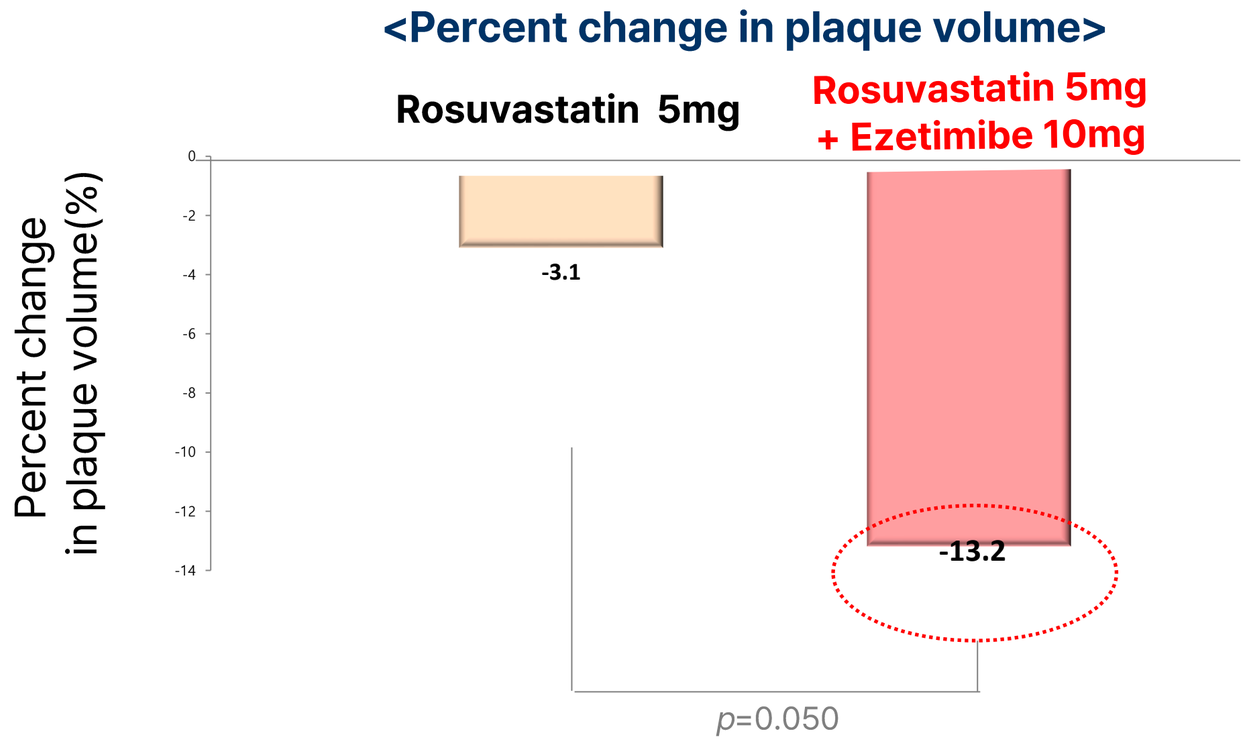
- ✓ **Methods**: Prospective, open-label blinded end-points trial was performed at 53 community and tertiary care centers in the United States, Canada, Europe, and Australia. A motorized IVUS pullback was used to assess coronary atheroma burden at baseline and after 24 months of treatment. Each pair 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.

Beneficial effects of statins & ezetimibe on plaque growth



Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (1)



✓ **Methods**: The aim of this study was to investigate the add-on effect of ezetimibe to a statin on coronary atherosclerosis evaluated by intravascular ultrasound (IVUS).In this prospective randomized open-label study, a total of 51 patients with stable coronary artery disease (CAD) requiring percutaneous coronary intervention (PCI) were enrolled, and assigned to a combination group (n = 26, rosuvastatin 5 mg/day + ezetimibe 10 mg/day) or a monotherapy group (n = 25, rosuvastatin 5 mg/day). Volumetric IVUS analyses were performed at baseline and 6 months after the treatment for a non-PCI site.

Ref.> Masuda J, et al. Int Heart K. 2015;56(3):278-285.

Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (2)

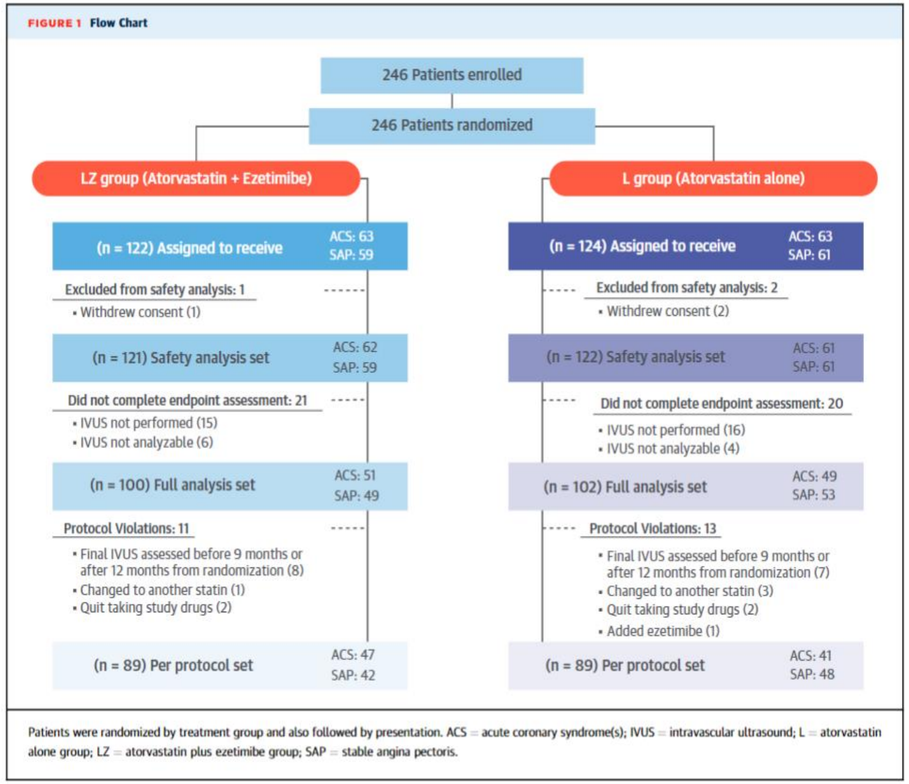


TABLE 2 Baseline and Follow-Up Laboratory Data

	Baseline		Follow-Up		Percent Change (%)		
	LZ Group (n = 100)	L Group (n = 102)	LZ Group (n = 100)	L Group (n = 102)	LZ Group (n = 100)	L Group (n = 102)	p Value
TC, mg/dl	177.3 ± 32.4	172.7 ± 32.6	129.4 ± 22.0	138.7 ± 26.2	-25 ± 17	-18 ± 18	0.006
HDL-C, mg/dl	41.1 ± 9.5	40.0 ± 10.3	45.6 ± 11.9	43.3 ± 11.5	14 ± 26	11 ± 25	0.5
LDL-C, mg/dl	109.8 ± 25.4	108.3 ± 26.3	63.2 ± 16.3	73.3 ± 20.3	-40 ± 18	-29 ± 24	<0.001
Triglycerides, mg/dl	114 (81 to 158)	116 (92 to 159)	92 (76 to 120)	111 (87 to 139)	-14 (-33 to 18)	-9 (-33 to 25)	0.3
Lipoprotein (a), mg/dl	21.5 (12.5 to 37.5)	18.0 (10.0 to 30.5)	17.0 (8.0 to 36.0)	14.0 (7.0 to 30.5)	-12 (-42 to 17)	-20 (-50 to 7)	0.1
Apolipoprotein A-I, mg/dl	112.8 ± 20.2	112.6 ± 21.6	128.1 ± 25.0	123.7 ± 24.5	15 ± 21	11 ± 17	0.2
Apolipoprotein B, mg/dl	96.9 ± 20.6	94.0 ± 19.2	62.5 ± 13.0	69.0 ± 16.1	-34 ± 16	-26 ± 20	0.001
Free fatty acid, μEq/l	402 (281 to 574)	431 (278 to 610)	384 (218 to 541)	376 (223 to 627)	-7 (-50 to 59)	-11 (-56 to 68)	0.8
MDA-LDL, U/l	122.9 ± 39.9	121.8 ± 40.5	81.8 ± 24.1	95.1 ± 30.8	-27.7 ± 27.0	-15.3 ± 38.5	0.1
RLP-C, mg/dl	3.8 (2.7 to 4.8)	3.5 (2.7 to 5.1)	2.6 (2.1 to 3.5)	3.1 (2.4 to 4.5)	-28 (-48 to 3)	-17 (-37 to 17)	0.02
sdLDL-C, mg/dl	32.7 ± 15.6	30.5 ± 11.8	20.6 ± 8.6	22.5 ± 10.1	-28.5 ± 33.5	-21.4 ± 35.0	0.2
Insulin, μIU/ml	6.8 (4.3 to 10.1)	7.3 (4.9 to 9.6)	7.9 (4.9 to 12.6)	8.4 (5.4 to 12.5)	15 (-33 to 73)	22 (-18 to 51)	0.99
HbA_{1c}, %	5.4 (5.1 to 6.3)	5.5 (5.3 to 6.3)	5.6 (5.2 to 6.0)	5.7 (5.4 to 6.1)	3 (-2 to 5)	2 (-4 to 4)	0.2
Total adiponectin, μg/ml	4.7 (3.4 to 7.0)	4.1 (2.7 to 5.7)	6.2 (3.9 to 8.3)	5.0 (3.3 to 7.2)	28 (-4 to 64)	19 (-5 to 63)	0.4
HMW adiponectin, μg/ml	1.9 (1.0 to 3.1)	1.4 (0.8 to 2.6)	2.3 (1.2 to 4.3)	1.6 (0.9 to 2.9)	24 (-25 to 74)	19 (-25 to 86)	0.9
Lathosterol, μg/ml	1.1 (0.7 to 2.3)	1.3 (0.7 to 2.1)	1.0 (0.8 to 1.4)	0.6 (0.4 to 0.9)	-15 (-53 to 45)	-53 (-71 to -22)	<0.001
Campesterol, μg/ml	4.4 (3.3 to 5.7)	3.7 (2.8 to 5.0)	2.3 (1.8 to 2.9)	4.9 (3.5 to 6.4)	-46 (-61 to -30)	22 (-5 to 61)	<0.001
Sitosterol, μg/ml	2.2 (1.7 to 3.0)	2.0 (1.5 to 2.7)	1.3 (1.0 to 1.9)	2.4 (1.8 to 3.4)	-39 (-53 to -20)	31 (-6 to 67)	<0.001
Lathosterol, μg/100 mg TC	68 (43 to 109)	73 (44 to 116)	81 (59 to 108)	49 (33 to 66)	14 (-28 to 68)	-36 (-57 to 2)	<0.001
Campesterol, μg/100 mg TC	252 (199 to 321)	215 (165 to 281)	183 (143 to 228)	362 (258 to 451)	-30 (-43 to -10)	53 (24 to 82)	<0.001
Sitosterol, μg/100 mg TC	129 (98 to 174)	113 (91 to 152)	101 (78 to 145)	178 (131 to 264)	-15 (-34 to 9)	60 (27 to 106)	<0.001
Campesterol/lathosterol	3.7 (2.2 to 6.5)	2.8 (2.0 to 5.0)	2.2 (1.5 to 3.6)	7.5 (4.3 to 12.5)	-40 (-66 to 10)	167 (48 to 267)	<0.001
hs-CRP, mg/l	3.0 (1.0 to 14.9)	3.7 (1.2 to 8.1)	0.4 (0.2 to 1.3)	0.3 (0.2 to 0.8)	-89 (-97 to -59)	-86 (-95 to -70)	0.9

Values are mean ± SD or median (IQR).
HDL-C = high-density lipoprotein cholesterol; HMW = high molecular weight; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MDA-LDL = malondialdehyde-modified LDL; RLP-C = remnant like particles cholesterol; sdLDL-C = small-dense LDL-C; TC = total cholesterol; other abbreviations as in Table 1.

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

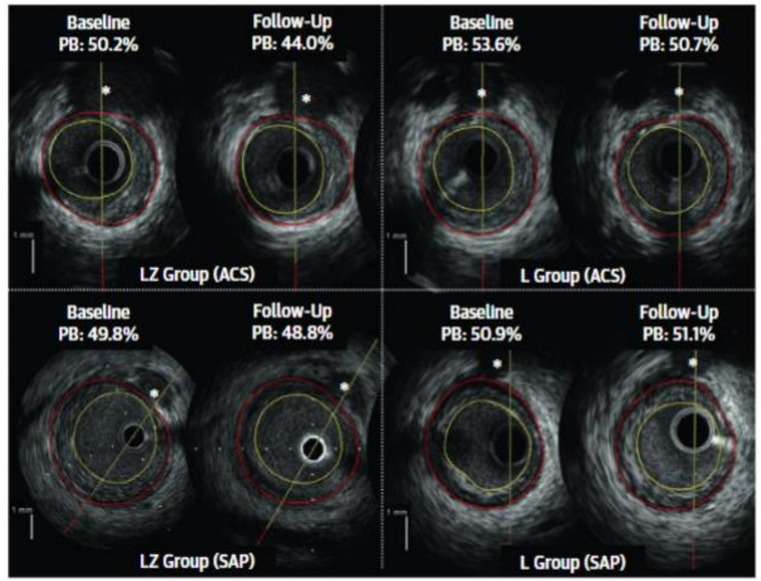
Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (2)

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



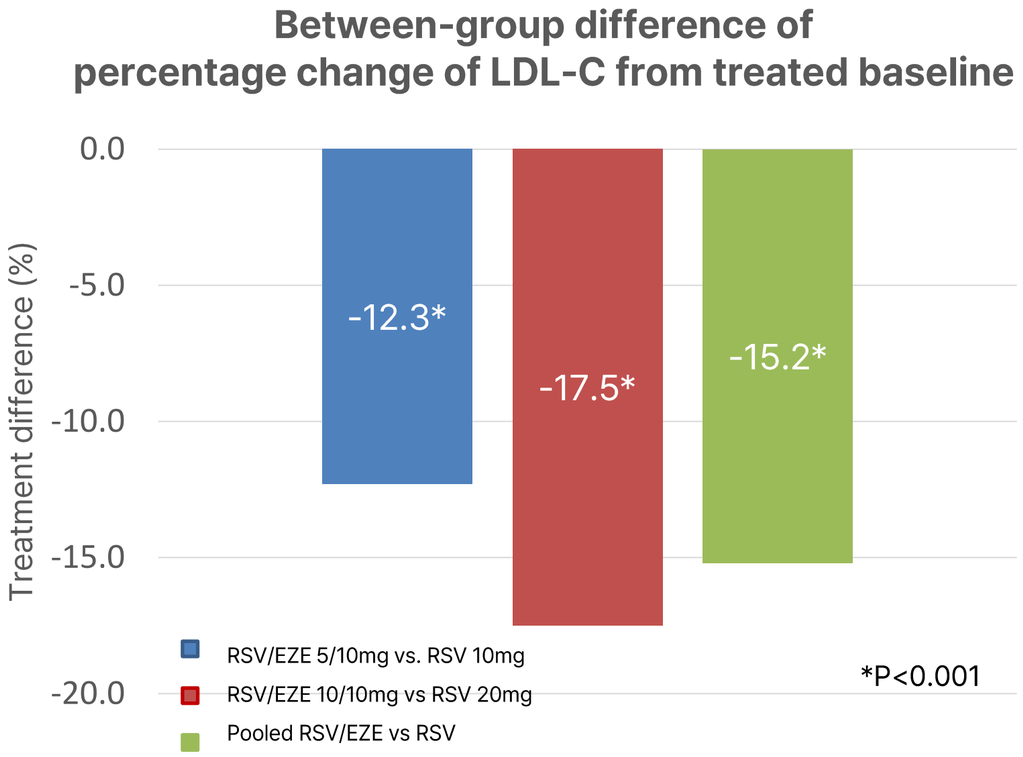
IVUS images of the same cross sections at baseline and follow-up show outlined leading edges of lumen **(yellow line)** and external elastic membrane **(red line)**. Note the substantial reduction in plaque area observed for the cross-sectional images, especially in the LZ group versus the L group.*Side 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

ACTE Ezetimibe 10mg provided significantly greater LDL-C reduction than doubling the statin dose



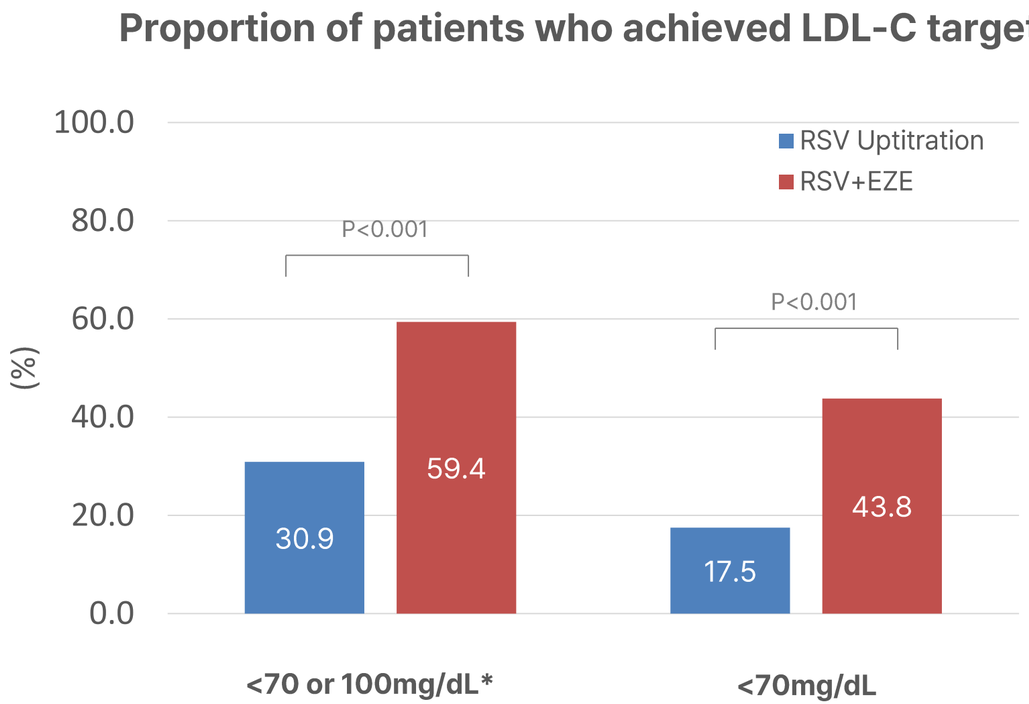
- Pooled data showed ezetimibe added to rosuvastatin 5/10mg reduced LDL-C by 21% vs 5.7% with rosuvastatin dose doubling (between-group difference 15.2%, p<0.001)
- Ezetimibe + rosuvastatin 5mg reduced LDL-C more than rosuvastatin 10mg (12.3% difference, p<0.001)
- Ezetimibe + rosuvastatin 10mg reduced LDL-C more than rosuvastatin 20mg (17.5% difference, p<0.001)

Study Design

Randomised, double-blind, parallel-group study. After 4-5 week open-label run-in period on rosuvastatin 5 or 10mg, patients not at LDL-C goals were randomised to receive either ezetimibe 10mg added to their rosuvastatin dose, or doubling their rosuvastatin dose for 6 weeks. Primary efficacy endpoint was the percentage change from baseline in LDL-C.

Abbreviation CHD, coronary heart disease; ; EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin;
Reference Bays HE et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). *Am J Cardiol.* 2011;108(4):523-530.

ACTE Ezetimibe 10mg provided significantly greater LDL-C goal attainment in high risk CHD patients



- Ezetimibe add-on led to greater attainment of LDL-C goals compared to rosuvastatin uptitration
  - < 70 or 100 mg/dL (59.4% vs 30.9%, p<0.001)
  - <70 mg/dL in all subjects (43.8% vs 17.5%, p<0.001)

* <100 mg/dL for moderately high-/high-risk subjects without AVD and <70 mg/dL for high-risk subjects with AVD

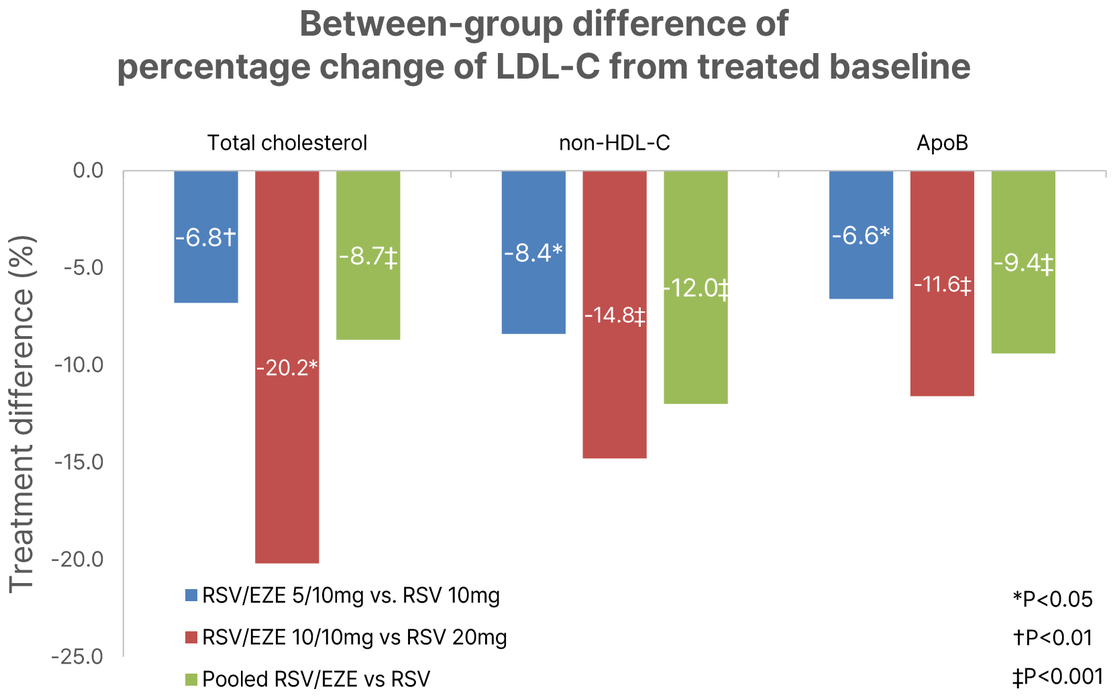
Study Design

Randomised, double-blind, parallel-group study. After 4-5 week open-label run-in period on rosuvastatin 5 or 10mg, patients not at LDL-C goals were randomised to receive either ezetimibe 10mg added to their rosuvastatin dose, or doubling their rosuvastatin dose for 6 weeks. Primary efficacy endpoint was the percentage change from baseline in LDL-C.

Abbreviation CHD, coronary heart disease; ; EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin; AVD, atherosclerotic vascular disease

Reference Bays HE et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). *Am J Cardiol.* 2011;108(4):523-530.

ACTE Ezetimibe 10mg produced significant improvements in other lipid parameters



- Ezetimibe add-on produced significantly greater reductions in total cholesterol, non-HDL-C, and apoB (p<0.001)

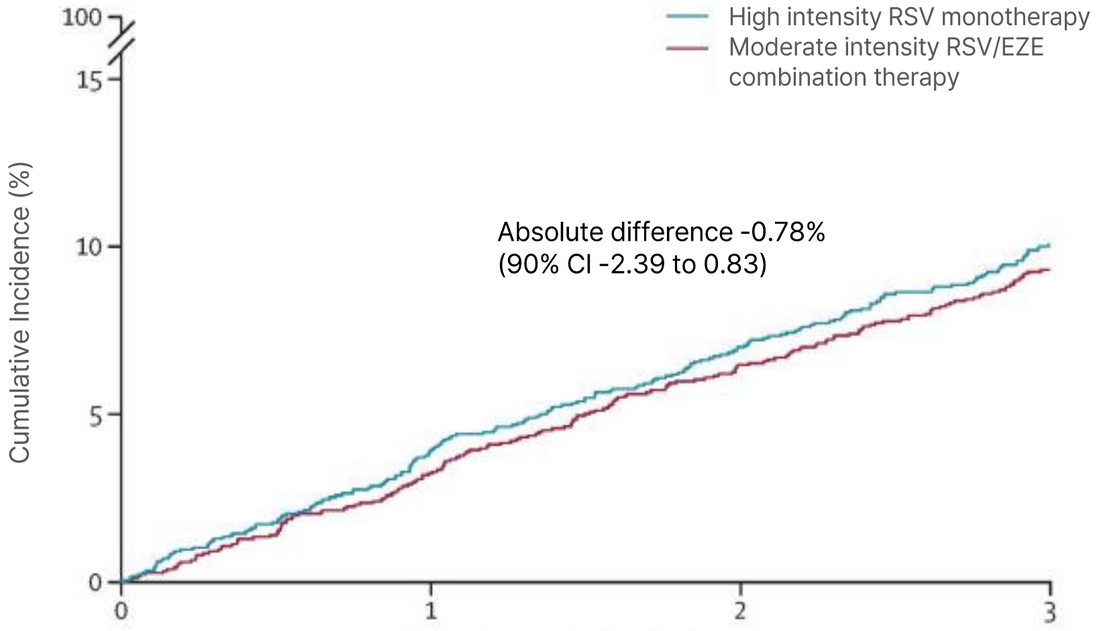
Study Design

Randomised, double-blind, parallel-group study. After 4-5 week open-label run-in period on rosuvastatin 5 or 10mg, patients not at LDL-C goals were randomised to receive either ezetimibe 10mg added to their rosuvastatin dose, or doubling their rosuvastatin dose for 6 weeks. Primary efficacy endpoint was the percentage change from baseline in LDL-C.

Abbreviation CHD, coronary heart disease; ; EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin;

Reference Bays HE et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). *Am J Cardiol.* 2011;108(4):523-530.

RACING Moderate intensity RSV/EZE was non-inferior to high intensity RSV monotherapy for 3-year CV events



Number at risk				
Monotherapy	1886	1786	1711	1639
Combination therapy	1894	1795	1724	1654

- 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)

* 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2.0%

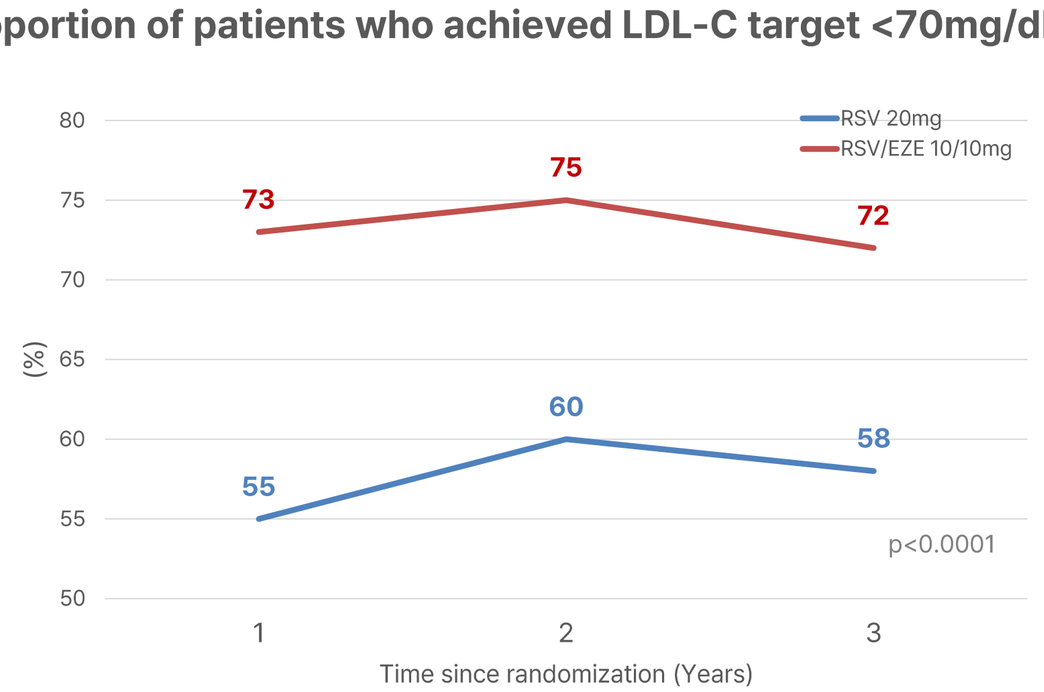
Study Design

Randomised, open-label, non-inferiority trial. Patients with ASCVD at 26 clinical centres in South Korea were randomly assigned to receive either moderate intensity rosuvastatin with ezetimibe (10mg rosuvastatin + 10mg ezetimibe) or high intensity statin monotherapy (rosuvastatin 20mg). The primary endpoint was 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2·0%

Abbreviation ASCVD, atherosclerotic cardiovascular disease; EZE, ezetimibe; RSV, rosuvastatin;

Reference Kim BK 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;400(10349):380-390.

RACING Moderate intensity RSV/EZE combination led to higher proportion of patients with LDL-C <70 mg/dL



- LDL cholesterol concentrations of less than 70 mg/dL at 1, 2, and 3 years were observed in:
  - 73%, 75%, and 72% of patients in the moderate intensity RSV/EZE combination therapy group
  - 55%, 60%, and 58% of patients in the high-intensity rosuvastatin monotherapy group (all p<0·0001).

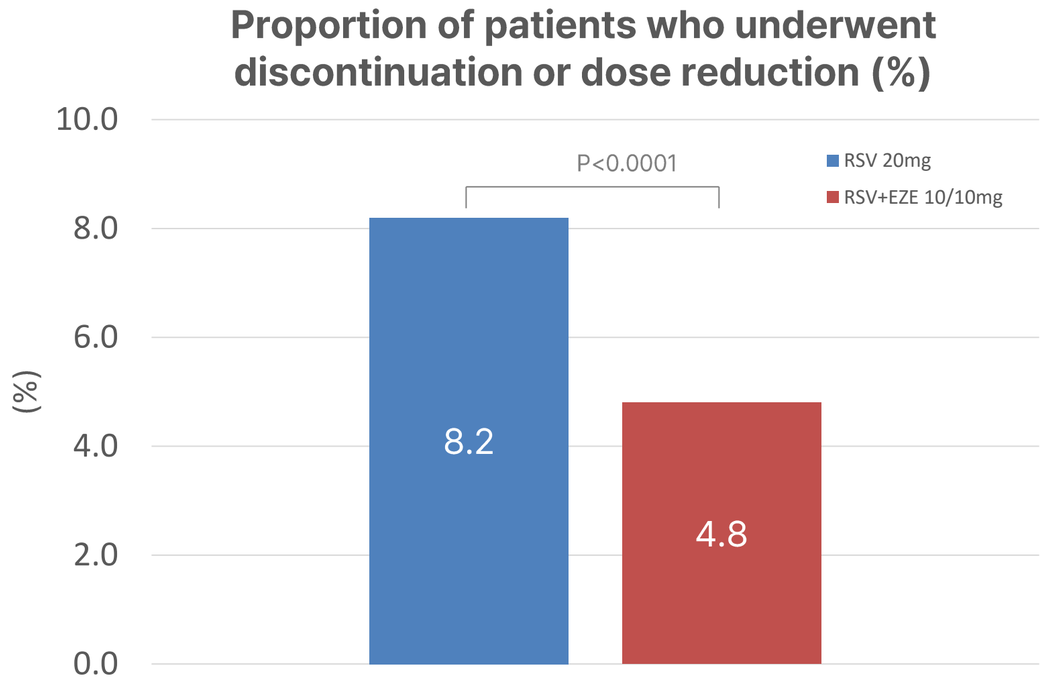
Study Design

Randomised, open-label, non-inferiority trial. Patients with ASCVD at 26 clinical centres in South Korea were randomly assigned to receive either moderate intensity rosuvastatin with ezetimibe (10mg rosuvastatin + 10mg ezetimibe) or high intensity statin monotherapy (rosuvastatin 20mg). The primary endpoint was 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2·0%

Abbreviation ASCVD, atherosclerotic cardiovascular disease; EZE, ezetimibe; RSV, rosuvastatin;

Reference Kim BK 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;400(10349):380-390.

RACING Moderate intensity RSV/EZE combination led to lower intolerance-related drug discontinuation or dose reduction



- Discontinuation or dose reduction of the study drug by intolerance was observed in: (p<0·0001)
  - 88 patients (4·8%) in moderate intensity RSV/EZE combination therapy group
  - 150 patients (8·2%) in high intensity RSV group

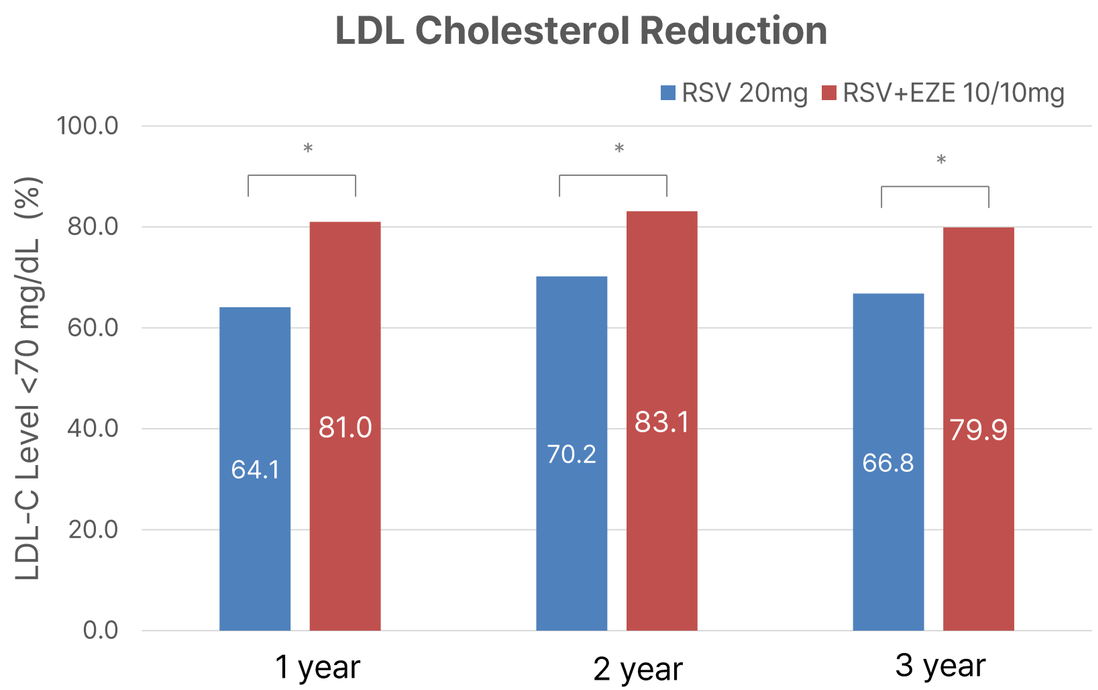
Study Design

Randomised, open-label, non-inferiority trial. Patients with ASCVD at 26 clinical centres in South Korea were randomly assigned to receive either moderate intensity rosuvastatin with ezetimibe (10mg rosuvastatin + 10mg ezetimibe) or high intensity statin monotherapy (rosuvastatin 20mg). The primary endpoint was 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2·0%

Abbreviation ASCVD, atherosclerotic cardiovascular disease; EZE, ezetimibe; RSV, rosuvastatin;

Reference Kim BK 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;400(10349):380-390.

RACING-DM Ezetimibe addition to Rosuvastatin resulted in greater LDL-C reduction in DM patients.



- The proportion of DM patients whose LDL-C<70mg/dL was consistently higher in the ezetimibe combination therapy group (P<0.001)

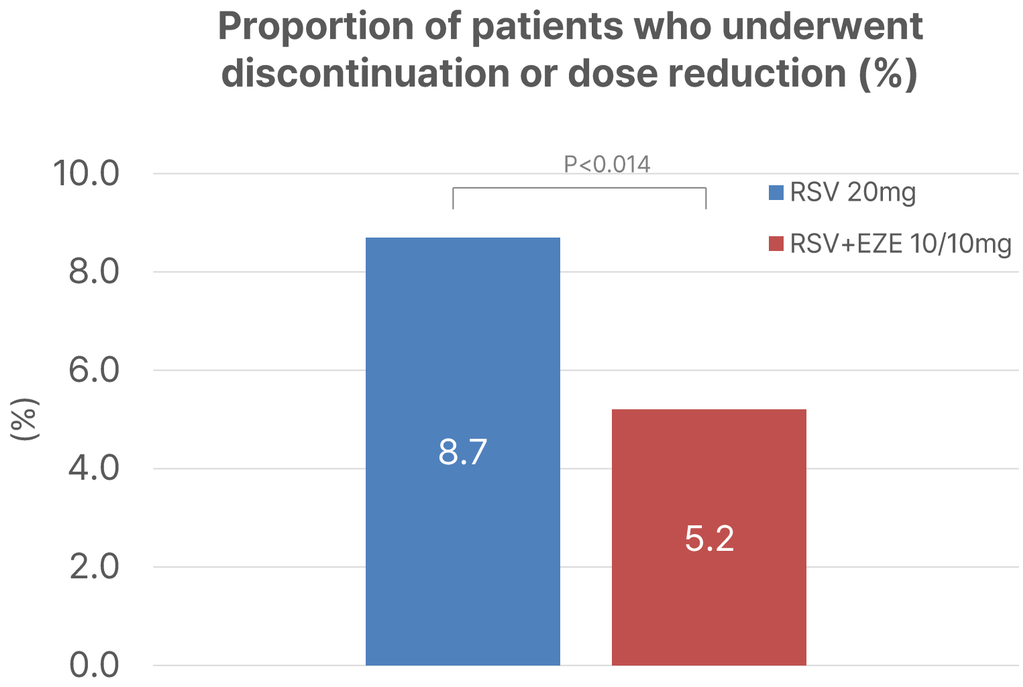
Study Design

Pre-specified, stratified subgroup analysis of the diabetes mellitus cohort from the RACING trial: Randomised, open-label, non-inferiority trial. Patients were randomised 1:1 to receive either rosuvastatin 10mg with ezetimibe, or rosuvastatin alone, and followed for 3 years. Primary endpoint was composite of CV death, major CV events, or non-fatal stroke.

Abbreviation DM, diabetes mellitus; EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin;

Reference Lee YJ et al. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. *Eur Heart J.* 2023;44(11):972-983.

RACING-DM Ezetimibe addition to Rosuvastatin resulted in lower rate of drug discontinuation in DM patients.



- The rate of discontinuation or dose reduction of the study drug due to intolerance was lower in the rosuvastatin+ezetimibe combination therapy group than in the rosuvastatin monotherapy group (5.2 vs. 8.7%; P=0.014)
- Rate of developing new-onset DM did not differ between the combination therapy group and the statin monotherapy group among patients without DM
(safety population, 17.1 vs. 16.7%; P= 0.833)

Study Design

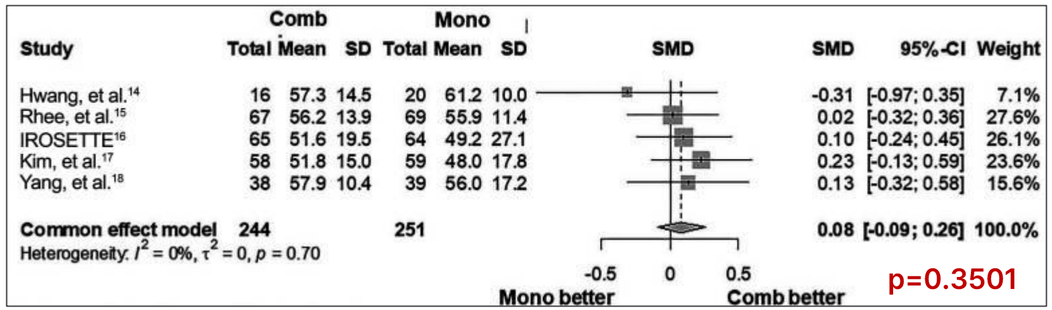
Pre-specified, stratified subgroup analysis of the diabetes mellitus cohort from the RACING trial: Randomised, open-label, non-inferiority trial. Patients were randomised 1:1 to receive either rosuvastatin 10mg with ezetimibe, or rosuvastatin alone, and followed for 3 years. Primary endpoint was composite of CV death, major CV events, or non-fatal stroke.

Abbreviation DM, diabetes mellitus; EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin;

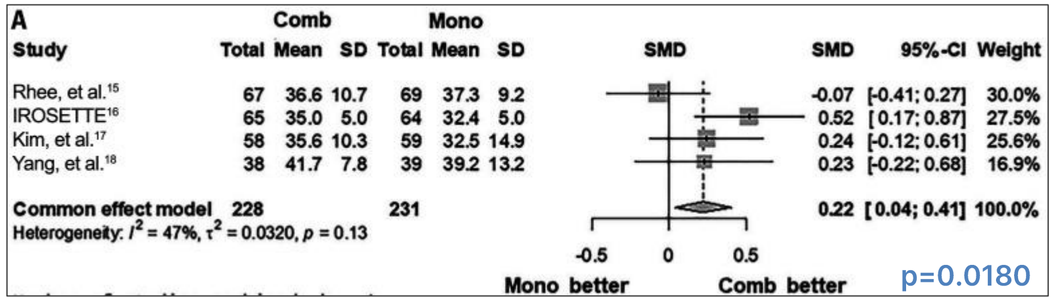
Reference Lee YJ et al. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. *Eur Heart J.* 2023;44(11):972-983.

Similar efficacy and tolerability of 5 mg RSV/10 mg EZE versus RSV 20 mg

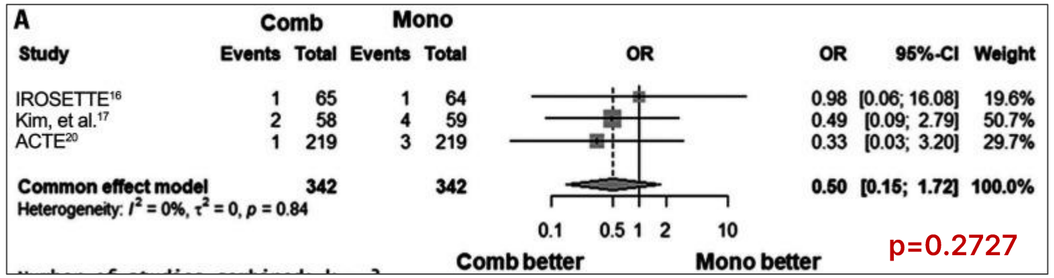
Reduction of LDL-C



Reductions of total cholesterol



Risk of composite AEs



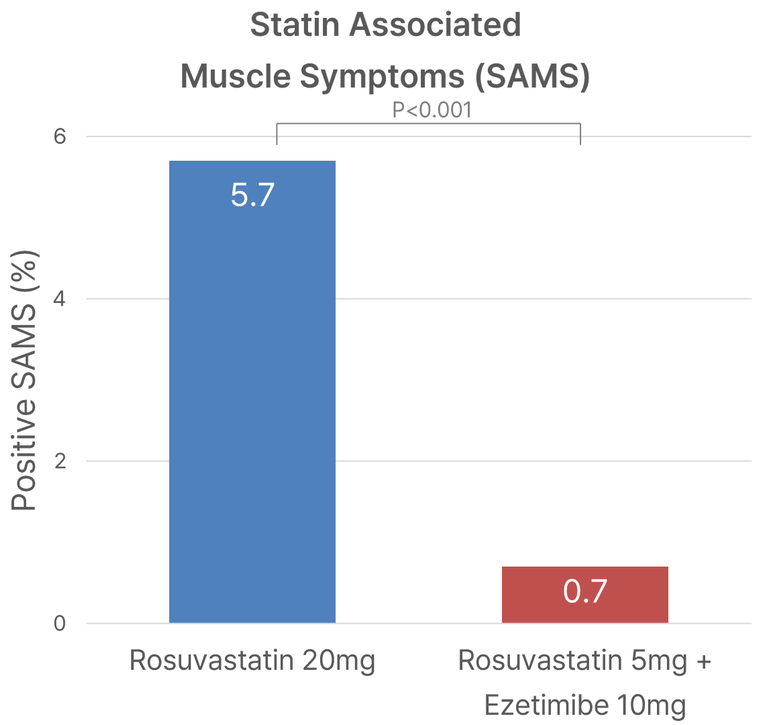
- The major findings of the current study were as follows:
  - **Reduction in LDL-C levels did not differ** between the two regimens
  - **Risk of composite AEs did not differ** between the two regimens
  - **Reduction in TC was higher** with the combination regimen than with the monotherapy regimen

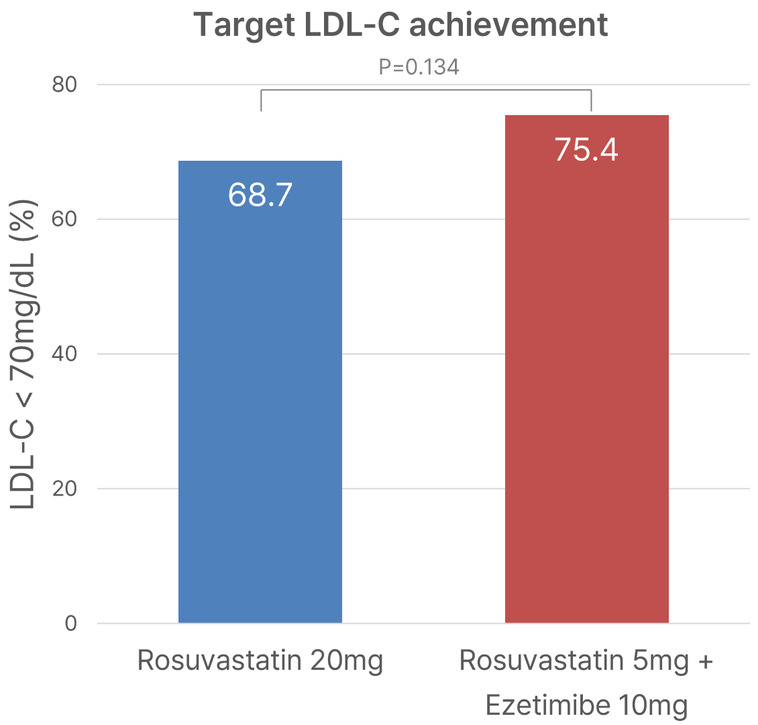
Study Design

Seven studies were included in this meta-analysis. We compared the lipid-modifying efficacy and safety of 5 mg rosuvastatin/10 mg ezetimibe to those of 20 mg rosuvastatin. Outcome variables included the percentage reduction in LDL-C and other lipid parameters and rates of composite adverse events (AEs), including muscle-related symptoms. A random-effects meta-analysis was performed after heterogeneity testing between studies.

Abbreviation EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin; Comb, combination regimen (5 mg rosuvastatin/10 mg ezetimibe); Mono, monotherapy regimen (20 mg rosuvastatin). SMD, standardized mean difference.
Reference Kang Y, Park JM, Lee SH. Moderate-Intensity Rosuvastatin/Ezetimibe Combination versus Quadruple-Dose Rosuvastatin Monotherapy: A Meta-Analysis and Systemic Review. Yonsei Med J. 2024 Jan;65(1):19-26.

Safety and efficacy of moderate-intensity statin with ezetimibe in elderly patients with ASCVD





- Moderate-intensity statin with ezetimibe combination therapy offers a **lower risk of SAMS** and **similar LDL-C reduction** in elderly patients with ASCVD, compared to high-intensity statin monotherapy

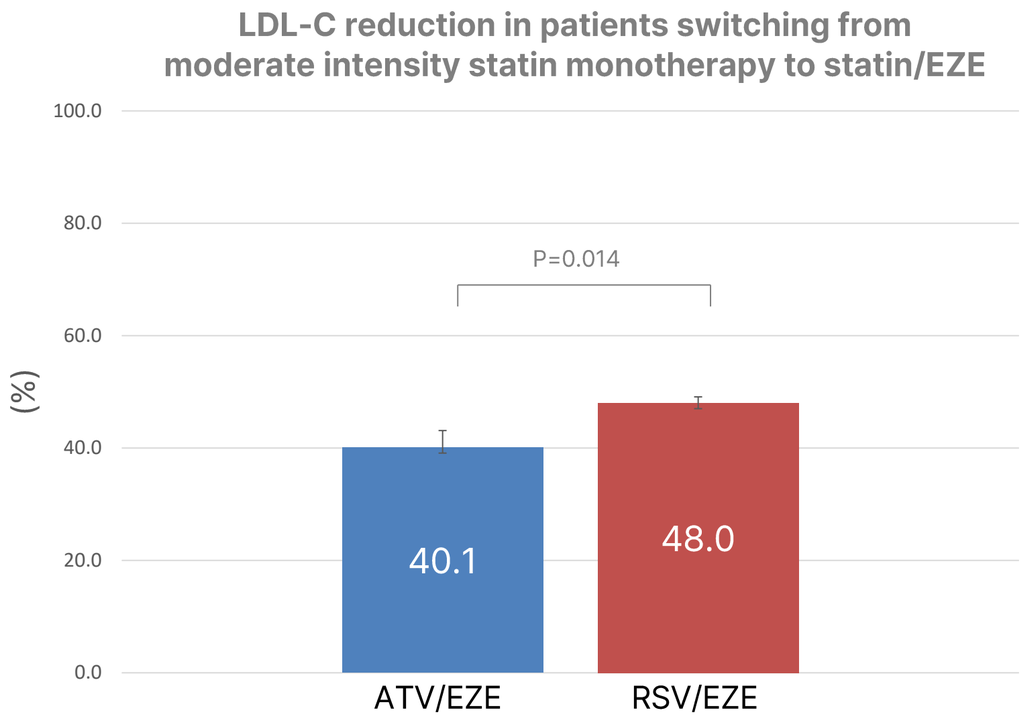
Study Design

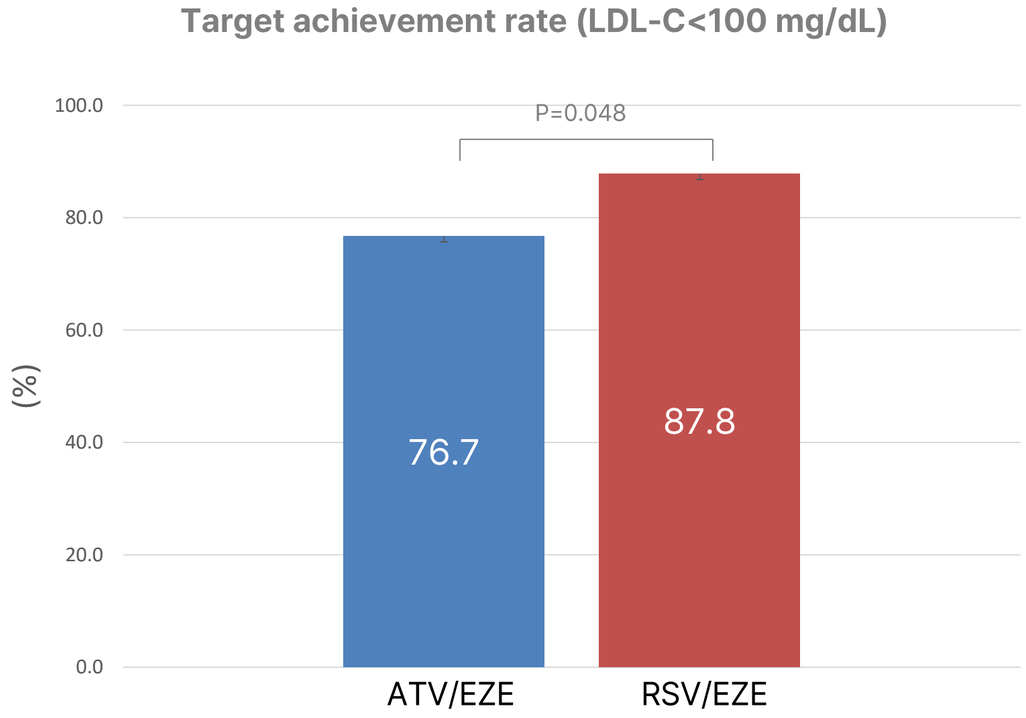
In a prospective, multicenter, open-label trial conducted in South Korea, 561 patients aged 70 years or above with ASCVD were randomly assigned to receive either moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 5 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg) over 6 months. The primary endpoint was the incidence of SAMS, and the key secondary endpoint was the achievement of target LDL-C levels (<70 mg/dL) within 6 months.

Abbreviation LDL-C, low density lipoprotein-cholesterol; SAMS, statin-associated muscle symptoms; ASCVD, Atherosclerotic cardiovascular disease

Reference Cha JJ, Kim JH et al. Safety and efficacy of moderate-intensity statin with ezetimibe in elderly patients with atherosclerotic cardiovascular disease. J Intern Med. 2024 Dec 22.

For patients switching from moderate intensity statin monotherapy, RSV/EZE showed a significantly greater LDL-C reduction compared to switching to ATV/EZE





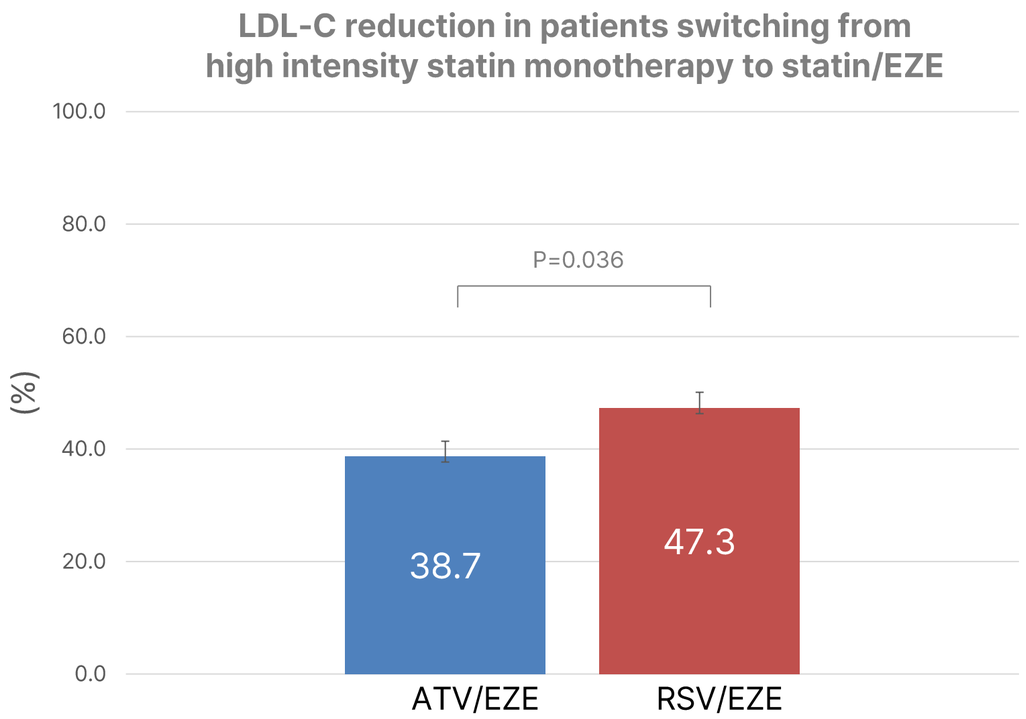
Study Design

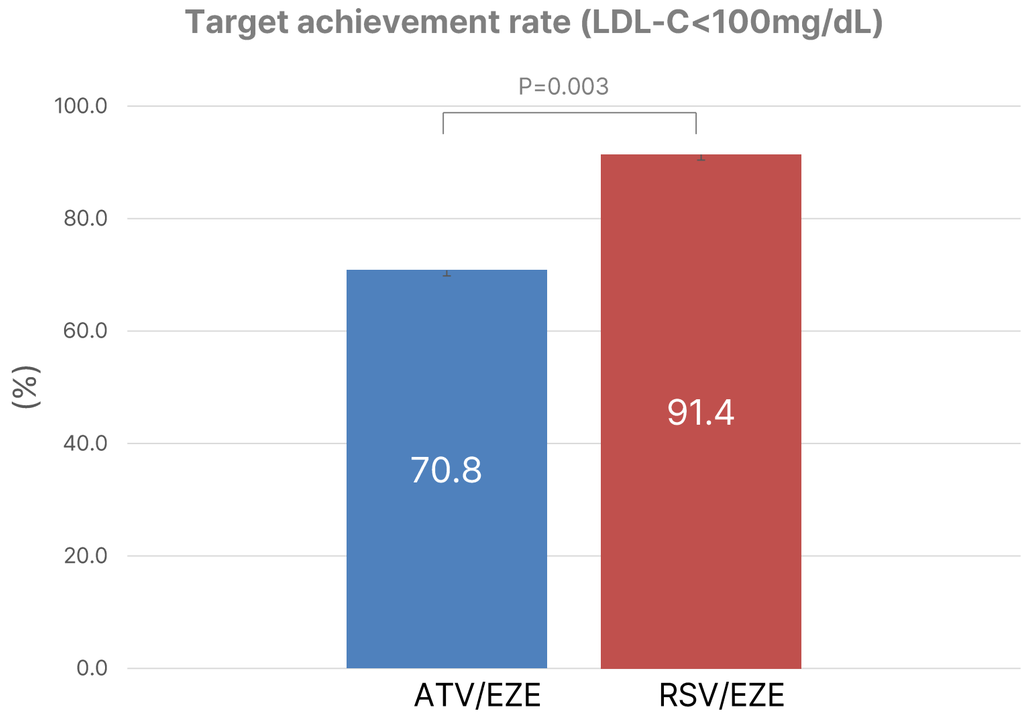
Retrospective analysis using electronic medical record data of patients who were prescribed statin/ezetimibe combination therapy to investigate the additional LD-C reductions and target achievement rates in patients after switching from statin monotherapy to statin/ezetimibe combination therapy in a real-world clinical setting

Abbreviation ATV, atorvastatin; EZE, ezetimibe; RSV, Rosuvastatin; LDL-C, low density lipoprotein-cholesterol; PAD, peripheral artery disease;
Reference Lee J et al. Low-density lipoprotein cholesterol reduction and target achievement after switching from statin monotherapy to statin/ezetimibe combination therapy: Real-world evidence. J Clin Pharm Ther. 2021;46(1):134-142.

For patients switching from high intensity statin monotherapy,

RSV/EZE showed a significantly greater LDL-C reduction compared to switching to ATV/EZE





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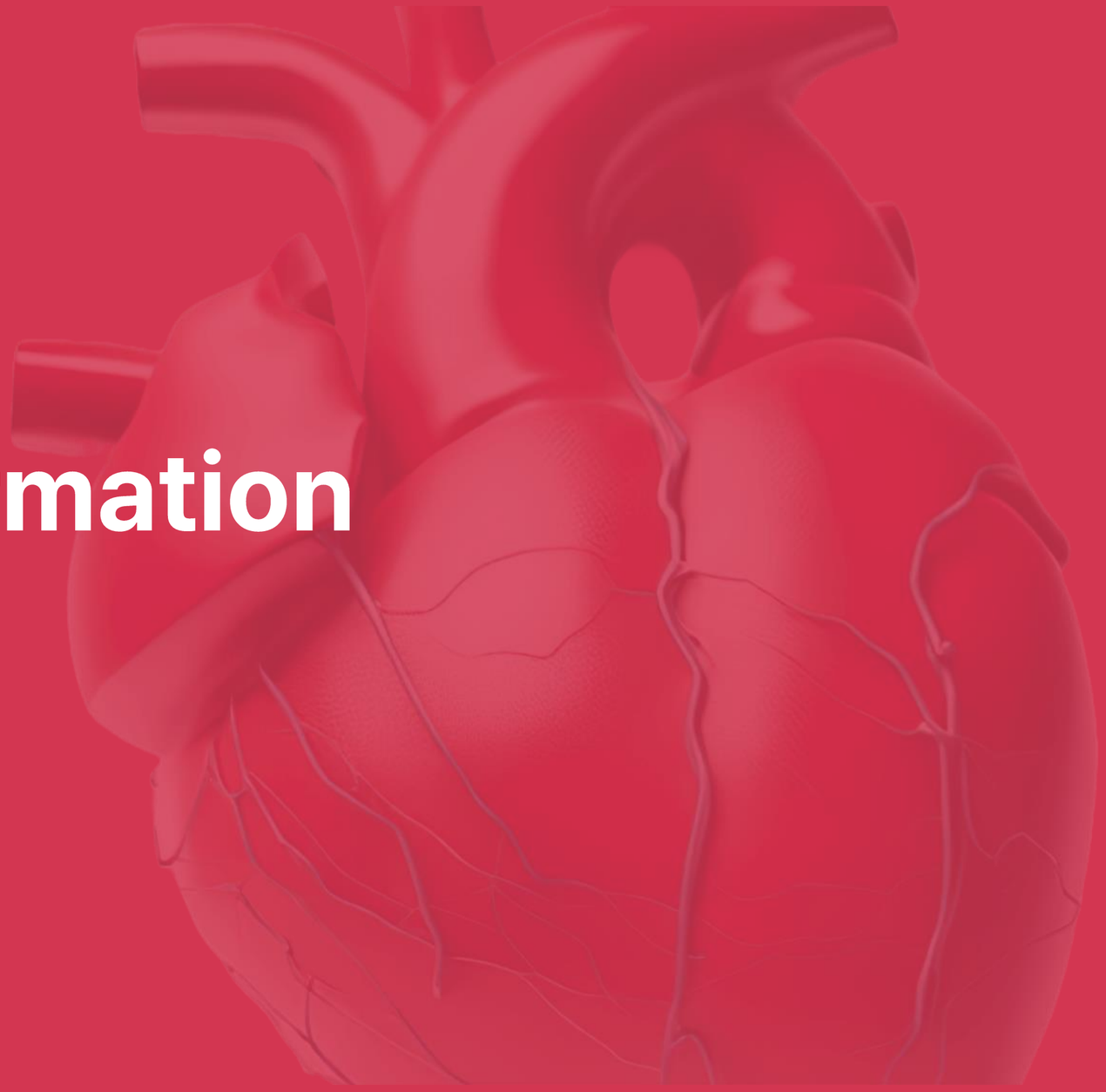
Abbreviation ATV, atorvastatin; EZE, ezetimibe; RSV. roLDL-C, low density lipoprotein-cholesterol; PAD, peripheral artery disease;

Reference Lee J et al. Low-density lipoprotein cholesterol reduction and target achievement after switching from statin monotherapy to statin/ezetimibe combination therapy: Real-world evidence. J Clin Pharm Ther. 2021;46(1):134-142.

04 *CREZET*
Product Information



Crezet ® Information

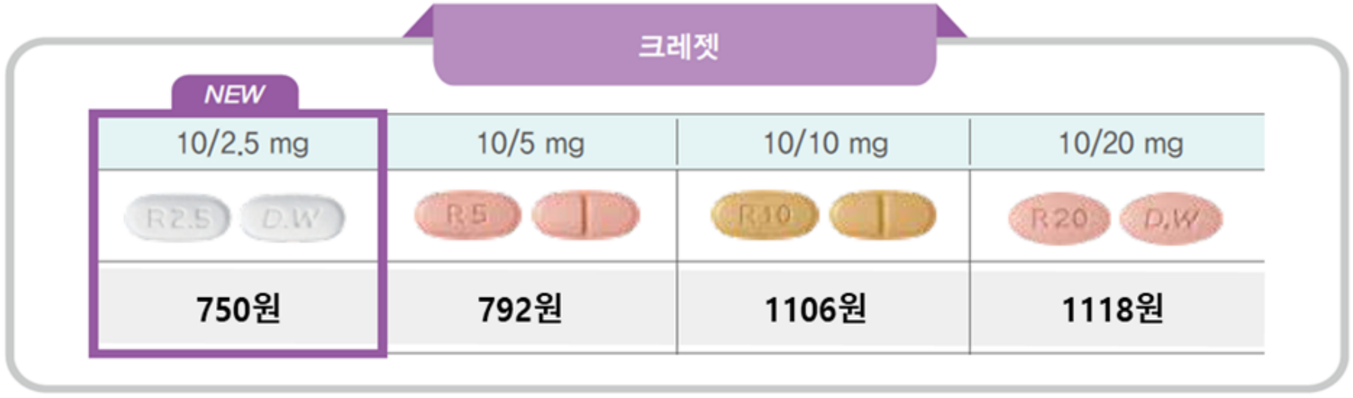
▣제품정보

1.제품명 : **크레젯 정(CREZET Tab.)**

2.성분명 : 에제티미브(Ezetimibe) 10mg, 로수바스타틴 칼슘(Rosuvastatin Calcium) 2.5/5/10/20mg

3.적응증 : 원발성 고콜레스테롤혈증

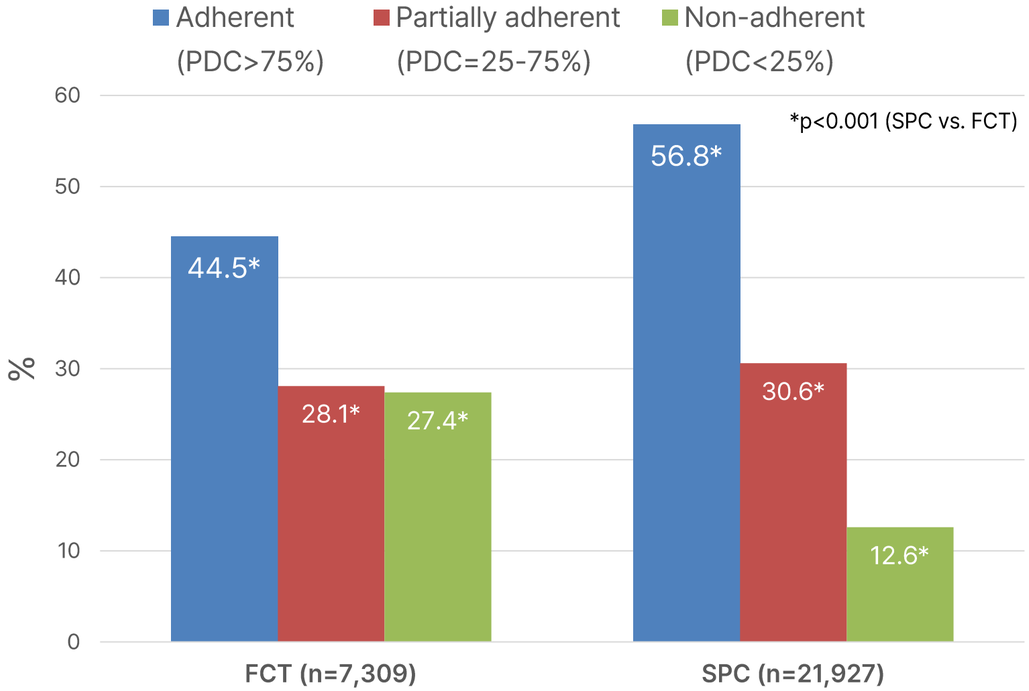
4.용법용량 : 1일 1회, 식사와 상관없이 하루 중 아무 때나 투약



※ 약물의 실제 크기와 다르며 사이즈는 장축x단축x두께로 나타냄

Treatment with RSV/EZE as SPC resulted in better adherence over FCT

Proportion of adherent, partially adherent, and non-adherent patients in SPC and FCT cohorts



- Significantly higher percentage of patients were **adherent (PDC > 75%) to SPC** when compared with FCT (56.8 vs. 44.5%, P < 0.001).

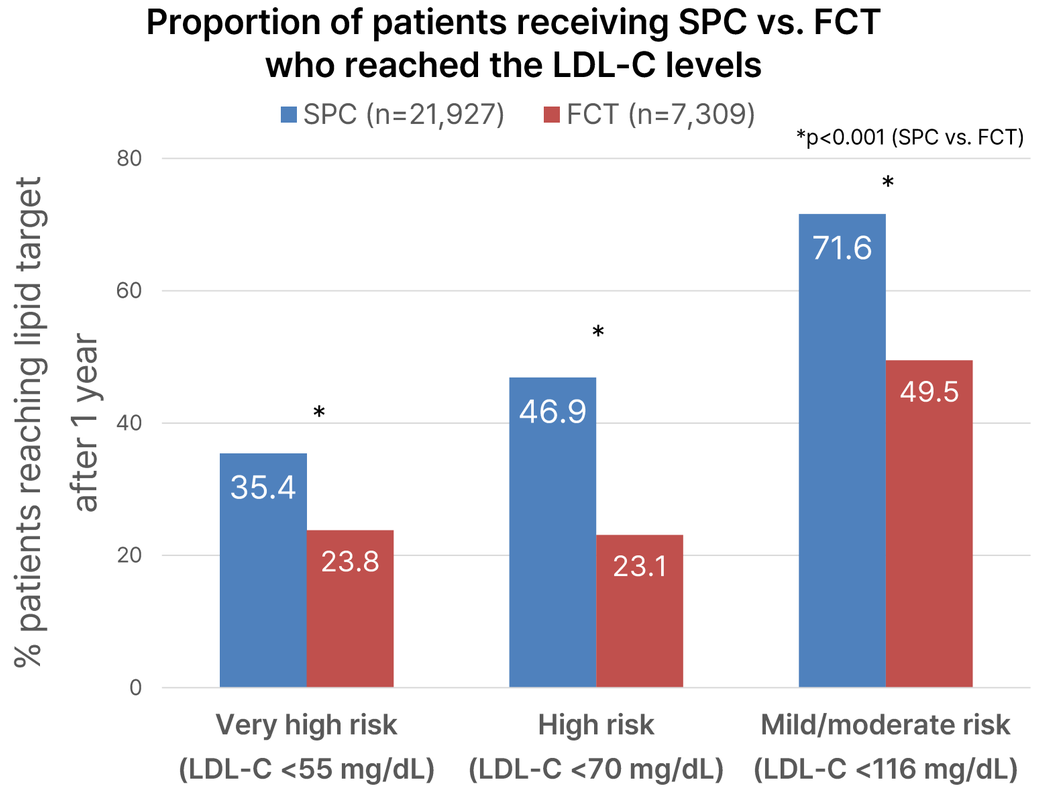
Study Design

Retrospective observational analysis on administrative databases to compare medication adherence, lipid goal attainment and healthcare costs among patients treated with rosuvastatin/ezetimibe(ROS/EZE) as single pill vs free combination treatment in Italy

Abbreviation EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin; SPC, Single pill combination; PDC, proportion of days covered

Reference Zambon A et al. A real-world analysis of adherence, biochemical outcomes, and healthcare costs in patients treated with rosuvastatin/ezetimibe as single-pill combination vs. free combination in Italy. Eur Heart J Open. 2024 Aug 28;4(5):oeae074.

Treatment with RSV/EZE as SPC resulted in higher chances of reaching lipid goals over FCT



- The proportion of patients reaching LDL-C level target at 1 year follow up was **higher in SPC** in all cardiovascular risk categories.

Study Design

Retrospective observational analysis on administrative databases to compare medication adherence, lipid goal attainment and healthcare costs among patients treated with rosuvastatin/ezetimibe(ROS/EZE) as single pill vs free combination treatment in Italy

Abbreviation EZE, ezetimibe; LDL-C, low density lipoprotein-cholesterol; RSV, rosuvastatin; SPC, Single pill combination; PDC, proportion of days covered

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LLT with SPC of RSV/EZE increases the chances of being adherent and achieving the recommended LDL-C target levels

SPC-treated were more likely to be adherent than FCT-treated

Adherence ↑

SPC-treated were more likely to reach the lipid goal set than FCT-treated

LDL-C ↓

SPC treatment was associated with lower healthcare costs than FCT

Healthcare Costs ↓

Study Design

Retrospective observational analysis on administrative databases to compare medication adherence, lipid goal attainment and healthcare costs among patients treated with rosuvastatin/ezetimibe(ROS/EZE) as single pill vs free combination treatment in Italy

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Reference Zambon A et al. A real-world analysis of adherence, biochemical outcomes, and healthcare costs in patients treated with rosuvastatin/ezetimibe as single-pill combination vs. free combination in Italy. Eur Heart J Open. 2024 Aug 28;4(5):oeae074.

Take home message

- Despite the guideline recommendations,a significant proportion of high-risk ASCVD patients fail to achieve target LDL-C levels

- In agreement with the "lower is better" principle for LDL-C reduction,
  evidence also suggests that "earlier and more sustained" LDL-C reduction provides benefit

- **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.

Thank you