THE SMALLER,
THE BETTER.

New concepts of Dyslipidemia Medication:
the Lower, the Smaller

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Rova**zet** ® Tab.
Ezetimibe+Rosuvastatin

CONTENTS

- **Change of Dyslipidemia Guidelines**

- **Efficacy of Rosuvastatin**

- **Combination with Ezetimibe**

- **Need of Lower statin/ezetimibe**

- **Benefits of Smaller tablet**

Ezetimibe

Rosuvastatin

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Rosuvastatin

Ezetimibe

Guidelines for Lipid Management

Algorithm about primary prevention of ASCVD

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■ **Class I** (Strong)   ■ **Class IIa** (Moderate)   ■ **Class IIb** (Weak)

▸ Primary Prevention

Primary prevention: Assess ASCVD risk in each age group emphasize adherence to healthy lifestyle

LDL-C ≥ 190 mg/dL (≥4.9 mmol/L) **No risk assessment; High-intensity statin** (Class I)

Daibetes mellitus and age 40-75 y Moderate-intensity statin (Class I)

Daibetes mellitus and age 40-75 y Risk assessment to consider high-intensity statin (Class II)

Age > 75 y Clinical assessment, Risk discussion

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of familial hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L)

Age 40-75 y and
LDL-C ≥ 70- ≤ 190 mg/dL (≥1.8- < 4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

ASCVD risk enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory desease (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥ 175 mg/dL (≥ 2.0 mmol/L))

In selected individuals if measured:
- hs-CRP ≥ 2.0 mg/L
- Lp(a) levels > 50 mg/dL or > 125 nmol/L
- apoB ≥ 130 mg/dL
- Ankle-brachial index (ABI) < 0.9

< 5% "Low Risk"

5% - <7.5% "Bordeline Risk"

≥ 7.5% - < 20% "Intermediate Risk"

≥ 20% "High Risk"

Risk discussion: Emphasize lifestyle to reduce risk factors (Class I)

Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

Risk discussion: Initiate statin to reduce LDL-C ≥ 50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lower risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100 + and/or ≥ 75th percentile, initiate statin therapy

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; hsCRP, high-sensitivity C-reactive protein

Ref. Grundy SM, et al. J Am Coll Cardiol. 2019;73(24):3168-3209.

Secondary prevention with clinical ASCVD

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Secondary Prevention

- **Class I** (Strong)
- **Class IIa** (Moderate)
- **Class IIb** (Weak)

Clinical ASCVD

↓

Healthy Lifestyle

ASCVD not at very high-risk

Age ≤ 75 y

High-intensity statin
(Goal: ↓ LDL-C ≥ 50%)
(Class I)

If high-intensity statin not tolerated, use moderate-intensity statin
(Class I)

If on maximal statin therapy and LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L). adding ezetimibe may be reasonable
(Class IIb)

Age > 75 y

Initiation of moderate or high-intensity statin is reasonable
(Class IIa)

Continuation of high-intensity statin is reasonable
(Class IIa)

Very high-risk ASCVD

High-intensity or maximal statin
(Class I)

If on maximal statin and LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L), adding ezetimibe is reasonable
(Class IIa)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I
(Class I)

Dashed arrow indicates RCT- supported efficacy, but is less cost effective

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥ 70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥ 100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; PCSK9-I, PCSK9 inhibitor
Ref. Grundy SM, et al. J Am Coll Cardiol. 2019;73(24):3168-3209.

Treatment goals for LDL-C

Treatment goals for LDL-C across categories of total CV disease risk

Treatment goal for LDL-C

3.0 mmol/L (116 mg/dL)

2.6 mmol/L (100 mg/dL)

1.8 mmol/L (70 mg/dL)

1.4 mmol/L (55 mg/dL)

& ≥50% reduction from baseline

- SCORE <1%

LOW

- SCORE ≥1% and <5%
- Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors

MODERATE

- SCORE ≥5% and <10%
- Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
- FH without other major risk factors
- Moderate CKD (eGFR 30-59 mL/min/1.73m^2)
- DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor

HIGH

- ASCVD (clinical/imaging)
- SCORE ≥10%
- FH with ASCVD or with another major risk factor
- Severe CKD (eGFR <30 mL/min/1.73m^2)
- DM & target organ damage ≥ 3 major risk factors; or early onset of T1DM of long duration (>20 years)

VERY HIGH

LOW   MODERATE   HIGH   VERY HIGH   **CV RISK**

Ref. Mach F, et al. *Eur Heart J.* 2020;41(1):111-188.

Clinical benefits of LDL-C lowering therapies

The expected clinical benefits of treatment to LDL-C depends on the intensity of therapy, the baseline LDL-C level, the expected absolute achieved reduction in LDL-C, and the baseline estimated risk of ASCVD.

Intensity of lipid lowering treatment	
Treatment	**Average LDL-C reduction**
☑ Moderate intensity statin	≈ 30%
☑ High intensity statin	≈ 50%
☑ High intensity statin plus ezetimibe	**≈ 65%**
☑ PCSK9 inhibitor	≈ 60%
☑ PCSK9 inhibitor plus high intensity statin	≈ 75%
☑ PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

% reduction LDL-C

Baseline LDL-C

Absolute reduction LDL-C

Relative risk reduction

Baseline risk

Absolute risk reduction

Ref. Mach F, et al. Eur Heart J. 2020;41(1):111-188.
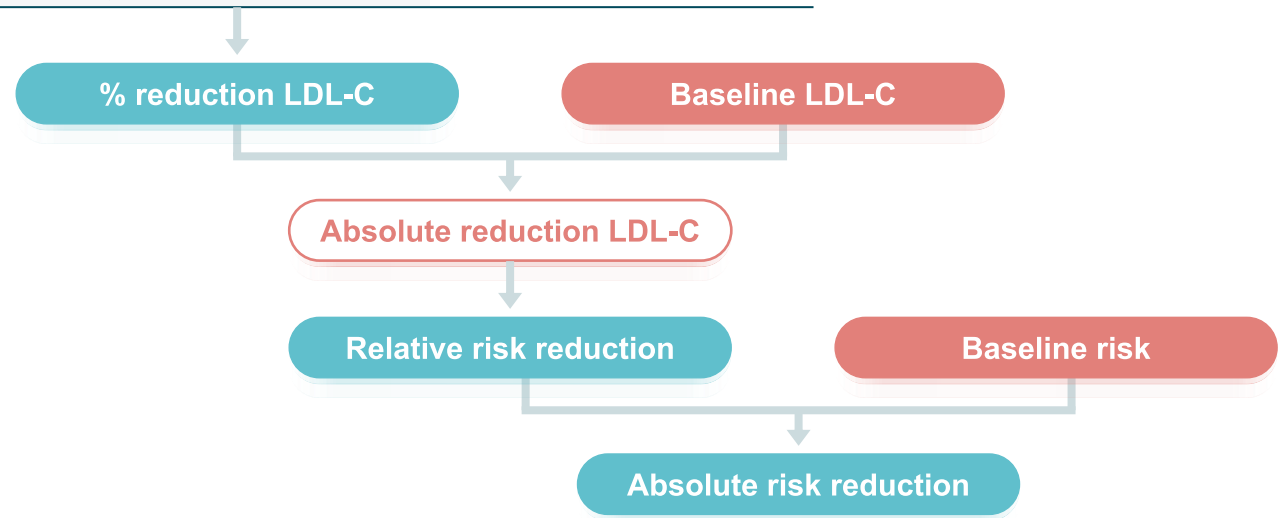
Treatment goals based on CV risk

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% form the baseline level.
†Age (men ≥ 45 years, women ≥ 55 years), family history of premature ASCVD, hypertension, smoking, and low HDL cholesterol level (<40 mg/dL)

1) In patients with acute myocardial infarction, statin is recommended irrespective of LDL-C level.
2) In diabetes mellitus with target organ damage (albuminuria, nephropathy, retinopathy and neuropathy) or major risk factor† ≥ 3; target LDL-C <55 mg/dL (optional)

LDL, low-density lipoprotein; non-HDL-C, non-high-density lipoprotein cholesterol
Ref. The Korean Society of Lipid & Atherosclerosis. Korean Guidelines for the Management of Dyslipidemia 5th Ed. 2022.

Evidence-guided approach algorithm

Assement of cardiovascular risk

Very high risk group
- Coronary artery disease

→ Target LDL-C: < 55 mg/dL (+ LDL-C reduction ≥ 50% from the basel ine level)

High risk group
- Atherosclerotic stroke and transient ischemic attack
- Carotid artery disease
- Peripheral artery disease
- Abdominal aortic aneurysm

→ Target LDL-C: < 70 mg/dL (+ LDL-C reduction ≥ 50% from the basel ine level)

Diabetes mellitus
- Diabetes mellitus with duration <10 years and no major risk factors
→ Target LDL-C: < 100 mg/dL

- Diabetes mellitus with duration ≥10 years or with 1-2 major risk factors
→ Target LDL-C: < 70 mg/dL

Optional: diabetes mellitus with target organ damage or major risk factors ≥ 3.
→ LDL-C: < 55 mg/dL

Moderate risk group
- Major risk factors ≥ 2

→ Target LDL-C: < 130 mg/dL

Low risk group
- Major risk factors ≤ 1

→ Target LDL-C: < 160 mg/dL

Statin

Reached LDL-C target level?

Yes → **Maintain current medications**

No → **Maximal tolerated dose of statin**

Target LDL-C not reached → **Add ezetimibe**

Target LDL-C not reached → **Add PCSK9 inhibitor (in very high or high risk group)**

LDL, low-density lipoprotein; PCSK9, low-density lipoprotein

Ref. The Korean Society of Lipid & Atherosclerosis. Korean Guidelines for the Management of Dyslipidemia 5th Ed. 2022.

Guideline recommendation of statin and ezetimibe

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🔴 **Continuous lowering** of LDL-C target level/ **Highlight of adding ezetimibe** after ACC 2016[11]

1988 ATP I	1993 ATP II	2001 ATP III	2004 ATP III Update	2006 AHA/ACC	2010 ADA	2011 ESC/EAS
					Diabetes patients without overt CVD	Very high risk pts
Goal < 130 mg/dL[1]	**Goal** ≤ 100 mg/dL[2]	**Goal** < 100 mg/dL[3]	**Goal** < 100 mg/dL[4]	**Goal** < 100 mg/dL[5]	**Goal** < 100 mg/dL[6]	**Goal** < 70 mg/dL[7]

Very-high-risk pts

Diabetes patients with overt CVD

High-risk pts

Optional goal: < 70 mg/dL[4] | **Reasonable:** < 70 mg/dL[5] | **Optional goal:** < 70 mg/dL[6] | < 100 mg/dL[7]

2013 ACC/AHA	2015 KSoLa Very-high-risk pts	2016 ESC/EAS Very-high-risk pts	2016 ACC update	2016 NICE	2016 ADA	2017 AACE/ACE Extremely high risk	2018 ACC/AHA	2019 ESC/EAS
No Goal[8]	**Goal** < 70 mg/dl[9]	**Goal** < 70 mg/dl or ≥ 50%[10]	**Goal** No evidence			**Goal** < 55mg/dl[14]		**Goal** < 40mg/dl[16]

Recommend Ezetimibe or PCSK9 inhibitor[11] | **Recommend Ezetimibe[12]** | **Recommend Ezetimibe[13]** | **Recommend Ezetimibe[15]**

Ref. **1.** NCEP ATP I. Arch Intern Med. 1988;148:36–69 **2.** NCEP ATP II. JAMA. 1993;269:3015–3023 **3.** NCEP ATP III. JAMA. 2001;285:2486–2497 **4.** Grundy SM, et al. Circulation. 2004;110:227–239; **5.** Smith SC Jr, et al. Circulation. 2006;113:2363–2372 **6.** ADA. Diabetes Care. 2010;33(suppl 1):S11–S61 **7.** Reiner Z, et al. Eur Heart J. 2011;32(14):1769-818. **8.** Stone NJ, et al. J Am Coll Cardiol 2014;63(25 Pt B):2889-934. **9.** KSoLA 2015; 3rd ver. **10.** European Society of Cardiology. European Heart Journal 2016;37:2999–3058 **11.** Lloyd-jones DM, et al. J Am Coll Cardiol. 2016;68(1):92-125 **12.** NICE guideline (TA385) **13.** ADA, Clin Diabetes. 2016 Jan;34(1):3-21. **14.** Garber AJ, et al. Endocr Pract. 2017;23(2):207-238 **15.** Grundy SM, et al. Circulation. 2019 Jun 18;139(25):e1082-e1143 **16.** Mach F, et al. Eur Heart J. 2020;41(1):111-188

Efficacy of Rosuvastatin

Potent lipid lowering efficacy of rosuvastatin

Rosuvastatin has -40 ~ -60% LDL-C mean change percentage, which can be controlled by dosage.

Statin dosage and LDL-C reduction rate

Chart: Mean change in LDL-C from untreated baseline (%)

Statin	Dose (mg)	Reduction
Lovastatin	20	-32 ~ -34
Pravastatin	40	-28 ~ -33
Simvastatin	20	-27 ~ -39
Atorvastatin	10	-39 ~ -44
Atorvastatin	20	-41 ~ -50
Atorvastatin	40	-52 ~ -59
Atorvastatin	80	-56
Rosuvastatin	5	-40 ~ -49
Rosuvastatin	10	-42 ~ -50
Rosuvastatin	20	-42 ~ -60
Pitavastatin	2	-38 ~ -44

Ref. The Korean Society of Lipid & Atherosclerosis. 2018 Korean Guidelines for the Management of Dyslipidemia 4th Ed.

STELLAR: Reduction of LDL-C

STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin

This multicenter trial showed the greater efficacy of rosuvastatin in reducing LDL-C, compared with atorvastatin, simvastatin, and pravastatin across dose ranges.

Change in LDL-C from baseline (%)

Rosuvastatin: 10 mg*, 20 mg[†], 40 mg[‡]
Atorvastatin: 10 mg, 20 mg, 40 mg, 80 mg
Simvastatin: 10 mg, 20 mg, 40 mg, 80 mg
Pravastatin: 10 mg, 20 mg, 40 mg

Rosuvastatin 10 mg (–46%)
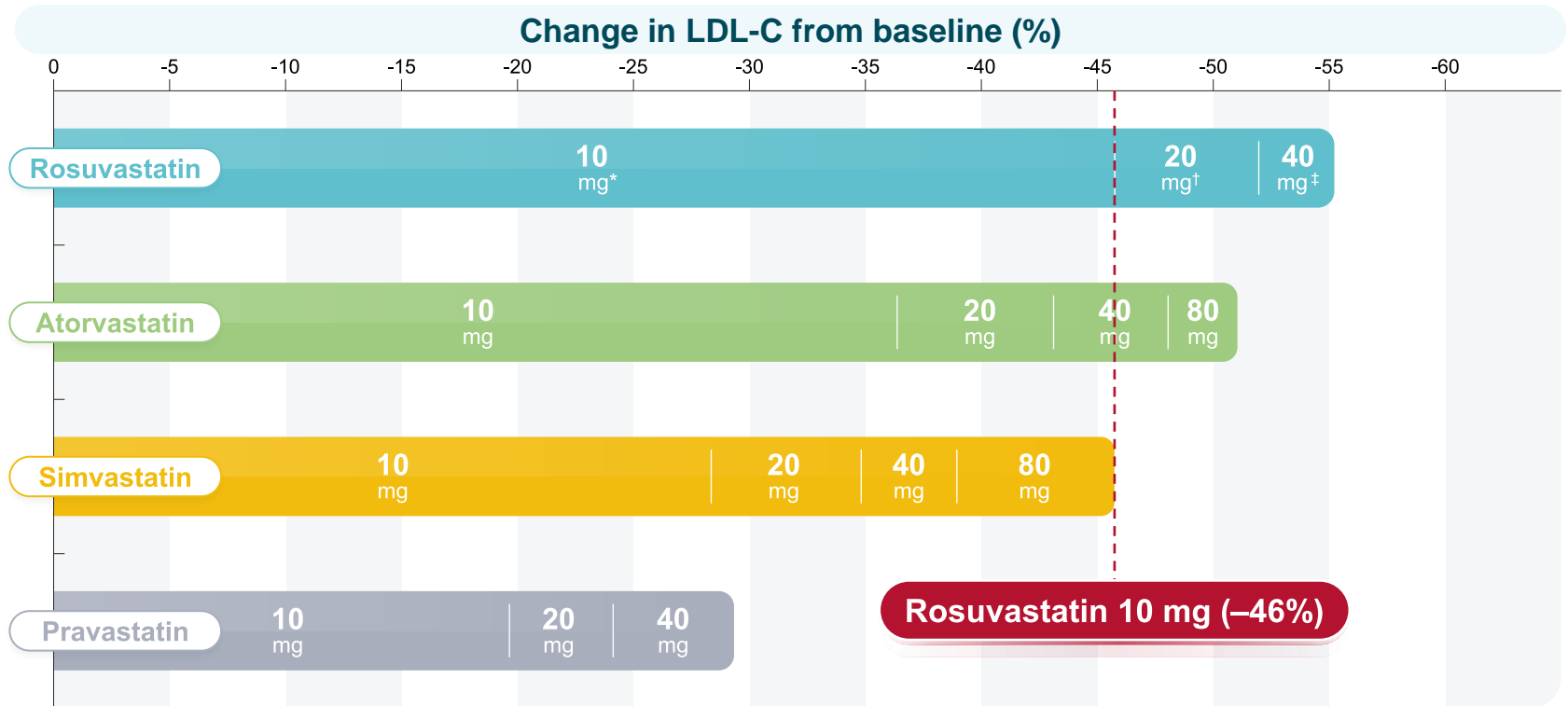
Study design A 6-week, parallel-group, open-label, randomized, multicenter study comparing LDL-C reducing efficacy of rosuvastatin vs atorvastatin, simvastatin, and pravastatin across the dose ranges in adults with hypercholesterolemia (n=2,431; per dose group, n=156-167), after dietary lead-in.

* $p<0.002$ vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
[†] $p<0.002$ vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg
[‡] $p<0.002$ vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

Ref. Jones PH, et al. *Am J Cardiol.* 2003;92(2):152-160.

ASTEROID: high dose rosuvastatin

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

Rosuvastatin 40 mg once daily showed highly significant regression of coronary atherosclerosis as assessed by serial intravascular ultrasonography.

Percent Atheroma Volume

Atheroma volume/Blood vessel volume, n=349

Percent atheroma volume (median, %)

p<0.001

39.9

-0.79%

38.5

Baseline — Study End

Total Atheroma Volume

n=349

Normalized total atheroma volume (median, mm^3)

p<0.001

204.7

-6.8%

186.8

Baseline — Study End
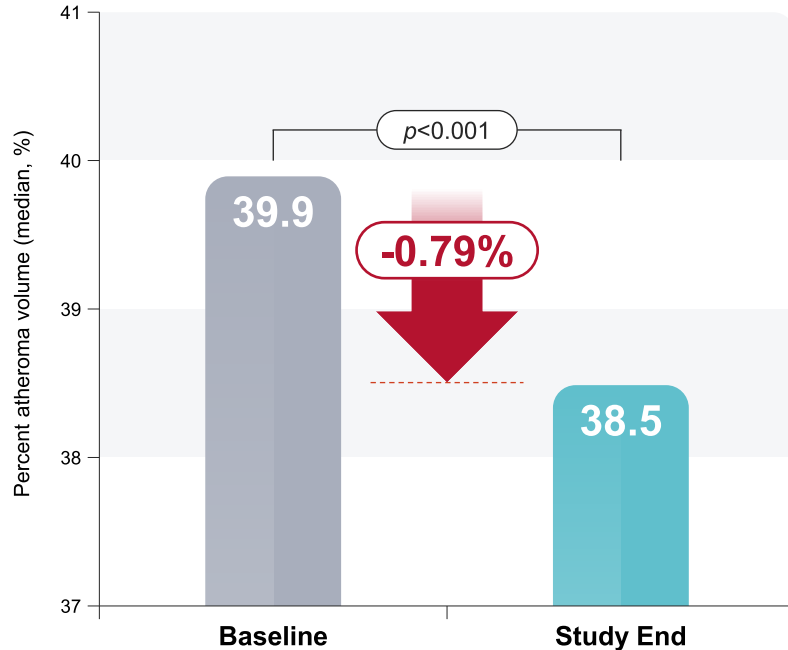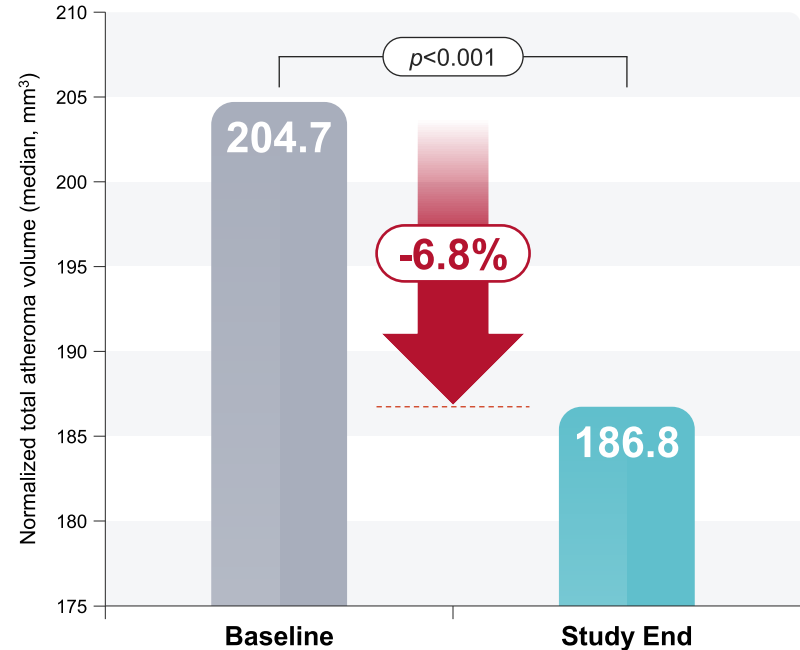
Study design — Prospective, open-label blinded end-points trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden [ASTEROID]) to assess whether very intensive statin therapy could regress coronary atherosclerosis as determined by IVUS imaging.

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

ARTMAP: compared with atorvastatin

ARTMAP = Atorvastatin Versus Rosuvastatin Therapy on Mild Coronary Atherosclerotic Plaques

Usual doses of rosuvastatin induced significant regression of coronary atherosclerosis.

Total Atheroma Volume (TAV), %

Atorvastatin 20 mg — -3.9

Rosuvastatin 10 mg — -7.4

$p=0.018$

Percentage change from baseline

Percent Atheroma Volume (PAV), %

Atorvastatin 20 mg — -0.3

Rosuvastatin 10 mg — -1.0

$p=0.157$

Nominal change from baseline
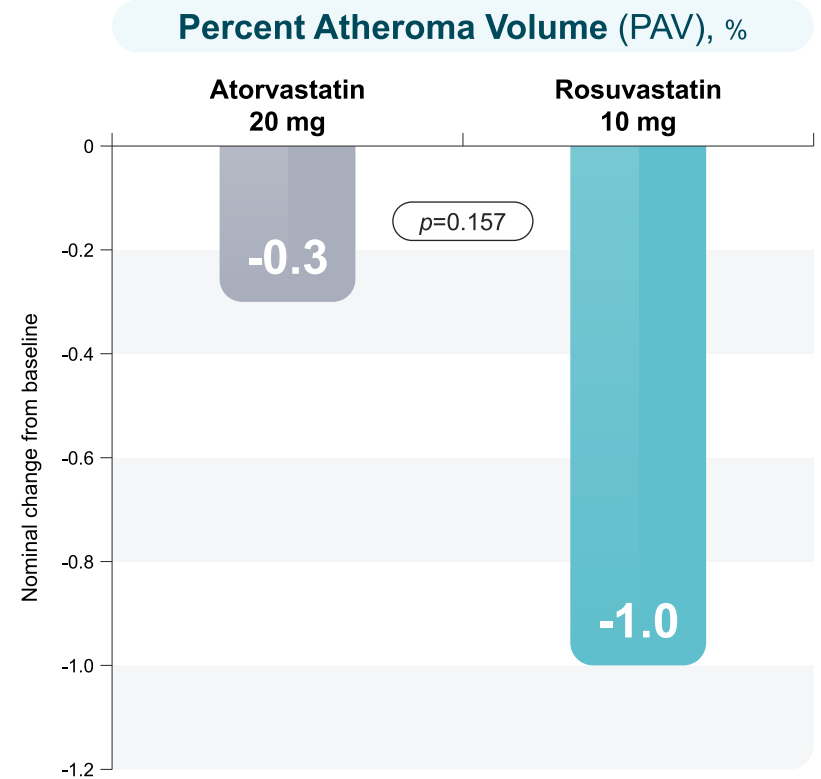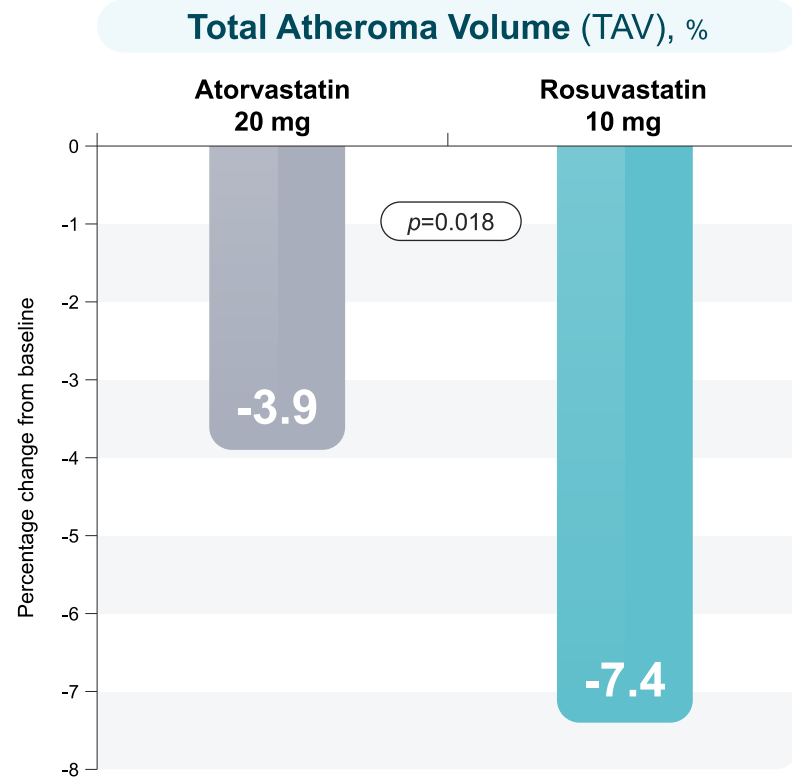
Study design

A prospective, single-center, open-label, randomized comparison trial involving statin-naïve patients ≥ 18 years old with clinically indicated percutaneous coronary intervention to compare the effects of atorvastatin versus rosuvastatin therapy with equivalent potency on mild coronary atherosclerotic plaques using intravascular ultrasound.

Ref. Lee CW, et al. *Am J Cardiol.* 2012;109(12):1700-1704.

JUPITER: Study design

JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

Methods

- 17,802 apparently healthy men and women with LDL-C levels of less than 130 mg/dL and high-sensitivity C-reactive protein (hs-CRP) levels of 2.0 mg/L or higher to rosuvastatin 20 mg daily, or placebo.

Primary endpoint

- Myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

Study Population	Trial Protocol	Endpoints
• Men ≥50, Women ≥60 • No History of CVD • LDL-C <130 mg/dL • hs-CRP >2.0 mg/L	**Randomly assigned (1:1)** • Rosuvastatin 20 mg (n=8,901) • Placebo (n=8,901) **Median follow-up** • 1.9 years (Max 5.0 years)	• MI • Stroke • Unstable angina • CVD death • Arterial revascularization

4-week run-in

Ref. Ridker PM, et al. *N Eng J Med.* 2008; 359(21): 2195-2207.
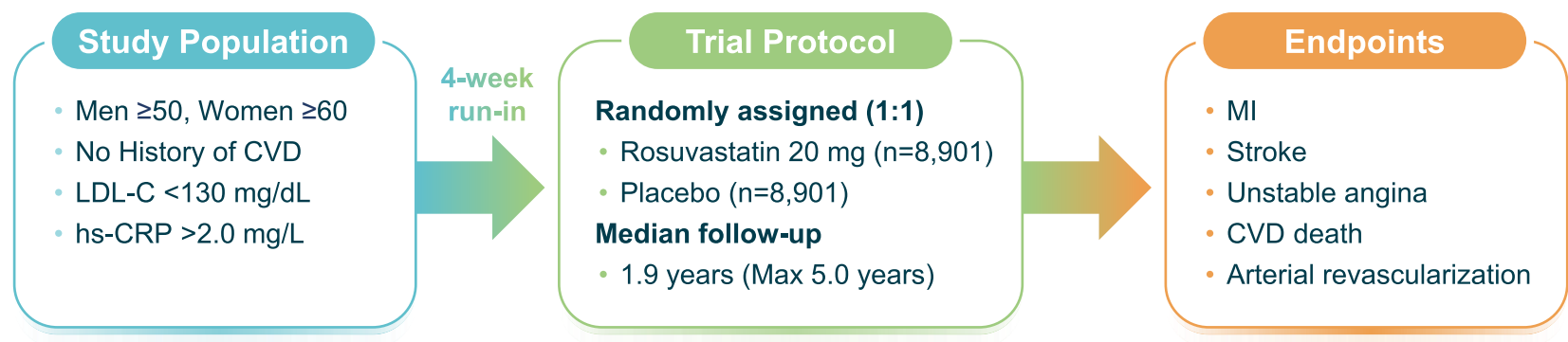
JUPITER: Reduction of LDL-C & hs-CRP

In JUPITER trial, LDL-C as well as high-sensitivity C-reactive protein levels were significantly low throughout study period.

LDL-C & hs-CRP levels during the follow up period (placebo vs. rosuvastatin)

Median LDL-C (mg/dL)

Median hs-CRP (mg/L)

Placebo LDL-C: 110, 108, 106, 109
Rosuvastatin LDL-C: 55*, 54*, 53*, 55*

Placebo hs-CRP: 3.5, 3.5, 3.5, 3.3
Rosuvastatin hs-CRP: 2.2*, 2.2*, 2.0*, 1.8*

Placebo LDL-C
Rosuvastatin LDL-C
* $p < 0.001$

Placebo hs-CRP
Rosuvastatin hs-CRP
* $p < 0.001$

Months

Months
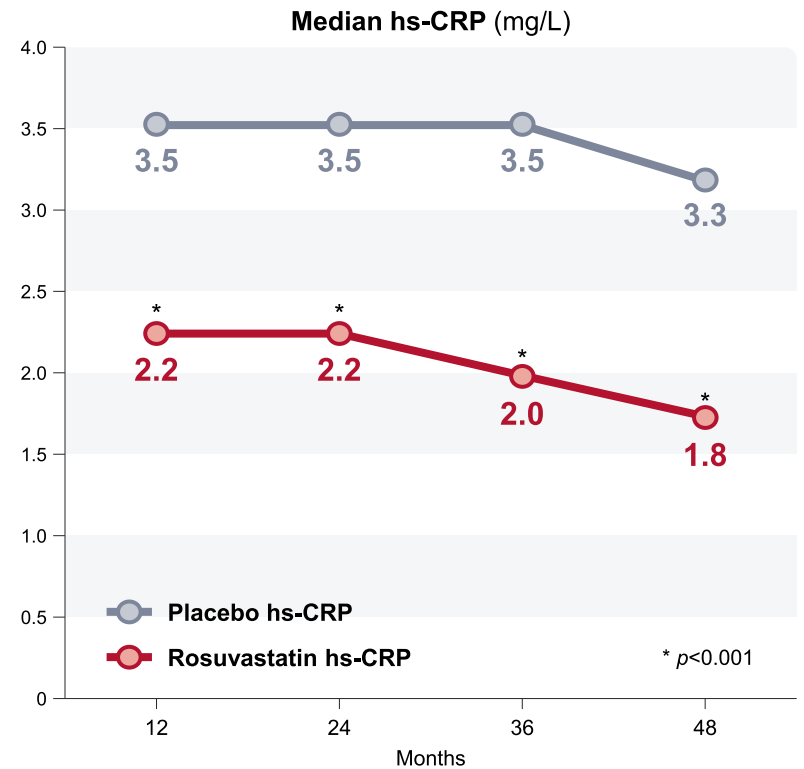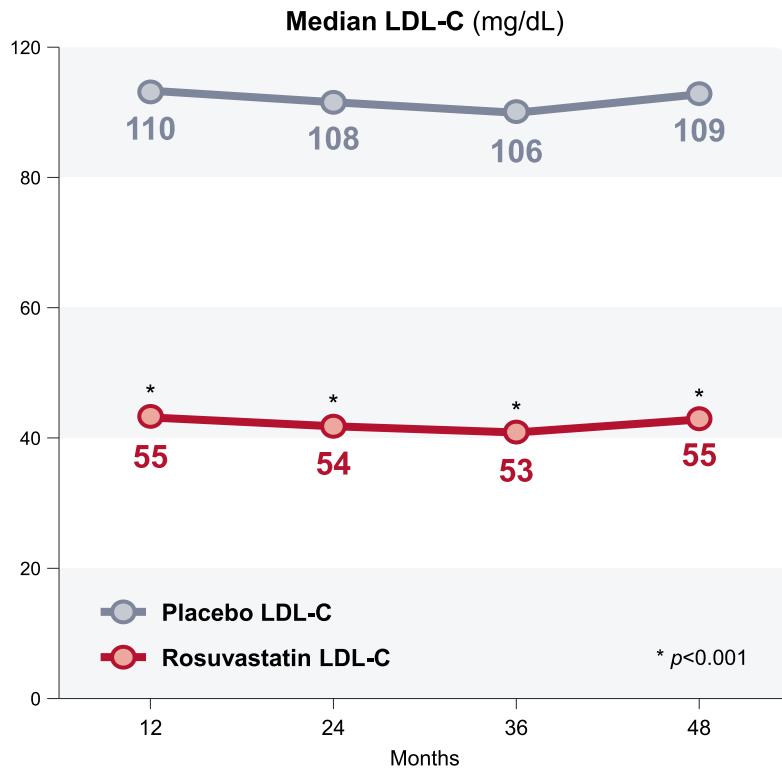
* Baseline characteristics of the trial participants,

LDL-C — **Rosuvastatin:** median 108 mg/dL (interquartile range 94-119)
Placebo: median 108 mg/dL (interquartile range 94-119)

hs-CRP — **Rosuvastatin:** median 4.2 mg/L (interquartile range 2.8-7.1)
Placebo: median 4.3 mg/L (interquartile range 2.8-7.2)

Ref. Ridker PM, et al. *N Engl J Med.* 2008;359(21):2195-2207.

JUPITER: Lower incidence of major CV event

Primary endpoint

HR 0.56, 95% CI 0.46-0.69
p < 0.00001

Number Needed to Treat to prevent
the occurrence of one primary endpoint
(NNT) = 25

Placebo

Relative
risk
reduction
44%

Rosuvastatin
20 mg

Cumulative incidence

Follow-up (years)
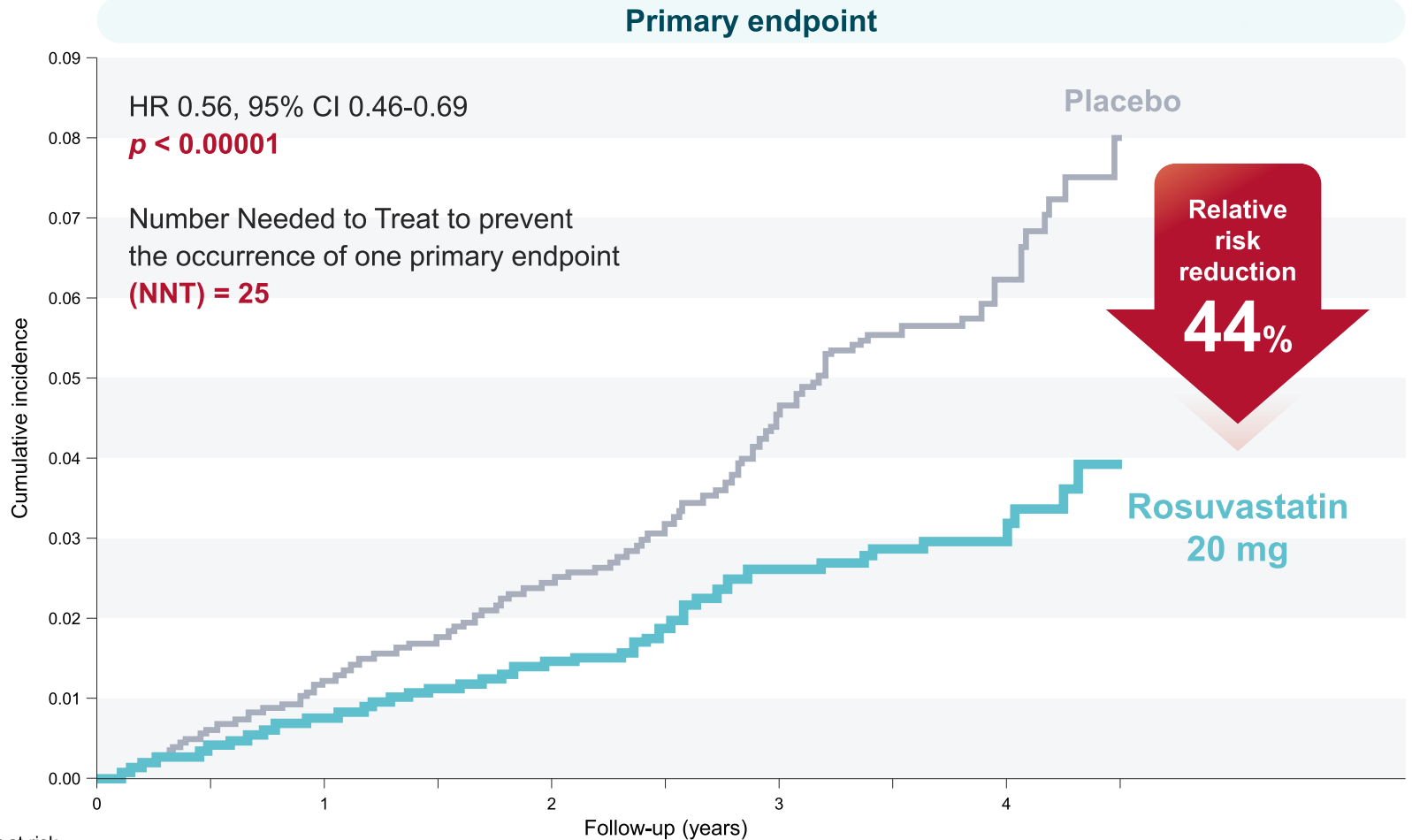
Number at risk									
Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	538	157
Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	531	174

Ref. Ridker PM, et al. *N Eng J Med*. 2008; 359(21): 2195-2207.

JUPITER: Significant lowering of total mortality

Death from any cause

HR 0.80, 95% CI 0.67-0.97
p = 0.02

Placebo

Relative risk reduction
20%

Rosuvastatin 20 mg

Cumulative incidence

0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00

Follow-up (years)
0   1   2   3   4
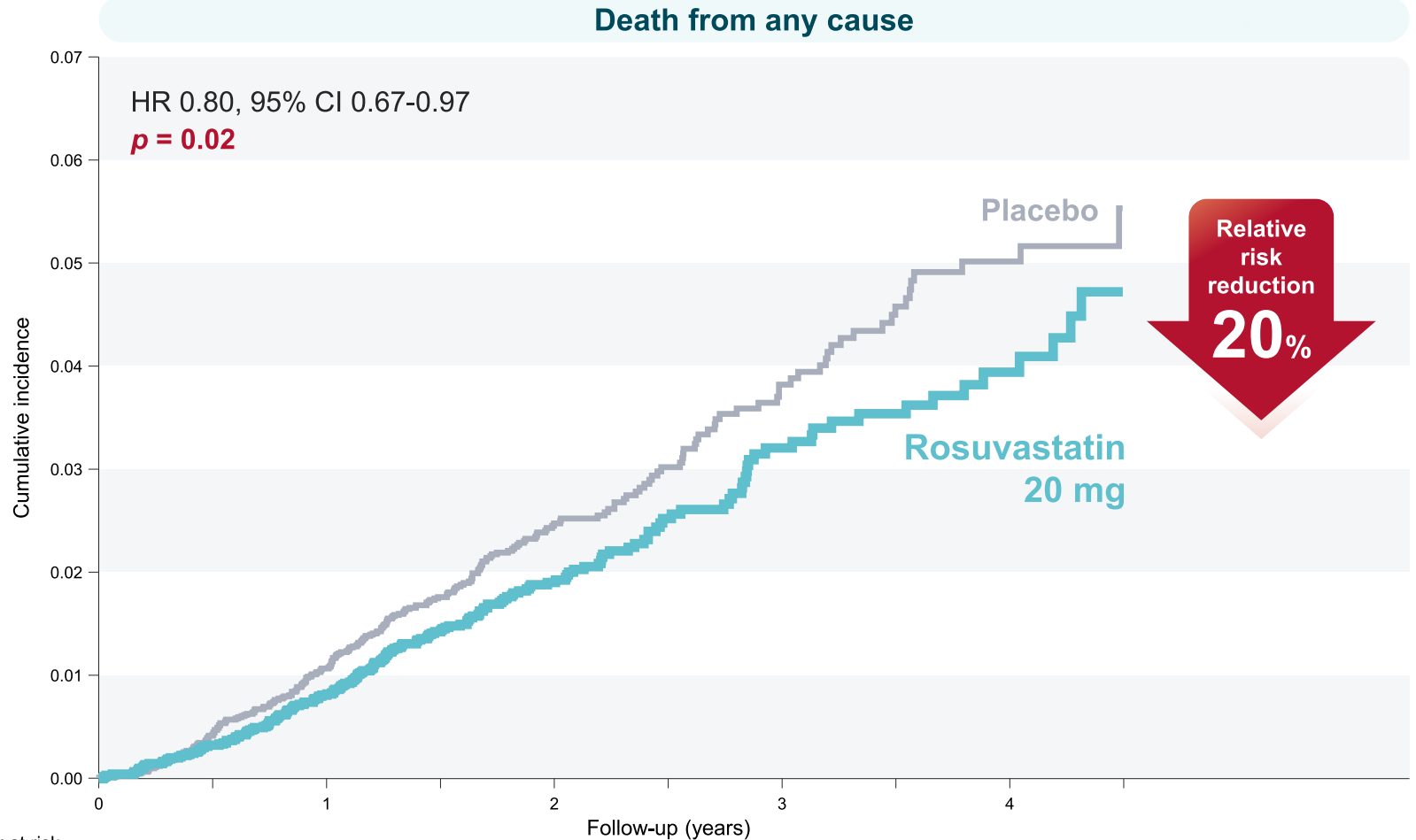
Number at risk

Rosuvastatin	8,901	8,847	8,787	6,999	4,312	2,268	1,602	1,192	676	227
Placebo	8,901	8,852	8,775	6,987	4,319	2,295	1,614	1,196	681	246

Ref. Ridker PM, et al. *N Eng J Med.* 2008; 359(21): 2195-2207.

JUPITER : Does rosuvastatin really increase NODM?

In this sub analysis of JUPITER trial, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes.

Cumulative incidence of CV events and total mortality

No major risk factor for diabetes
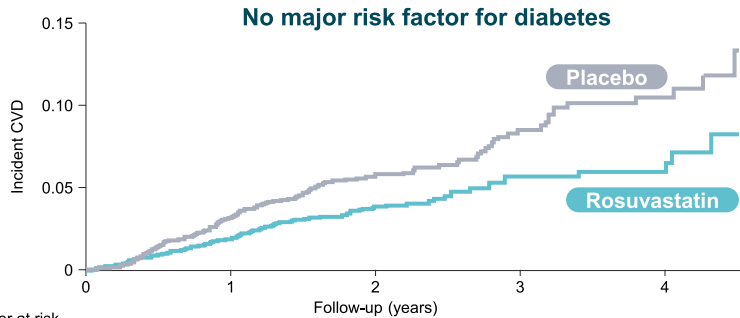
Number at risk									
Rosuvastatin	3,065	2,964	2,889	2,283	1,390	648	444	319	165	39
Placebo	3,030	2,924	2,824	2,227	1,342	647	447	314	174	55

One or more major risk factors for diabetes
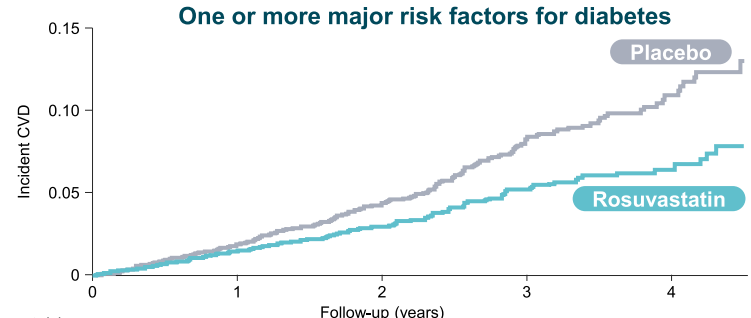
Number at risk									
Rosuvastatin	5,743	5,574	5,426	4,178	2,450	1,280	890	652	365	115
Placebo	5,765	5,593	5,428	4,193	2,466	1,281	864	624	348	115

Cumulative incidence of diabetes

No major risk factor for diabetes
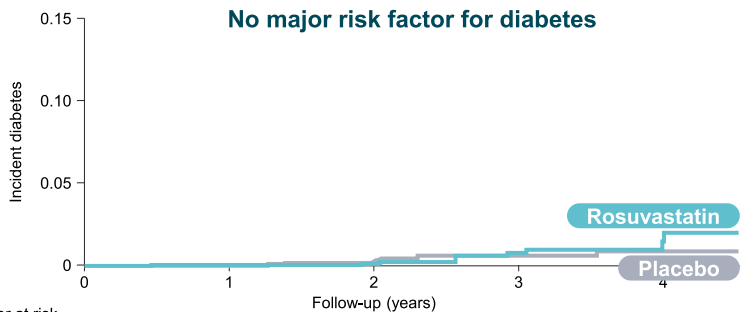
Number at risk									
Rosuvastatin	3,065	2,969	2,902	2,477	1,555	725	473	343	189	48
Placebo	3,030	2,944	2,856	2,448	1,521	739	488	348	195	69

One or more major risk factors for diabetes
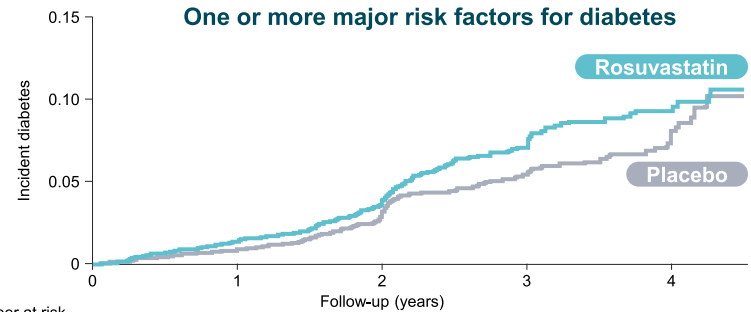
Number at risk									
Rosuvastatin	5,743	5,564	5,394	4,515	2,639	1,330	870	624	365	126
Placebo	5,765	5,600	5,442	4,580	2,685	1,386	909	644	368	128

CVD, cardiovascular disease.

Ref. Ridker PM, et al. Lancet. 2012;380(9841): 565–571.

HOPE-3: Study design

Methods

- Multicenter, long-term, international, double-blind, randomized, placebo-controlled trial at 228 centers in 21 countries.
- **12,705 participants** who did not have cardiovascular disease and were at intermediate risk.
- Median follow-up **5.6 years**, 2 by 2 factorial design.

Endpoint

- Co-primary 1: Composite of death from CV cause, nonfatal myocardial infarction, nonfatal stroke.
- Co-primary 2: Composite of Co-primary 1 + resuscitated cardiac arrest, heart failure, revascularization.
- Secondary endpoints: Composite of Co-Primary 2 + angina with evidence of ischemia.

Rosuvastatin 10 mg	Candesartan/HCTZ		Rosuvastatin margins
	Active	**Placebo**	
Active	**n=3,180**	**n=3,181**	n=6,361
Placebo	**n=3,176**	**n=3,168**	n=6,344
Candesartan/HCTZ Margins	n=6,356	n=6,349	

Ref. Yusuf S, et al. *N Engl J Med.* 2016;374(21):2021-2031.

HOPE-3: Reduction of LDL-C

The overall mean low-density lipoprotein cholesterol (LDL-C) was 26.5% lower in the rosuvastatin group than that in the placebo group.

Number at risk				
Placebo	495	495	495	495
Rosuvastatin	480	480	480	480

Ref. Yusuf S, et al. *N Engl J Med.* 2016;374(21):2021-2031.
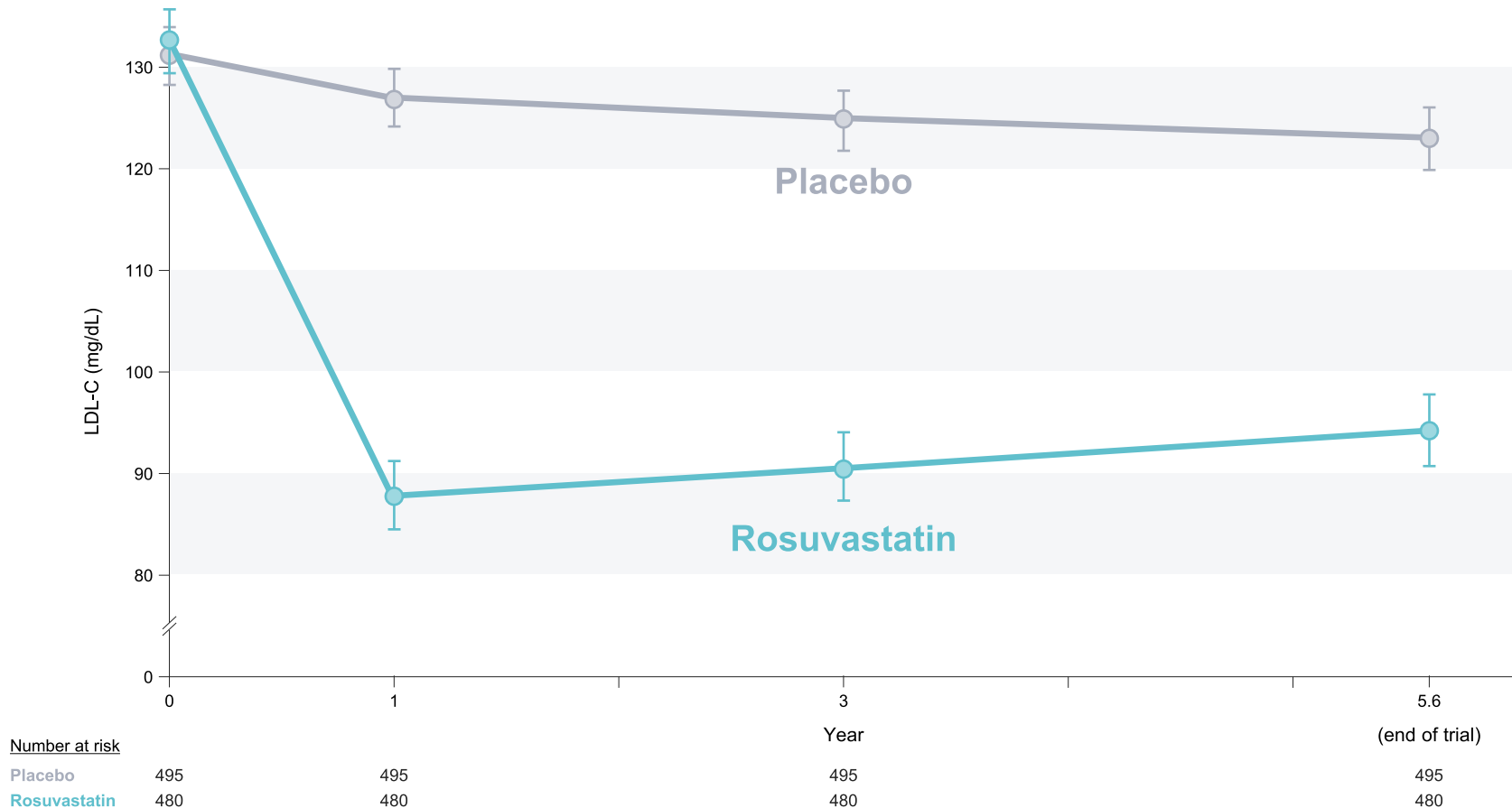
HOPE-3: Lower incidence of major CV event

- Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk.

Analysis for Co-primary outcome: rosuvastatin vs. placebo comparison

Relative risk reduction **25%**

HR (95% CI) = 0.75 (0.64-0.88)
p<0.001
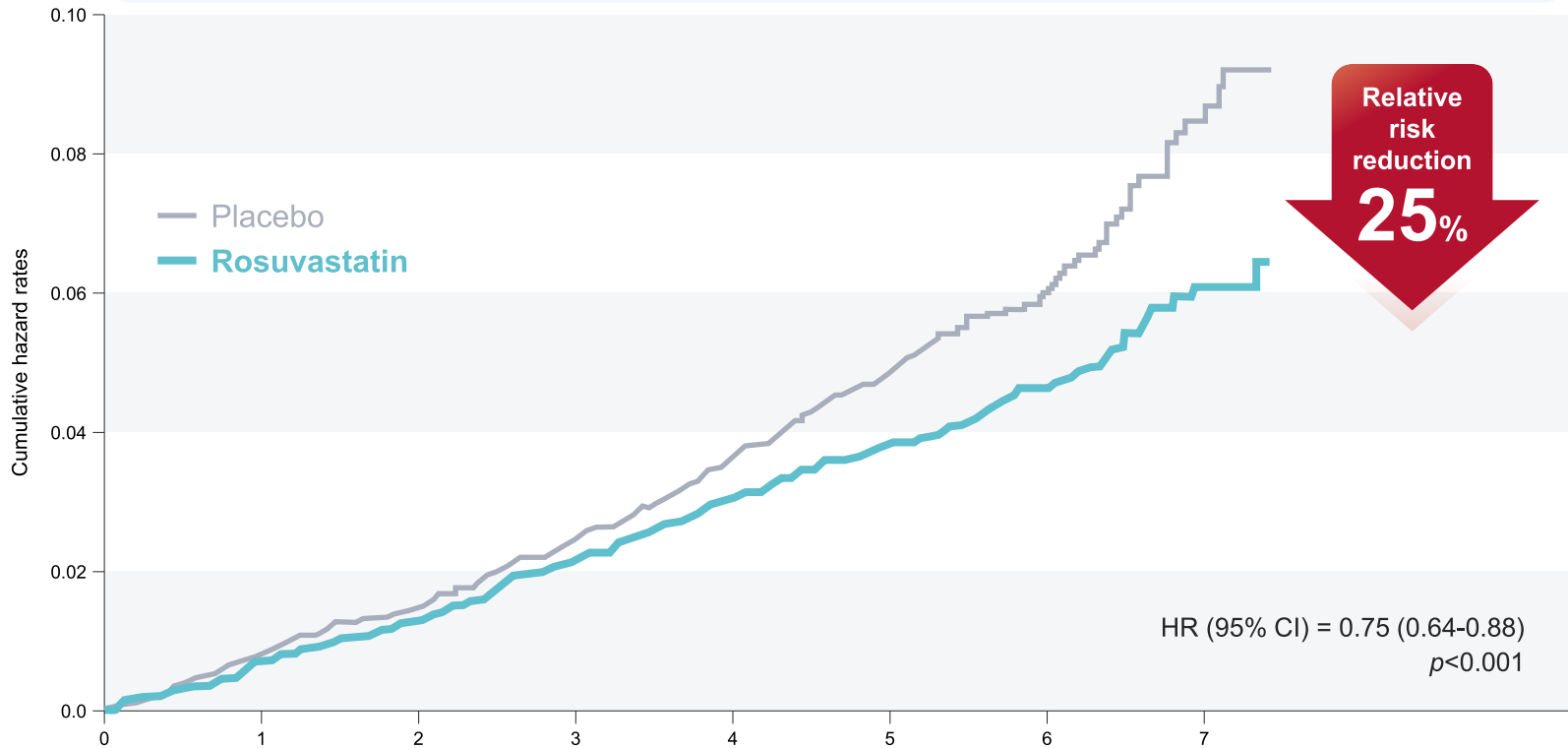
Number at risk

Rosuvastatin	6,361	6,241	6,039	2,122
Placebo	6,344	6,192	5,970	2,073

Ref. Yusuf S, et al. *N Engl J Med.* 2016;374(21):2021-2031.

HOPE-3: Conclusion

Proven effect of rosuvastatin 10 mg in intermediate risk patients*

* Intermediate risk: **Male ≥ 55 years, Female ≥ 65 years. No CVD but with at least one CVD risk factor.**

Rosuvastatin 10 mg: CVD 25% reduction compared with placebo
- Stroke 30%, MI 36%, revascularization 32%, CAD 26%, hospitalization for CV causes 25%

Candesartan+HCTZ+Rosuvastatin 10 mg: 30% reduction in major vascular event

5.6 years evidence in primary prevention (12,705 pts.) – (JUPITER : 1.9 yrs, 17,802 pts.)

Asian population 49.1% (non-white 80%)

No routine monitoring (visit : 6 monthly, lipid level: baseline, 1yr, 3yr, end)

No difference on new-onset DM

Ref. Yusuf S, et al. *N Engl J Med.* 2016;374(21):2021-2031.

Combination with Ezetimibe

Insufficient effect of statin monotherapy

Many patients receiving lipid-lowering therapy, particularly in very high risk patients, did not achieve their LDL-C goals.

Success rate in achieving appropriate LDL-C goals for the patient's level of risk

LDL-C success rate, %

86%	74%	67%	30%
Low risk (n=2,066)	Moderate risk (n=1,959)	High risk/CHD (n=5,930)	Very high risk (n=2,334)
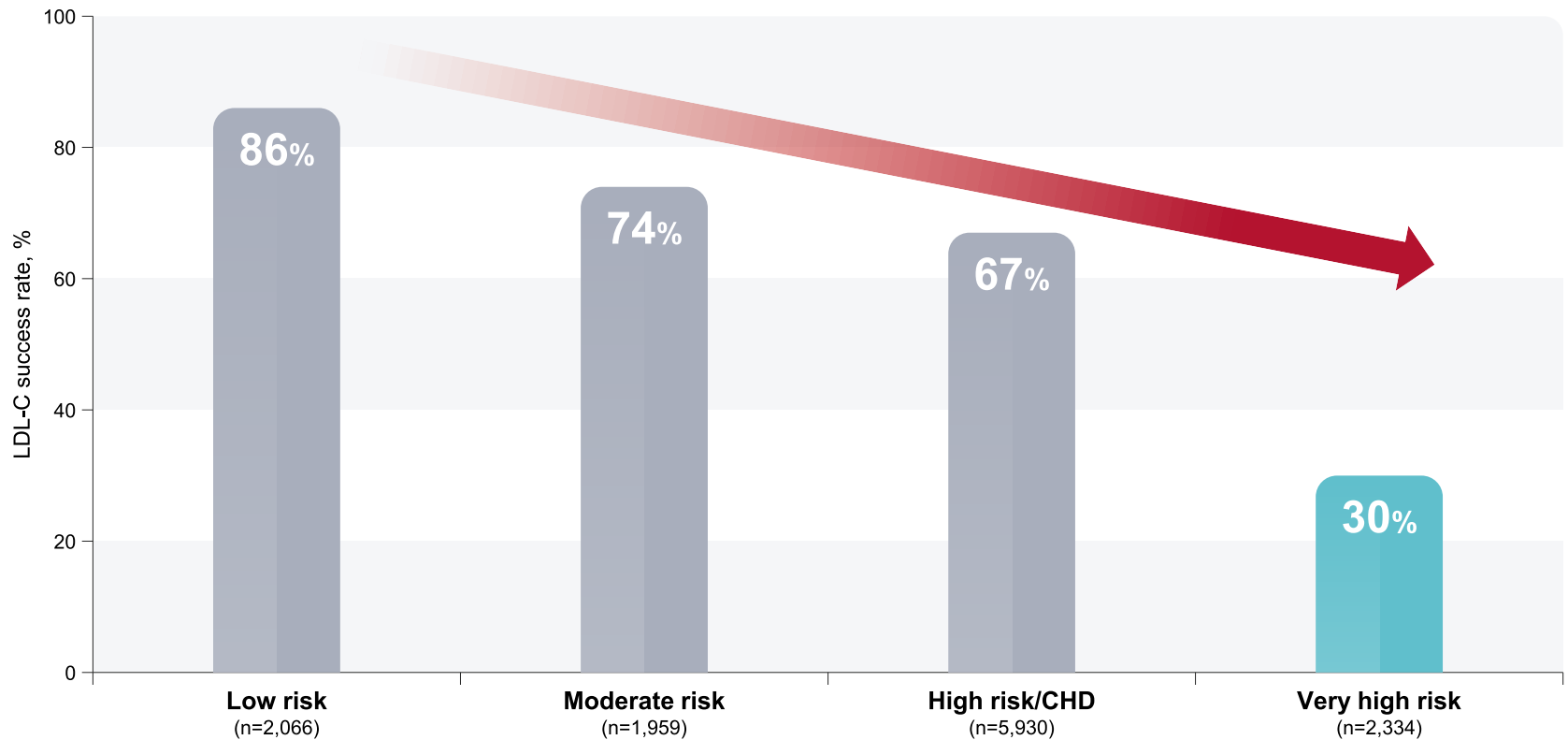
75% of patients were on statin therapy

Low-risk patients = 0 or 1 risk factor. Moderate-risk patients = 2 or more risk factors. High-risk/CHD patients = coronary or other atherosclerotic vascular disease, or diabetes. Very high–risk patients = CHD with 2 or more risk factors (LDL-C goal <70 mg/dL [1.8 mmol/L]).

Ref. Waters DD, et al. *Circulation.* 2009;120(1):28-34.

Dual action of statin & ezetimibe

Cholesterol metabolism

Exogenous

Endogenous

33% Dietary Chol

67% Biliary Chol

Bile Acids

Free Chol

Acetyl CoA

Cholesterol Pool (Micelle)

Ezetimibe NPC1L1

Rosuvastatin HMG-CoA

Hepatic Apo B 100

LDLR

Remnant receptors

Small intestine

Liver

VLDL

LDL

IDL

Fecal sterols

Chylomicron

CMR
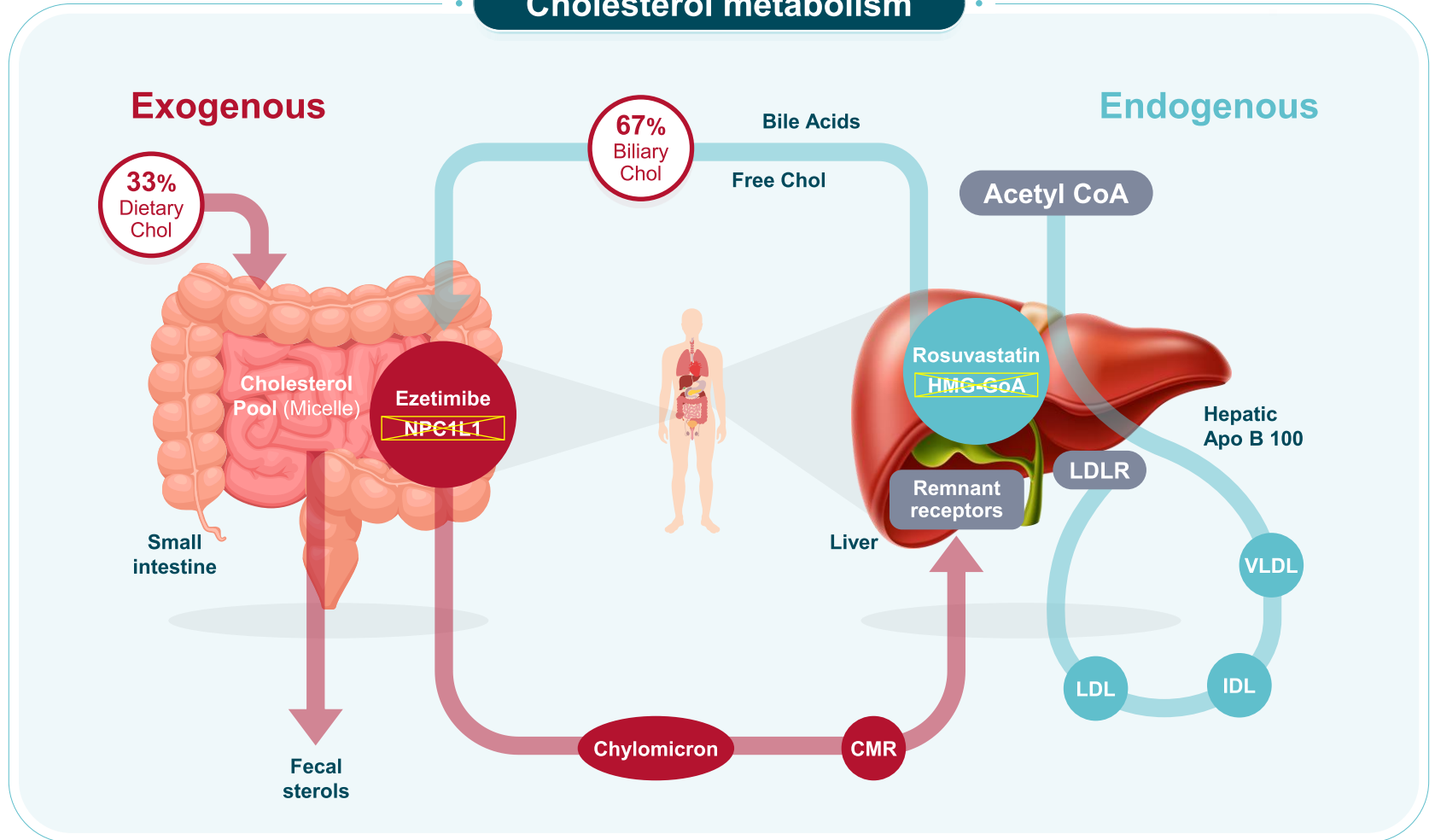
Apo B 100, apolipoprotein B 100; VLDL, very low-density lipoprotein; LDLR, low density lipoprotein receptor; NPC1L1, Niemann-Pick C1-Like 1; CMR, chylomicron remnant; IDL, intermediate-density lipoprotein

Ref. 1. Cohen DE, Armstrong EJ. In: Principles of pharmacology: The Pathophysiologic Basis of Drug Therapy. 2nd ed. Philadelphia PA:Lippincott, Williams & Wilkins; 2007:417-438. 2. Wang DQH, et al. *Annu Rev Physiol.* 2007;69:221-248.

More lipid lowering by ezetimibe add-on

Ezetimibe add-on to any statin provided additional **25 - 31%** reduction of LDL-C in **5 separate clinical trials**.

Percent changes of LDL-C from baseline
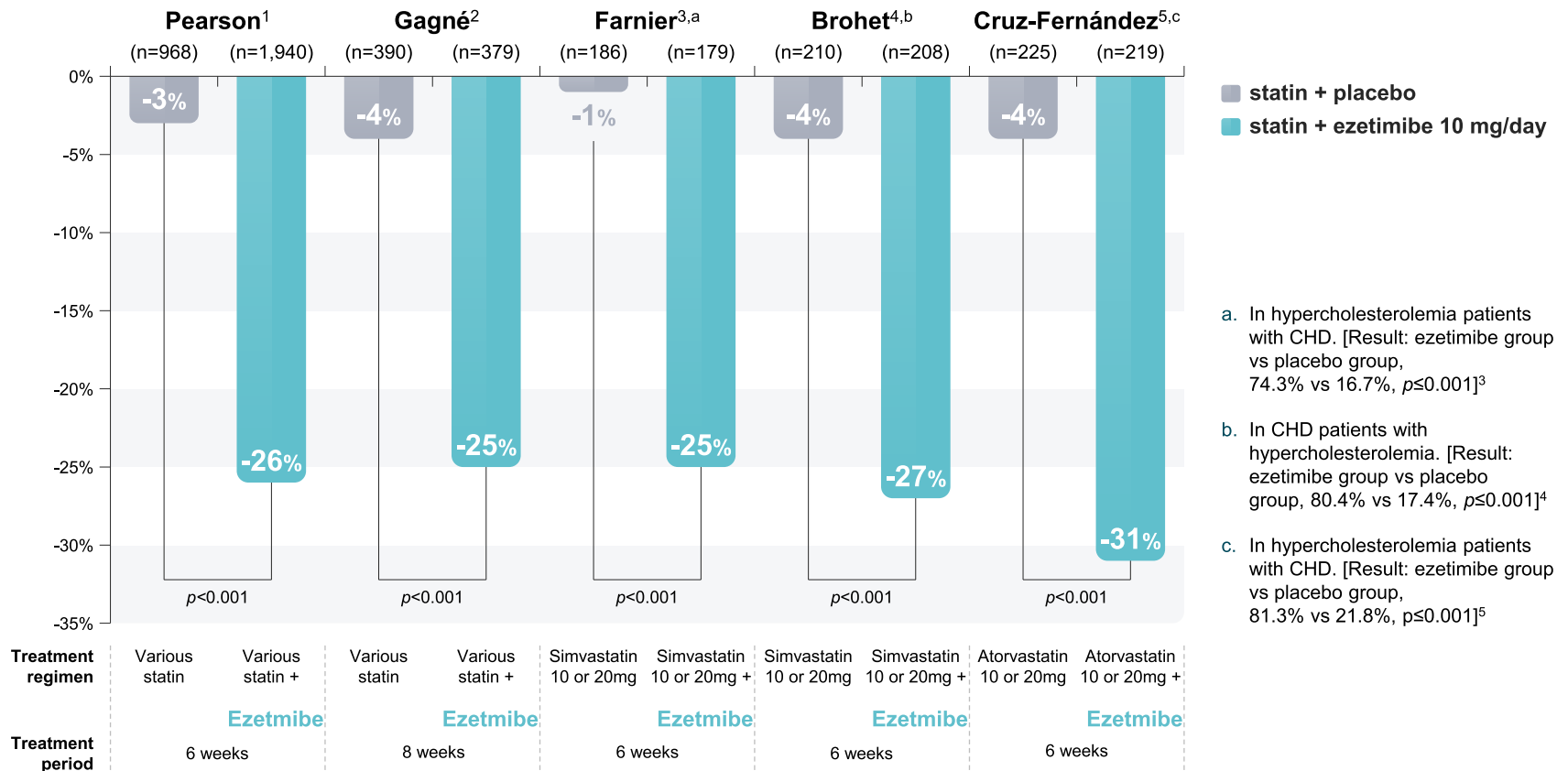
- a. In hypercholesterolemia patients with CHD. [Result: ezetimibe group vs placebo group, 74.3% vs 16.7%, *p*≤0.001][3]

- b. In CHD patients with hypercholesterolemia. [Result: ezetimibe group vs placebo group, 80.4% vs 17.4%, *p*≤0.001][4]

- c. In hypercholesterolemia patients with CHD. [Result: ezetimibe group vs placebo group, 81.3% vs 21.8%, p≤0.001][5]

Ref **1.** Pearson TA, et al. *Mayo Clin Proc.* 2005;80:587-595. **2.** Gagné C, et al. *Am J Cardiol.* 2002;90:1084-1091. **3.** Farnier M, et al. *Int J Cardiol.* 2005;102:327-332. **4.** Brohet C, et al. *Curr Med Res Opin.* 2005;21:571-578. **5.** Cruz-Fernández JM, et al. *Int J Clin Pract.* 2005;59:619-627.

Effectiveness of fixed-dose statin/ezetimibe (vs. separate pills)

The reduction in LDL-C when statin and ezetimibe were prescribed in combination was considerably larger for FDC.

LDL-C reduction of fixed dose combination compared with separate pills of statin/ezetimibe

Ref Katzmann JL, et al. Clin Res Cardiol. 2022;111(3):243-252.
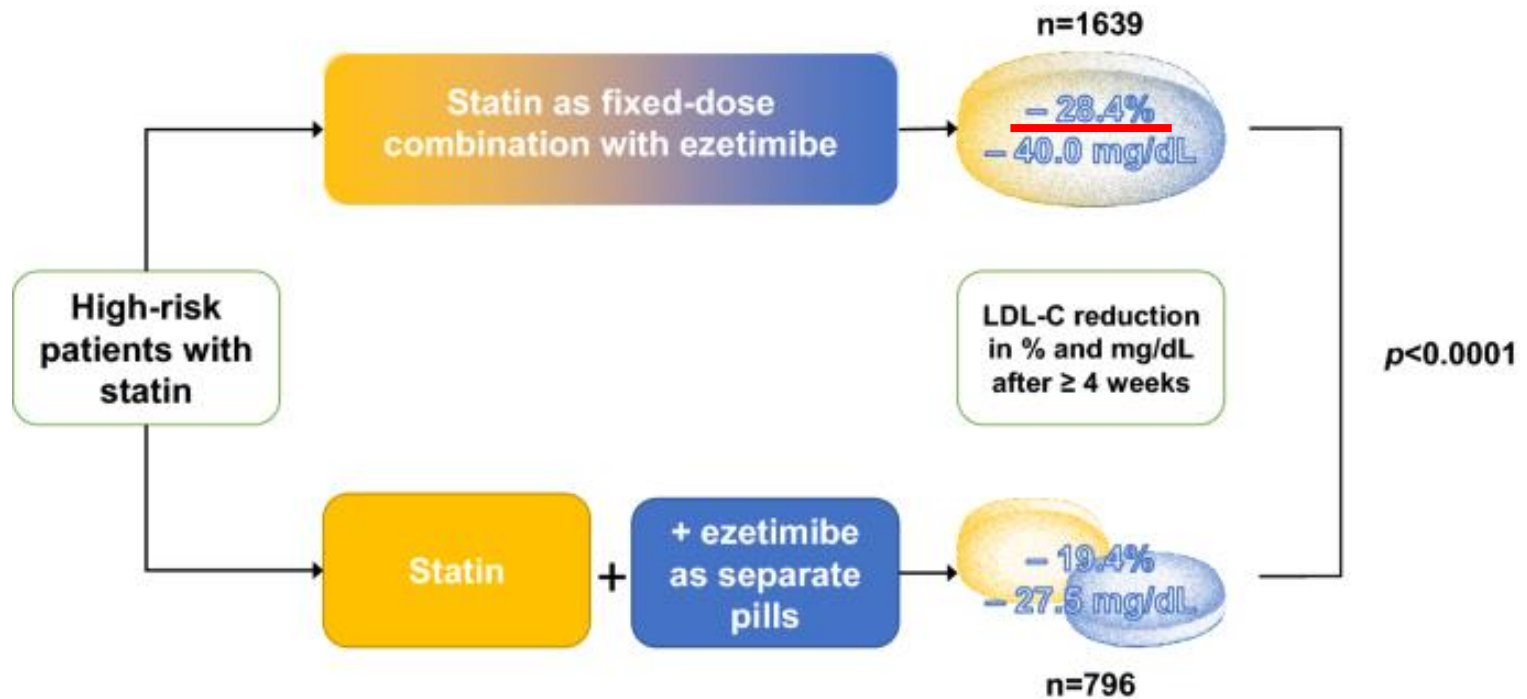
Improve plaque stability

106 patients with borderline lesions and (or) severe ASCVD who cannot or are unwilling to undergo PCI or CABG; 1YR F/U CAG and IVUS

The combination of ezetimibe and rosuvastatin apparently diminished lipid levels and plaque burden and improves plaque stability.

Primary endpoint and major adverse events in the two treatment groups		
	Ezetimibe + rosuvastatin group	**Rosuvastatin group**
☑ **New myocardial infarction**	0(0)	1(2.1)
☑ **Recurrent myocardial infarction**	0(0)	0(2.1)
☑ **Unstable angina pectoris**	2(4.0)	5(10.4)
☑ **Cardiac death**	0(0)	0(0)
☑ **Stroke**	0(0)	0(0)
☑ **Abnormality of laboratory value AST or ALT > 3xULN**	2(4.0)	1(2.1)
☑ **Myalgia**	1(2.0)	1(2.1)
☑ **Creatine kinase (CK) > 5xULN**	0(0)	0(0)
☑ **Rhabdomyolysis**	0(0)	0(0)
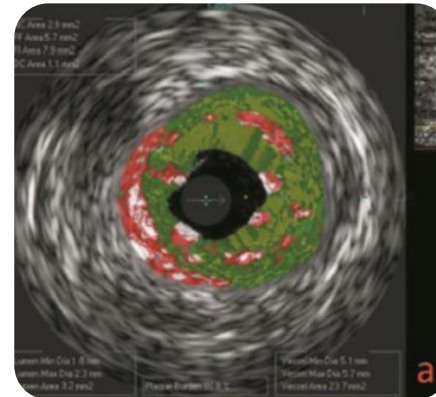
Plaque burden (%)

BEFORE

Combined treatment with ezetimibe + rosuvastatin

73.4±19.8%
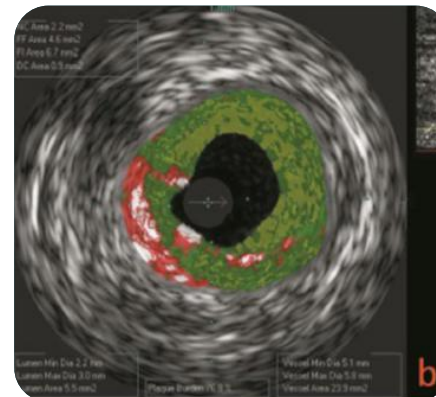
Plaque burden (%)

AFTER

Combined treatment with ezetimibe + rosuvastatin

62.1±7.2%

Ref. Wang X, et al. *Heart, Lung Circ.* 2016:25;459–465.

IMPROVE-IT: Ezetimibe add-on

The addition of ezetimibe to statin therapy in stable patients who had an ACS and who had LDL cholesterol levels within guideline recommendations further lowered the risk of cardiovascular events.

18,144 patients stabilized post ACS ≤10 days: LDL-C 50–125 mg/dL
(or 50–100 mg/dL if prior lipid lowering Rx)

Ezetimibe/simvastatin 10/40 mg

Simvastatin 40 mg

Primary Endpoint

CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization)**, or stroke**

Duration: Minimum 2½ year follow-up (at least 5,250 events)

LDL-C change

AT 1 YEAR

Ezetimibe+ Simvastatin provided an additional

24% LDL-C reduction

vs Simvastatin ($p<0.001$)

69.9 mg/dL

Simvastatin 40 mg

53.2 mg/dL

Ezetimibe + Simvastatin 10/40 mg

Mean LDL-C (mg/dL)

Time since randomization (months)

QE R 1 4 8 12 16 24 36 48 60 72 84 96

CV outcome

34.7% **Simva** 2,742 events

32.7% **EZ/Simva** 2,572 events

HR 0.936 CI (0.89, 0.99)
p=0.016

Event rate (%)

Time since randomization (years) 7-year event rates

0 1 2 3 4 5 6 7

Ref. 1. Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387–2397. 2. Bohula EA, et al. *Circulation.* 2015;132(13):1224-1233.

Updates of guidelines after IMPROVE-IT study

More aggressive lipid-lowering therapy is warranted for both high and very high risk patients.

Ezetimibe add-on therapy is spotlighted with an evidence from IMPROVE-IT study.

Ezetimibe is considered as **the first-line of choice** in case of

- Patients whose **therapeutic goal is not achieved at the maximal tolerated statin dose***.
- Patients who are **intolerant to statins.**
- Patients who have **contraindications to statins.**

* not a firm trigger for adding medication, but a factor that may be considered within the broader context of an individual patient's clinical situation

Ref. 1. Catapano AL, et al. *Eur Heart J.* 2016;37(39):2999-3058. 2. Grundy SM, et al. *Circulation.* 2019;139(25):e1082-e1143.

RACING: moderate-intensity statin/ezetimibe (vs. high dose statin)

RACING = Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease

Among patients with ASCVD, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke. (Hazard ratio 0.92; 95% CI 0.75 to 1.13; p-value 0.43)

Kaplan-Meier curves of the primary endpoint
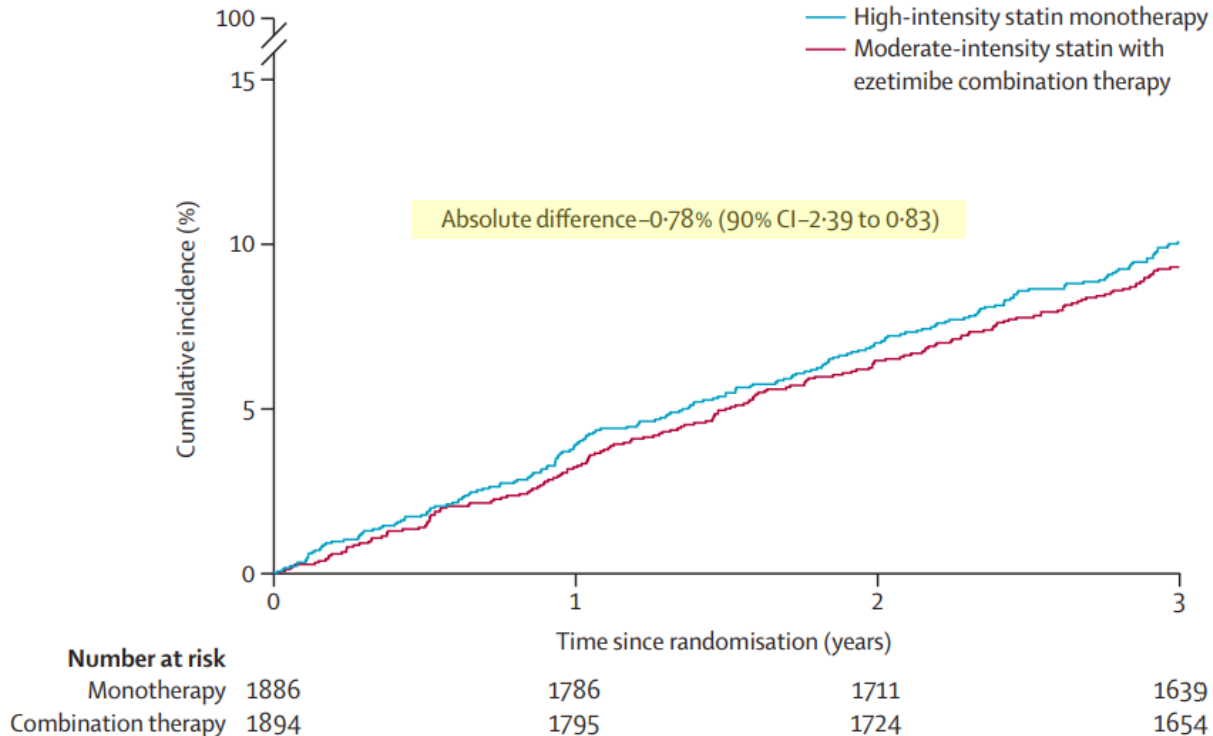
Number at risk				
Monotherapy	1886	1786	1711	1639
Combination therapy	1894	1795	1724	1654

Ref. Kim BK, et al. Lancet. Published online July 18, 2022

RACING: moderate-intensity statin/ezetimibe (vs. high dose statin)

RACING = Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease

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

Proportions of the patients with LDL cholesterol concentrations

	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, et al. Lancet. Published online July 18, 2022

Major side effects with high dose statins

Myopathy[1] — **10.5**%

Hepatic toxicity[2] — **0.98**%

New onset DM[3] — **9**%

Hemorrhage[4] — **4**%

Ref 1. Bruckert, et. al. *Cardiovasc Drugs Ther.* 2005;19:403–414. 2. Clarke AT, et al. *PloS One.* 2016;11(3):e0151587. 3. Sattar N, et al. *Lancet.* 2010;375:735–742. 4. Ziff, et al. *J Neurol Neurosurg Psychiatry.* 2019;90:75–83.

Myopathy and elevation of aminotransferase

For most of the statins examined, there is a clinically relevant increase in CK or ALT with an increase in LDL-C reduction with increasing statin dose, but for rosuvastatin, the change with increasing dose is minimal.

Occurrence of CK Elevations >10 X ULN

- Cerivastatin (0.2, 0.3, 0.4, 0.8 mg)
- Pravastatin (20, 40 mg)
- Simvastatin (40, 80 mg)
- Atorvastatin (10, 20, 40, 80 mg)
- Rosuvastatin (10, 20, 40 mg)

Occurrence of CK >10 x ULN (%)
% LDL-C Reduction

Occurrence of ALT >3 X ULN

- Fluvastatin (20, 40, 80 mg)
- Lovastatin (20, 40, 80 mg)
- Simvastatin (40, 80 mg)
- Atorvastatin (10, 20, 40, 80 mg)
- Rosuvastatin (10, 20, 40 mg)

Occurrence of ALT >3 x ULN (%)
% LDL-C Reduction

Ref. Brewer HB, et al. *Am J Cardiol.* 2003;92(suppl):23K-29K.

New onset diabetes mellitus

Higher potency statin use is associated with a moderate increase in the risk of new onset diabetes compared with lower potency statins (rate ratio 1.15, 95% confidence interval 1.05 to 1.26).

Rate ratios for new onset diabetes within two years of starting higher potency or lower potency statins after a major CV event or procedure (as-treated analysis).

Subgroup	Low dose statins		High dose statins		Rate ratio (95% CI)	Weight (%)	Rate ratio (95% CI)
	Case	Controls	Case	Controls			
☑ ≤2 years of current therapy							
• Alberta	68	531	90	944		5.2	0.66 (0.44 to 0.98)
• CPRD	103	1,064	247	2,266		9.2	1.17 (0.87 to 1.57)
• Manitoba	47	447	170	1,514		5.2	1.27 (0.85 to 1.88)
• Marketscan	180	1,853	502	4,652		25.3	1.12 (0.94 to 1.34)
• Nova Scotia	18	125	23	216		1.3	0.54 (0.24 to 1.21)
• Ontario	236	2,658	675	6,196		26.5	1.29 (1.08 to 1.53)
• Quebec	260	2,775	507	4,681		23.1	1.21 (1.00 to 1.46)
• Saskatchewan	42	378	188	1,585		4.3	1.04 (0.67 to 1.61)
☑ Total	**954**	**9,831**	**2,402**	**22,054**		**100.0**	**1.15 (1.05 to 1.26)**

Favours high potency — Favours low potency

RACING: moderate-intensity statin/ezetimibe (vs. high dose statin)

RACING = Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease

Moderate-intensity statins were not only non-inferior to high-intensity statins in terms of CV events, but were also less likely to cause dose reductions and discontinuations due to intolerance

Secondary safety endpoint of the safety population

	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)
• 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)
• 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)

Greater effects of statin in Korean patients

Several studies on Koreans have reported that the **same dose of statin leads to a greater reduction of LDL-C** among Koreans than among foreigners.

> Therefore, statin treatment can be initiated with **a lower dose** than suggested in foreign guidelines, especially in American guidelines

Comparison of LDL-C reduction effects of statins between foreigners and Koreans
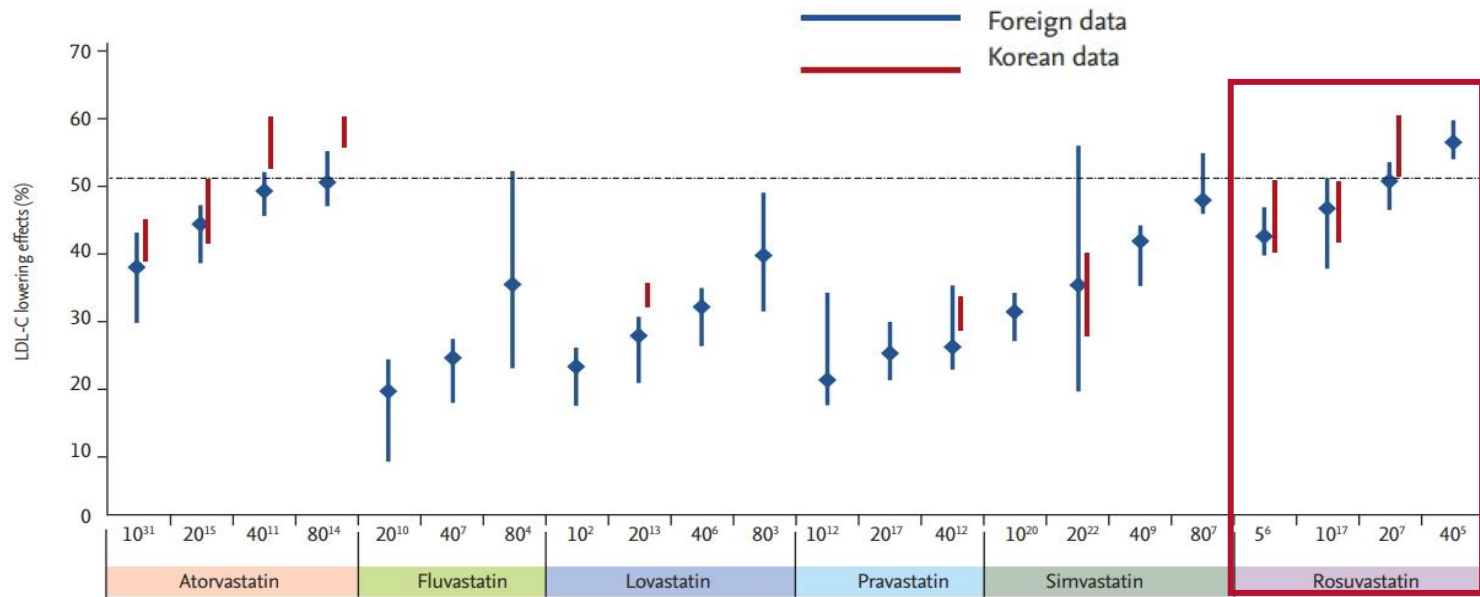
People who are prone to statin intolerance

Statin intolerance is associated with suboptimal lipid-lowering therapy and a high risk of first and recurrent CVD events, vulnerable factors include Asian race, female gender, high statin dose, and old age.

In patients with statin intolerance, an altered dosing regimen of **very low doses of statins** should be attempted, and also **other lipid-lowering drugs** may be needed

176 studies
4,143,517 patients

Asian race ↑25.4%

Age ↑33.1%

Age ≥ 65 years ↑31.2%

Black race ↑29.3%

Female ↑47.9%

Obesity ↑30.6%

Depression ↓12.2%

Hypothyroidism ↑37.6%

Overall prevalence 9.1% (8.1-10%)

Chronic liver disease ↑24.3%

Diabetes mellitus ↑26.6%

Chronic renal failure ↑25.2%

Antiarrhythmics ↑31.2%

Calcium channel blockers ↑35.5%

Alcohol consumption ↑22%

Exercise ↑23.2%

High statin dose ↑37.5%

Smoking

Arterial hypertension

Duration of statin therapy

White race

Caucasian race

Hispanic race

Warfarin

Ref. 1. Bytyçi I, et al. Eur Heart J. 2022;43(34):3213-3223. 2.Stulc T, et al. Curr Atheroscler Rep. 2015;17(12):69.

Excellent LDL-C goal achievement

More than 80% of moderate to high risk patients with hypercholesterolemia achieved their lipid goals after the 8-week short treatment of rosuvastatin 2.5mg

Changes in proportions of achievement of lipid goals in patients with hypercholesterolemia
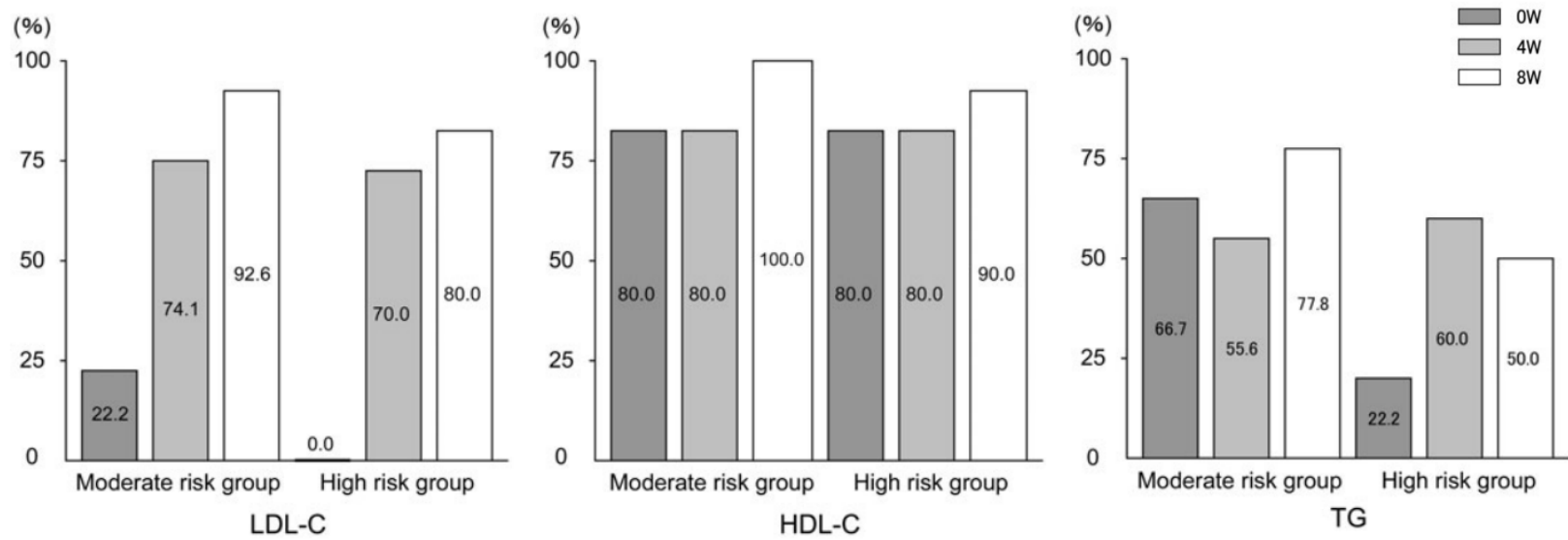
Reduction of LDL-C/HDL-C ratio

In both moderate and high risk patients, the mean LDL-C/HDL-C ratio, which is considered as a prospective index for plaque regression, was significantly reduced. (p<0.001 for both the moderate and high risk groups)

LDL-C/HDL-C ratio change

Ref.Hiroyuki O. J Rural Med. 2008; 3(1): 10-14
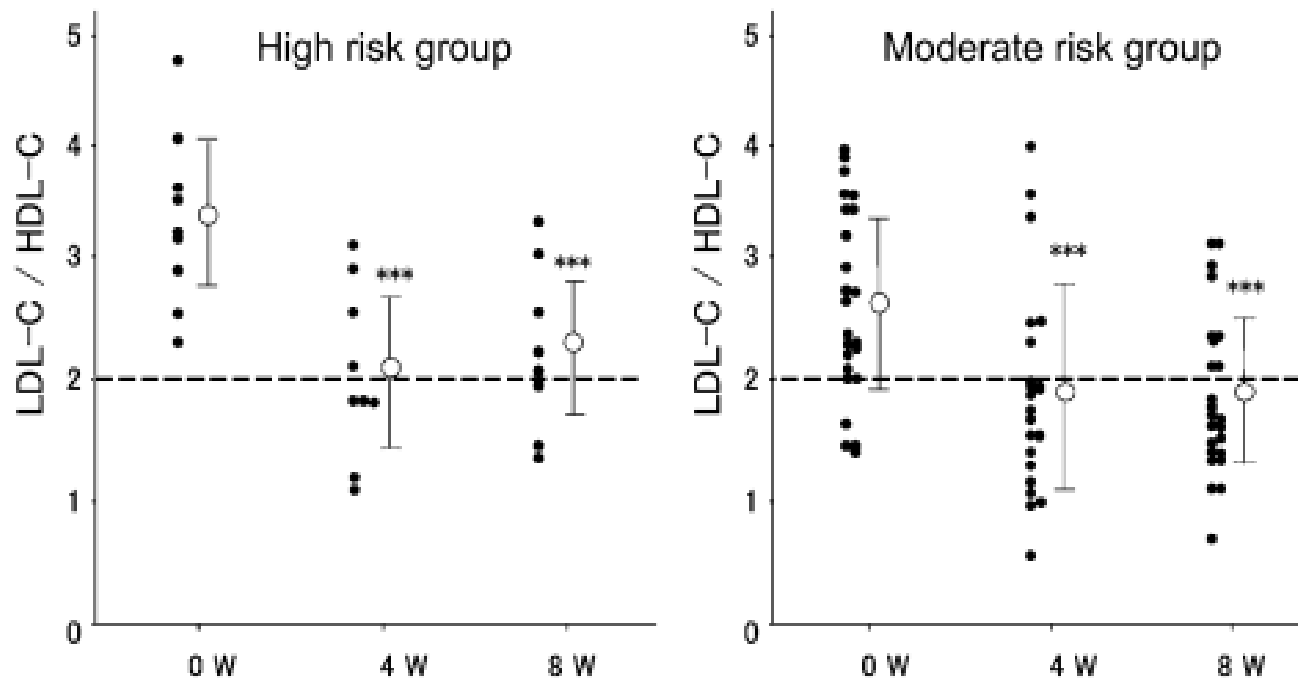
Reduction of LDL-C

 The decrease in LDL-C levels at the 8-week follow-up (primary end point) was significantly greater(-46%) in the combination therapy group than in the other groups.

Percent changes in the lipid parameters.
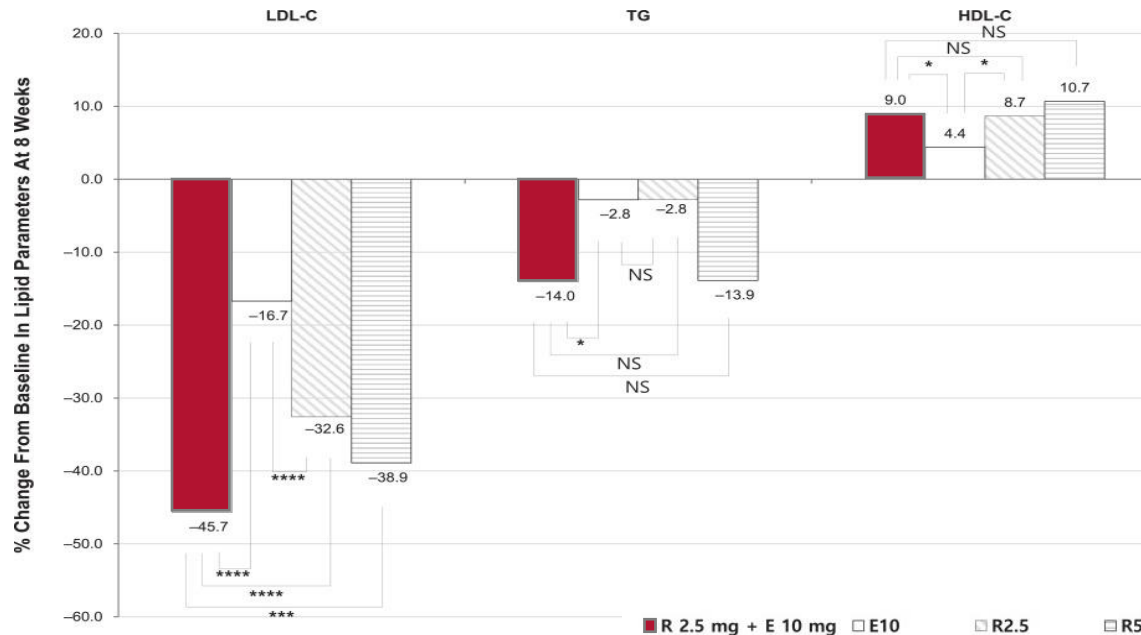
Study design
- **Patients:** patients with hypercholesterolemia
- **Intervention:** rosuvastatin/ezetimibe 2.5/10mg • **Control:** rosuvastatin 2.5mg, 5mg, ezetimibe 10mg
- **Outcome:** percentage change of LDL

Ref. Lee SA, et al. Clin Ther. 2021;43(9):1573-1589.

LDL-C goal achievement

In patients with low and moderate risk, **all patients achieved the target LDL-C levels in the R2.5+E10 group (100%)** compared to 13.0% in the E10 group, 47.6% in the R2.5 group, and 65.2% in the R5 group.

LDL-C goal achievement according to SCORE risk category at 8 weeks.

Ref. Lee SA, et al. Clin Ther. 2021;43(9):1573-1589.
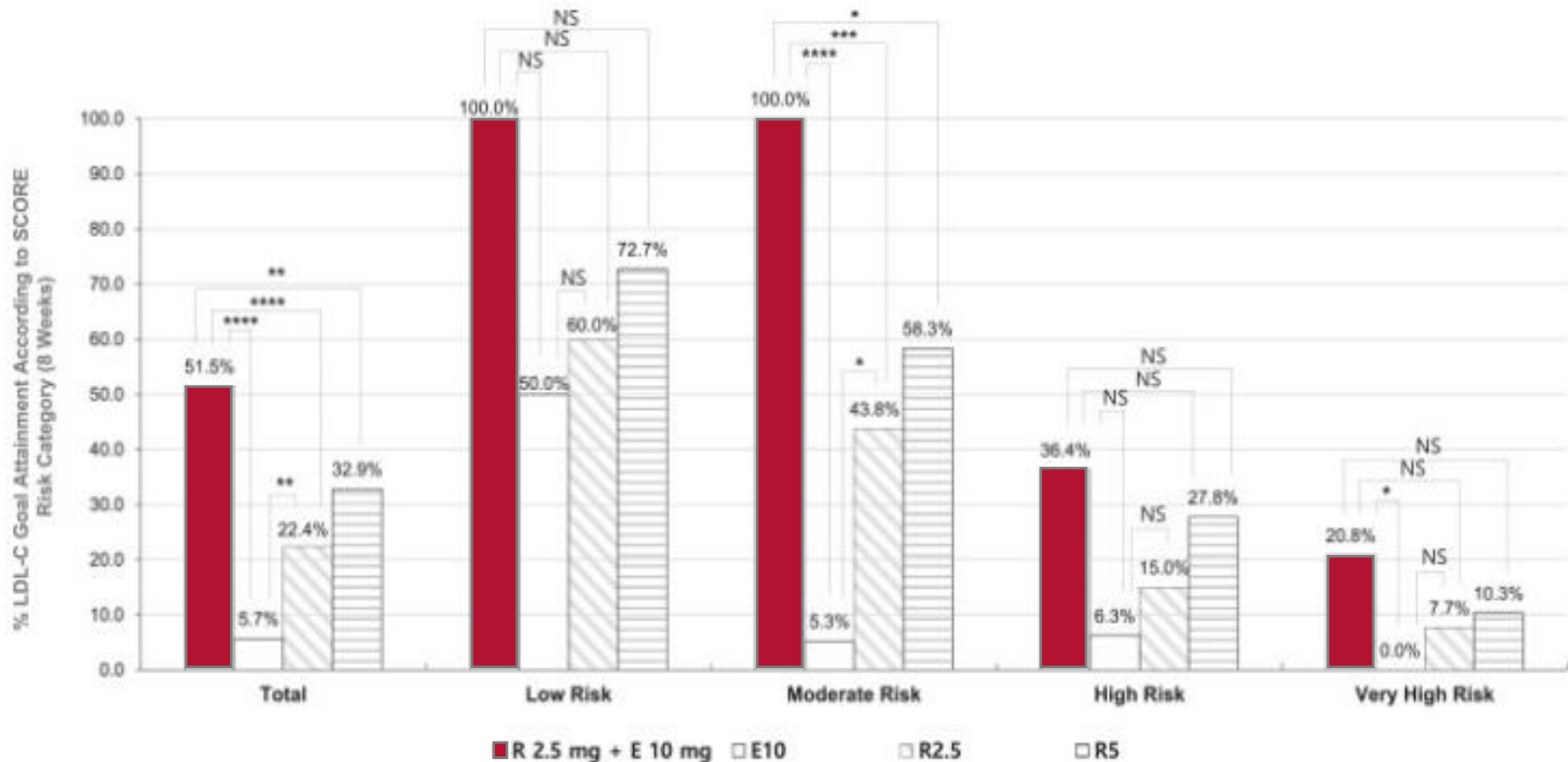
Tolerable adverse events

> There were no differences in adverse effects between the treatment groups, and most adverse events were mild.

Treatment related side effects

Variable	Rosuvastatin 2.5 mg and Ezetimibe 10 mg (n = 70)	Ezetimibe 10 mg (n = 70)	Rosuvastatin 2.5 mg (n = 68)	Rosuvastatin 5 mg (n = 71)
Adverse drug reaction	2 (2.9)	1 (1.4)	2 (2.9)	2 (2.8)
Mild	1 (1.4)	1 (1.4)	2 (2.9)	1 (1.4)
Moderate	1 (1.4)	0 (0)	0 (0)	1 (1.4)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse drug reaction	0 (0)	0 (0)	0 (0)	0 (0)
Adverse drug reaction leading to withdrawal	1 (1.4)	0 (0)	1 (1.5)	0 (0)
Reported adverse drug reaction				
Abdominal distension	0 (0)	0 (0)	1 (1.5)	0 (0)
Dyspepsia	0 (0)	1 (1.5)	1 (1.5)	0 (0)
Alanine aminotransferase increased	0 (0)	0 (0)	0 (0)	1 (1.4)
Aspartate aminotransferase increased	0 (0)	0 (0)	0 (0)	1 (1.4)
Blood creatine phosphokinase increased	0 (0)	0 (0)	0 (0)	1 (1.4)
Myalgia	1 (1.4)	0 (0)	0 (0)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	1 (1.4)
Pruritus	1 (1.4)	1 (1.5)	0 (0)	0 (0)

Ref. Lee SA, et al. Clin Ther. 2021;43(9):1573-1589.

Lipid lowering in patients with T2DM

The combination of rosuvastatin and ezetimibe not only achieves **quantitative** but also **qualitative** improvement of serum lipid levels in type 2 diabetic patients.

Percent changes from baseline of Serum lipids
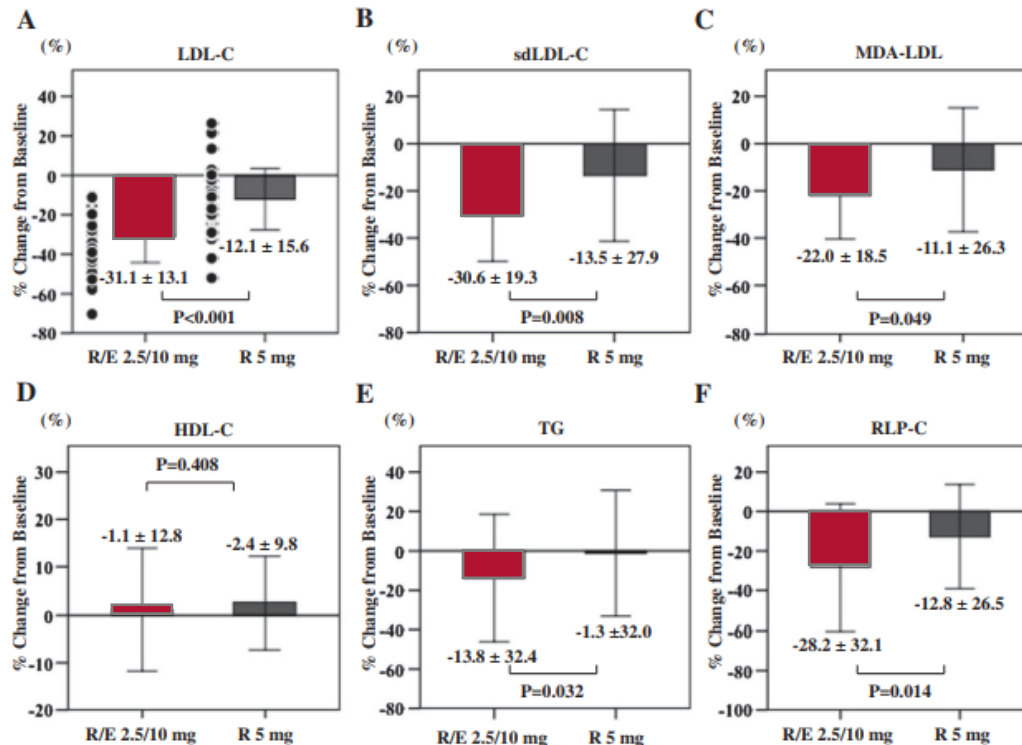
Study design

- **Patients:** type 2 diabetic patients under treatment with rosuvastatin 2.5mg
- **Intervention:** rosuvastatin/ezetimibe 2.5/10mg   • **Control:** rosuvastatin 5mg
- **Outcome:** Change of lipid profile

Ref. Torimoto K, et al. Lipids Health Dis. 2013;12:137.

Improvement of lipid profile

Improvement of lipid profile by rosuvastatin/ezetimibe 2.5/10mg was superior to that of rosuvastatin 5mg.

Improvement of lipid profile

	LDL-C	TC	TG	Non-HDL-C	ApoB
Rosuvastatin 5mg	-40.2	-27.2	-14.2	-37.4	-37.3
Rosuvstatin/ezetimibe 2.5/10mg	**-49.8**	**-33.8**	**-20.1**	**-45.7**	**-43.0**

■ Rosuvastatin 5mg   ■ **Rosuvstatin/ezetimibe 2.5/10mg**
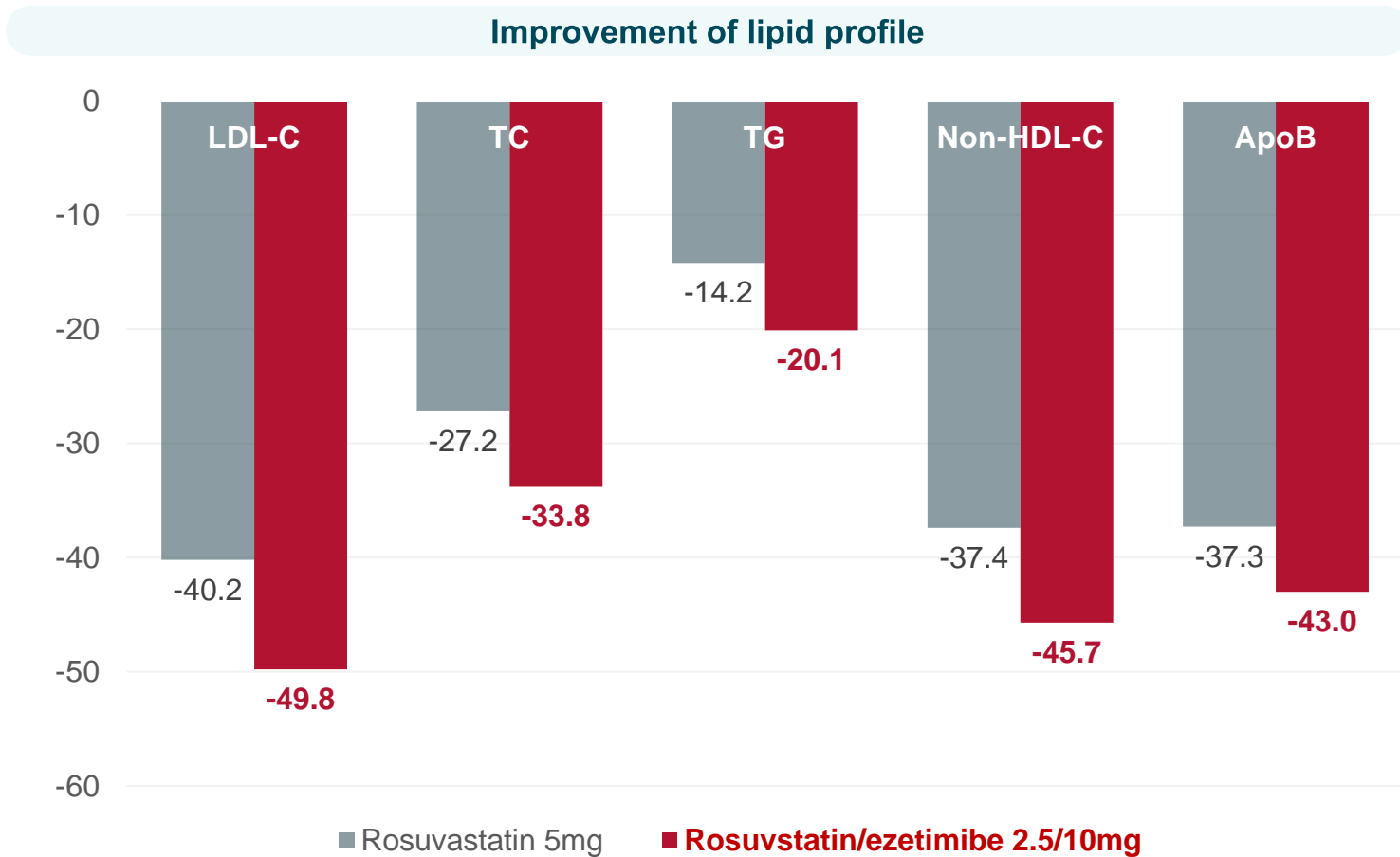
Patient-specific LDL-C reduction

> Trough formulation of various dosage, Rovazet® tablet can provide LDL-C reduction tailored to the patients' risk categories and characteristics

Ezetimibe/Rosuvastatin의 용량별 LDL-C 강하효과

기저치 대비 LDL-C 강하율(%)

Eze 10mg[1]	Rsv 2.5mg[1]	Rsv 5mg[1]	Eze/Rsv 10/2.5mg[1]	Rsv 10mg[2]	Rsv 20mg[2]	Eze/Rsv 10/5mg[2]	Eze/Rsv 10/10mg[2]	Eze/Rsv 10/20mg[2]
-16.7	-32.6	-38.9	-45.7	-46.8	-48.0	-51.8	-55.8	-61.7
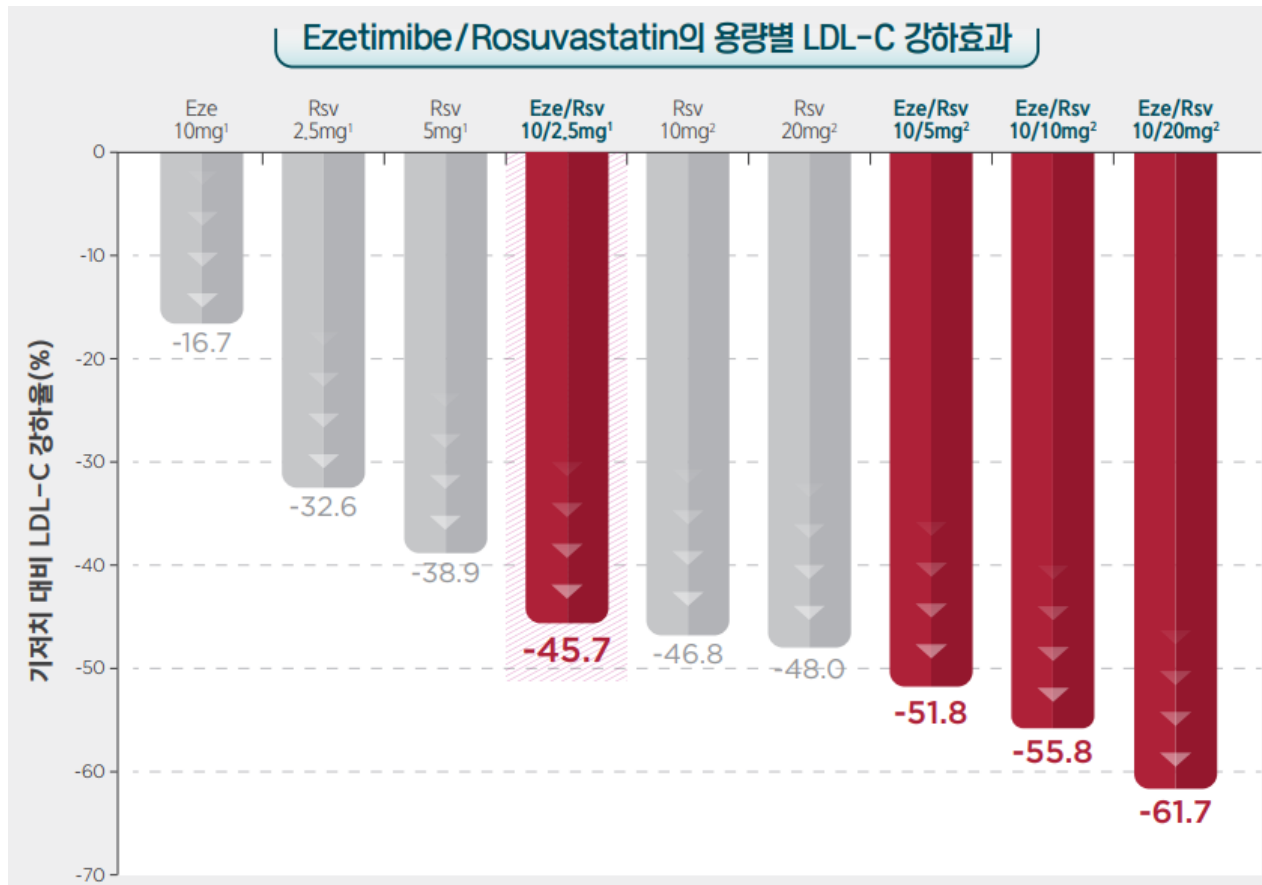
*indirect comparison between two clinical trials.

Ref. 1. Lee SA, et al. Clin Ther. 2021;43(9):1573-1589 2. Kim W, et al. Clin Ther. 2018;40(6):993-1013.

Benefits of Smaller tablet

Current status of dyslipidemia treatment in Korea

- **The number of people adherent to treatment has markedly increased (60 times) over the last 16 years.**

- **Only 4.6 million people were adherent to treatment,** comprising approximately **40% of all patients with dyslipidemia.**

Estimated number of people diagnosed, treated and adherent to treatment for dyslipidemia

x1000 persons

Legend:
- Diagnosed[1]
- Treated[2]
- Adherent to treatment[3]

Diagnosed values: 1,495 / 1,904 / 2,283 / 2,886 / 3,272 / 3,731 / 4,165 / 4,947 / 5,553 / 6,159 / 6,780 / 7,505 / 8,258 / 8,955 / 9,914 / 10,655 / 11,558

Treated values: 600 / 815 / 1,022 / 1,357 / 1,748 / 2,119 / 2,462 / 2,996 / 3,429 / 3,829 / 4,273 / 4,713 / 5,256 / 5,825 / 6,582 / 7,203 / 7,694

Adherent to treatment values: 76 / 127 / 189 / 284 / 434 / 612 / 833 / 1,117 / 1,388 / 1,645 / 2,002 / 2,383 / 2,677 / 3,081 / 3,611 / 4,113 / 4,641

Years: 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 (year)

Data source: National Health Insurance Big Data 2002-2018   Age 20+ years

1) Diagnosis of dyslipidemia is defined as ≥ 1 health insurance claim for dyslipidemia diagnosis [ICD-10 code E78] each year.

2) Treatment is defined as ≥ 1 health insurance claim for dyslipidemia diagnosis and lipid-lowering drug prescription each year.

3) Adherence to treatment is defined as the condition wherein lipid-lowering drugs were prescribed more than 290 days [80%] each year

Ref. The Korean Society of Lipid & Atherosclerosis. Dyslipidemia Fact Sheets in Korea 2020.

Better lipid profile among adherent patients

Without doubt, patients who are adherent to statin therapy had significant reduction of LDL-C, non-HDL-C, TC, and attainment of goal cholesterol levels compared with those who were not adherent.[1]

Results of multiple linear regressions in adherent vs non-adherent groups[2]

reduction from baseline

Outcome variable (mg/dl)	Parameter estimate	95% CI	P value
• LDL-C	-20.98	-22.86, -19.33	<0.0001
• Non-HDL-C	-24.31	-26.16, -22.46	<0.0001
• TC	-24.06	-25.98, -22.14	<0.0001

Relationship between MPR range and LDL cholesterol goal attainment (<100 mg/dl)[3]

Ref. 1. Jia X, et al. Am J Med. 2019;132(9):e693–e700. 2. Kazerooni R, et al. Pharmacotherapy. 2013;33(10):1044-52. 3. Alwhaibi M, et al. Patient Prefer Adherence. 2019;13:2111-2118.
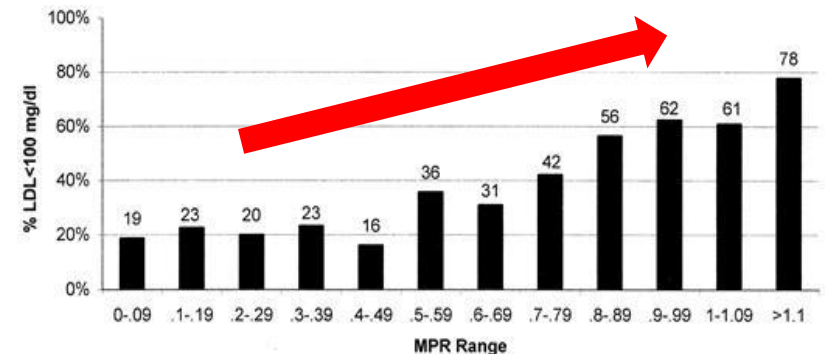
Adherence to statin therapy and all-cause mortality

- **After multivariable adjustment, adherence levels were significantly associated with 1-year mortality.**

- **Patients with an MPR <50% had an HR for 1-year mortality of 1.30 (95%CI: 1.27-1.34), compared with the most adherent patients (MPR ≥90%). The effect size was attenuated but remained significant after adjustment for LDL-c levels.**

Statin adherence and all cause mortality
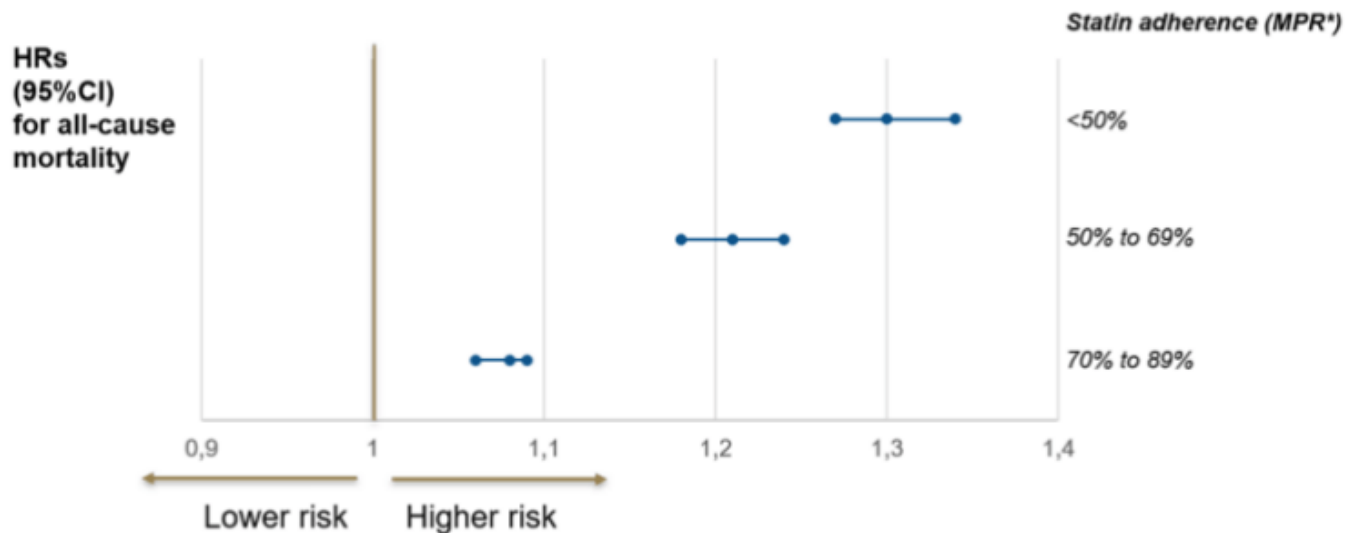
*MPR (medication possession ratio), Statin adherence was defined by the medication possession ratio (MPR), the number of days of outpatient statin supplied during a 12-month period divided by the number of days that the patient was not hospitalized and alive during the 12-month period

Ref. Rodriguez F, et al. JAMA Cardiol. 2019;4(3):206-213.

Association between statin adherence with mortality
- Patients with AMI

- **Among statin users, compared with their high-adherer, the risk of mortality was**
  - **12% higher among patients with intermediate** (PDC 40-79%) **adherence**
    (adjusted hazard ratio, 1.12; 95% confidence interval, 1.01- 1.25; P =.03)

  - **25% higher among patients with poor** (PDC < 40%) **adherence**
    (adjusted hazard ratio, 1.25; 95% confidence interval, 1.09-1.42; P=.001)

Kaplan-meier estimates of time to death for statin, β-blocker, and calcium channel blocker users according to adherence level
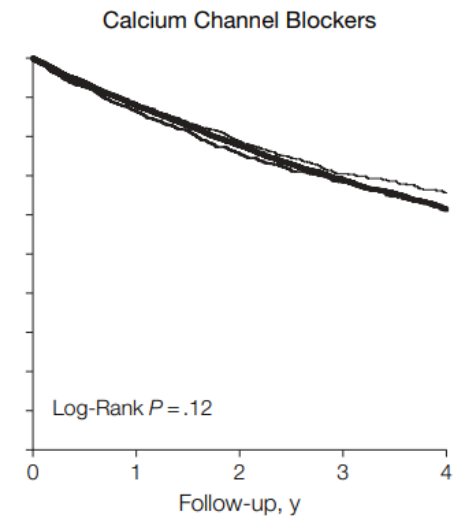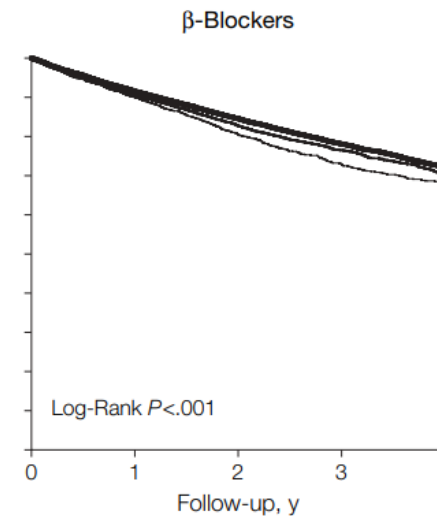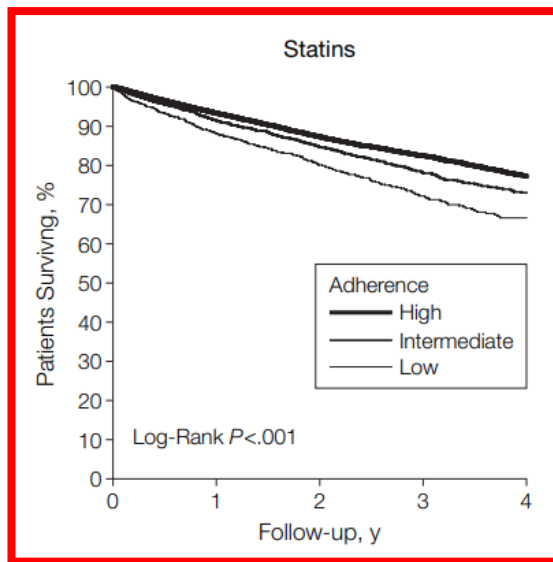
No. at Risk														
High Adherence	14 345	13 393	8787	5129	2200	17 868	16 361	11 197	6827	3058	6243	5492	3702	2211	1023
Intermediate Adherence	2407	2202	1435	810	345	4287	3880	2729	1689	806	1506	1303	874	558	256
Low Adherence	1071	944	566	317	147	2164	1947	1325	795	384	1419	1255	856	512	238

Ref. Rasmussen JN, et al. JAMA. 2007;297(2):177–186.

Adherence with statin in elderly patients

Persistence with statin therapy in older patients declines substantially over time, with the greatest drop occurring in the first 6 months of treatment.

Proportion of patients classified as adherent, partially adherent, and non-adherent

Ref. Benner JS, et al. JAMA. 2002;288(4):455-61.
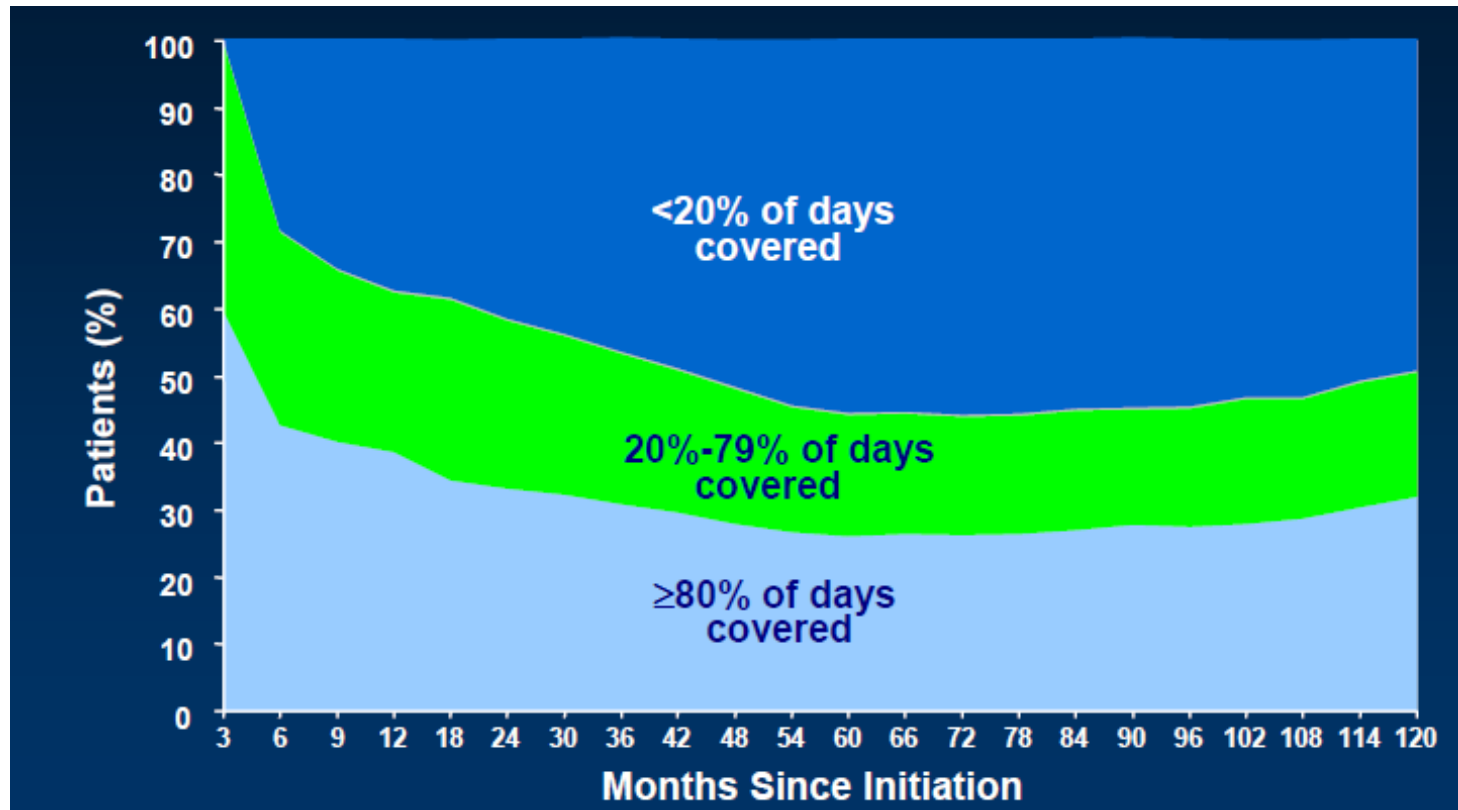
Polypharmacy among Korean Elderly

- It can be confirmed that more than 40% of the elderly outpatients who visit a public hospital in Seoul are taking multiple drugs, and the risk of taking multiple drugs was higher in men, medical benefit recipients, and patients with multiple chronic diseases.[1]

- Of the Korean elderly studied, 86.4% had polypharmacy, 44.9% had major polypharmacy and 3.0% had excessive polypharmacy.[2]

Prevalence of polypharmacy, major polypharmacy, and excessive polypharmacy

Category	Number	%	95% Confidence Interval
Polypharmacy (≧6 drugs)	275,881	86.4	86.3 to 86.6
Major polypharmacy (≧11 drugs)	143,218	44.9	44.6 to 45.0
Excessive polypharmacy (≧21 drugs)	9,669	3.0	2.7 to 3.4

doi:10.1371/journal.pone.0098043.t002

Ref. 1. HJ Koo, et al. Korean J Fam Pract 2020; 10(2): 136-142 2. HA Kim, et al. PLoS One. 2014; 9(6): e98043.

Decreased adherence in patients using polypharmacy

- Among patients taking antihypertensive and lipid-lowering medications, adherence to those regimens became less likely as the number of prescription medications increased.

- Adherence declined with incremental increases in prescription burden among patients taking 3 or fewer medications.

## The one-year proportion of days covered (PDC)
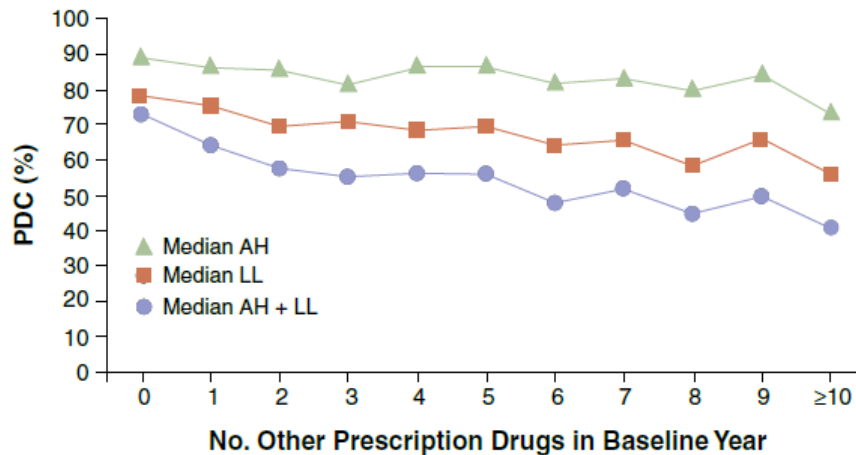
Percentage of patients adherent

Ref. Benner JS, et al. Am J Health Syst Pharm. 2009;66(16):1471-7.
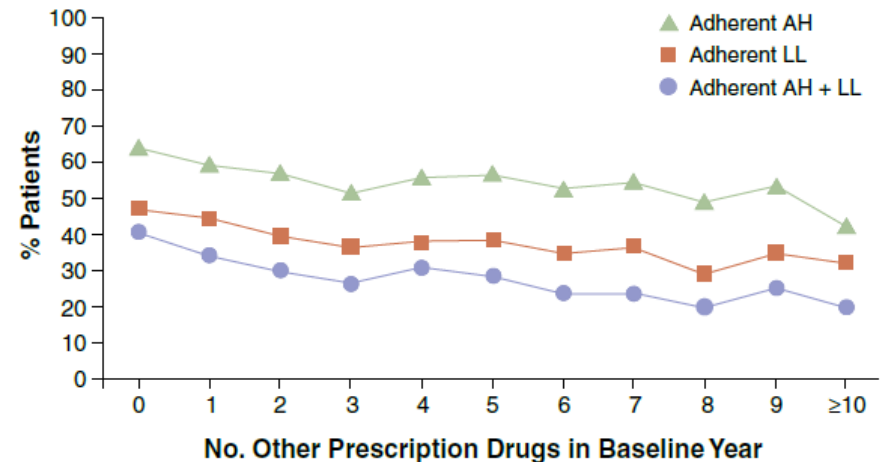
Intentional non-adherence due to swallowing difficulties

- **Many polypharmacy patients attending community pharmacies have swallowing difficulties.**

- **The large size and sticky coating of drugs were perceived as the main causes of swallowing difficulties.**

- **Intentional non adherence (23 % of patients) and altering the oral dose formulation were the most common and potentially harmful strategies used by patients to overcome their swallowing difficulties.**
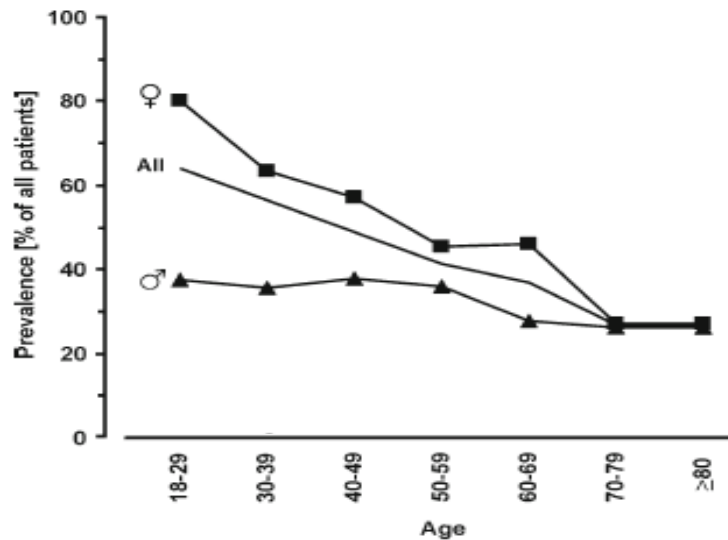
Causes of swallowing difficulties

Ref. Marquis J, et al. Int J Clin Pharm. 2013;35(6):1130-6.
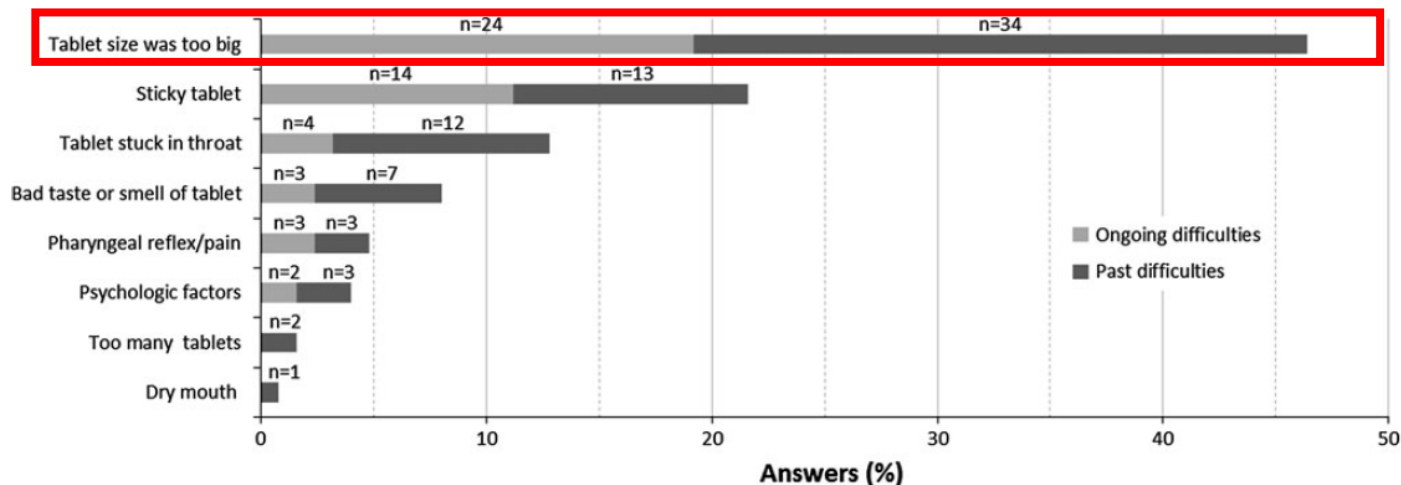
Prevalence and cause of swallowing difficulties

- Actually, 27.2 % (240) of all patients who returned a completed and plausible medication list also had swallowing difficulties with their current tablets and capsules.

- Reasons given for difficulties related to the dosage form were **size (74.6 %)**, surface (70.5 %), shape (43.5 %), and flavor (22.1 %).

Prevalence of swallowing difficulties

Proportion of non-adherence due to swallowing difficulties

Ref. Schiele JT, et al. Eur J Clin Pharmacol. 2013;69(4):937-48.
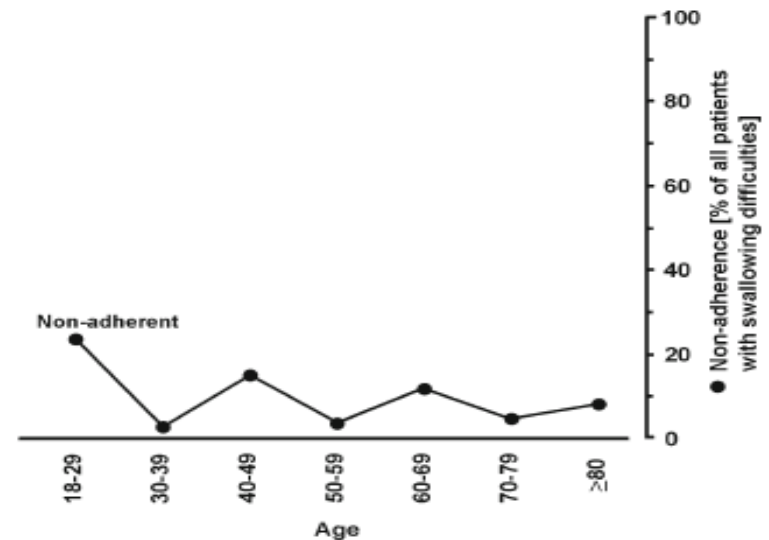
Threshold size of medication

- The threshold size of tablets/capsules that patients feel are too large to ingest is **length + width + depth = 21 mm.**

- When designing or altering tablets/capsules, if length + width + depth is ≥ 21 mm, the drug should be scored, split into smaller doses, or redesigned as an orally disintegrating formulation.

Ref. Kabeya K, et al. Patient Prefer Adherence. 2020;14:1251-1258.
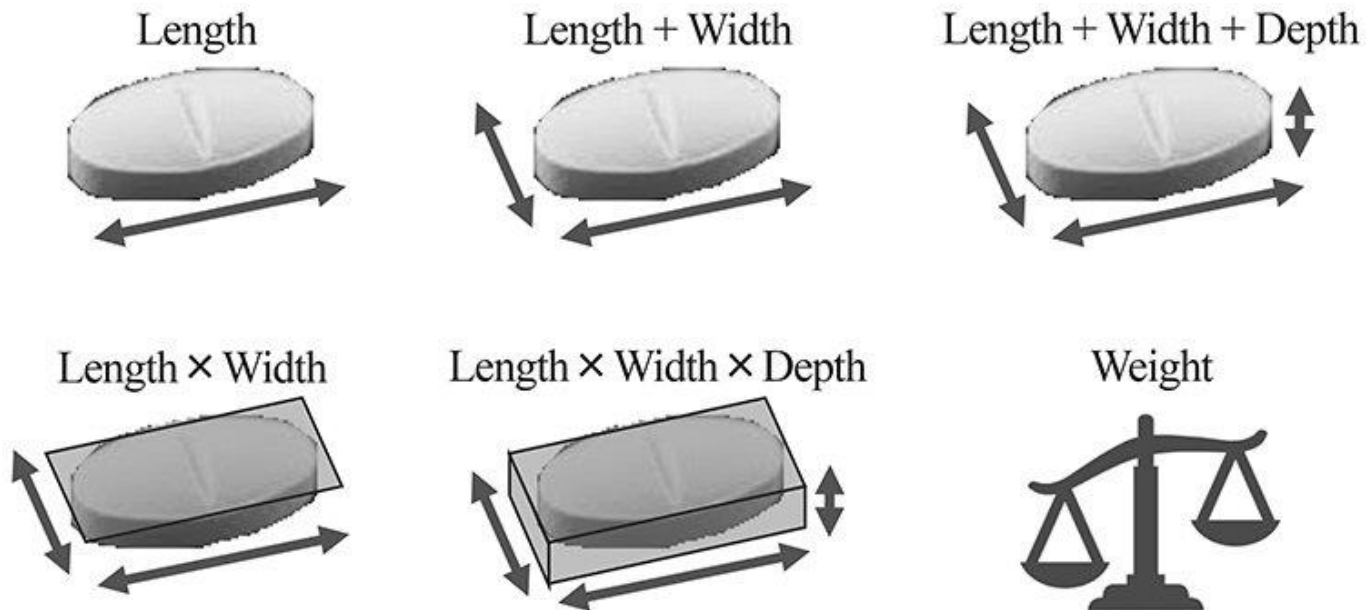
Rovazet® weight & size

BEFORE

AFTER

NEW

10/5mg 10/10mg 10/20mg → 10/2.5mg 10/5mg 10/10mg 10/20mg

Dose	Weight			Size		
	Rovazet (Before)	Rovazet (After)	Compare	Rovazet (Before)	Rovazet (After)	Compare
☑ 10/2.5mg	New line-up					
☑ 10/5mg	319mg	139mg	56%⬇	22.85mm (12.65+6.1+4.1)*	17.80mm (9.1+5.1+3.6)*	22%⬇
☑ 10/10mg	319mg	160mg	50%⬇	23.05mm (12.65+6.1+4.3)*	18.30mm (9.1+5.1+4.1)*	21%⬇
☑ 10/20mg	432mg	268mg	38%⬇	26.35mm (14.6+6.45+5.3)*	21.70mm (10.2+6.1+5.4)*	18%⬇

* (장축+단축+두께).

Summary

LDL-C lowering treatment is recommended for high risk patients such as CHD in recent guidelines.

According to various studies, rosuvastatin is highly effective in reducing LDL-C, plaque burden, and major CV events.

Ezetimibe combination could be an answer with superior efficacy and less side effects for high risk patients in secondary prevention reducing of the concerns regarding new DM associated with high-dose statin.

The use of lower-dose, smaller lipid-lowering drugs may be a way to reduce drug discontinuation and non-adherence due to side effects in patients..

Rovazet® (Rosuvastatin + Ezetimibe) could be recommended as the optimal treatment option in high risk dyslipidemic patients.

Rovazet® profile

성분명	**Ezetimibe + Rosuvastatin**
효능·효과	**원발성 고콜레스테롤혈증, 혼합형 이상지질혈증**
용법·용량	**1일 1회 투여** (식사무관)
초회용량	**10/2.5 mg**
용량·약가	**10/2.5 mg (638원)** **10/5 mg (877원)** **10/10 mg (1,226원)** **10/20 mg (1,237원)**

전문의약품

로바젯정 10/5밀리그램
(에제티미브/로수바스타틴칼슘)

10/5mg
30정

효능·효과
- 원발성 고콜레스테롤혈증(이형접합 가족형 및 비가족형) 또는 혼합형 이상지질혈증 환자의 상승된 총 콜레스테롤(total-C), LDL-콜레스테롤(LDL-C), 아포 B 단백(Apo B), 트리글리세라이드(TG) 및 non-HDL-콜레스테롤을 감소시키고, HDL-콜레스테롤(HDL-C)을 증가시키기 위한 식이요법의 보조제로서 이 약을 투여한다.

용법·용량
- 로바젯 정은 식사와 관계없이 1일 1회 투여한다.
- 로바젯 정을 투여하기 전 또는 투여 중인 환자는 반드시 표준 콜레스테롤 저하식을 지속적으로 해야 한다.
- 로바젯 정의 투여량은 환자의 LDL-콜레스테롤의 기저치, 권장되는 치료 목표치 및 환자의 반응에 따라 조절되어야 한다.