Lower Is Better
& Combination Is Better

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Disclosure

- No potential conflicts of interest

Contents

1. Importance of dyslipidemia management

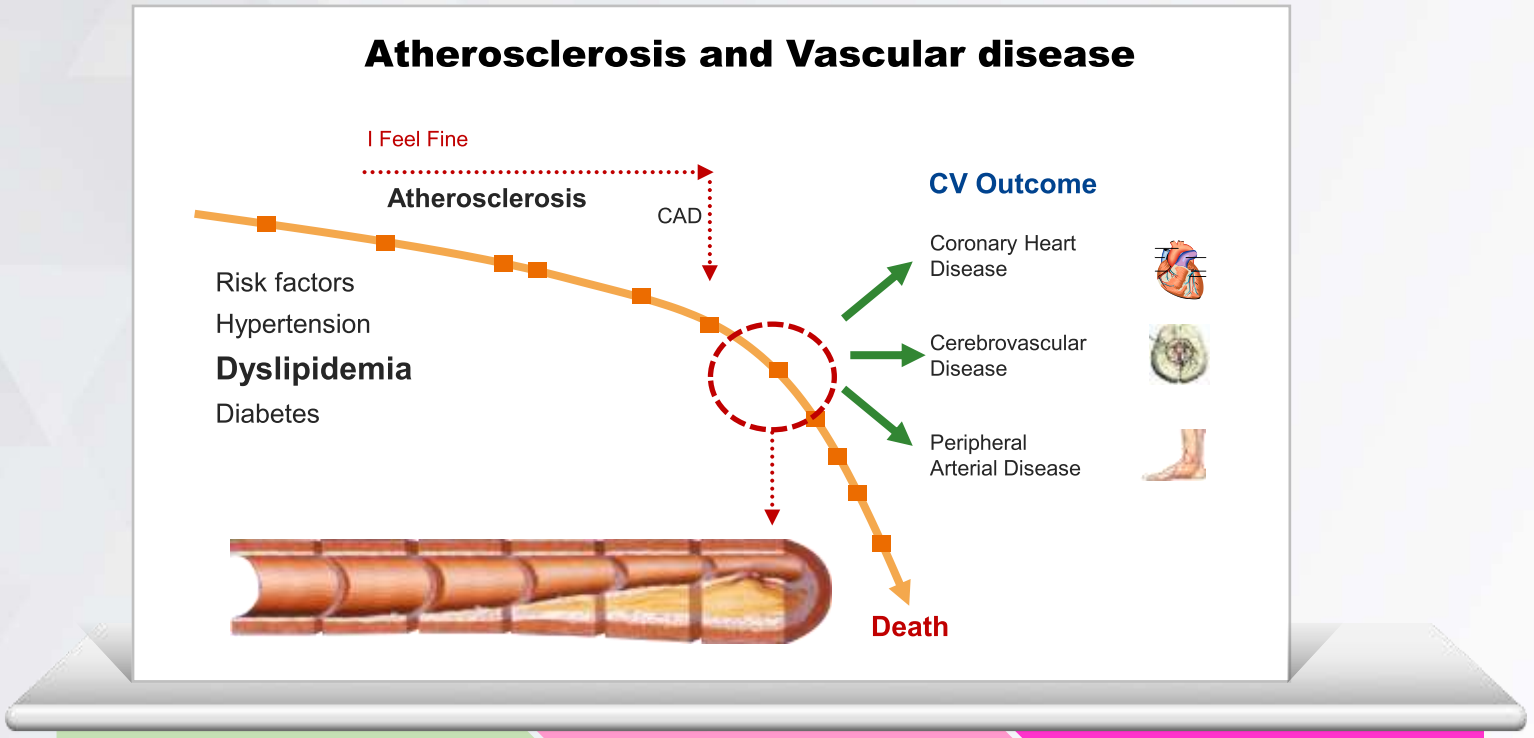
    - Dyslipidemia and Cardiovascular disease
    - Guidelines for dyslipidemia

2. Another way of lowering LDL-C

    - Superior statin Rosuvastatin
    - Additional benefits from Ezetimibe

3. Clinical efficacy and safety of CREZET®

From dyslipidemia to atherosclerosis and vascular disease

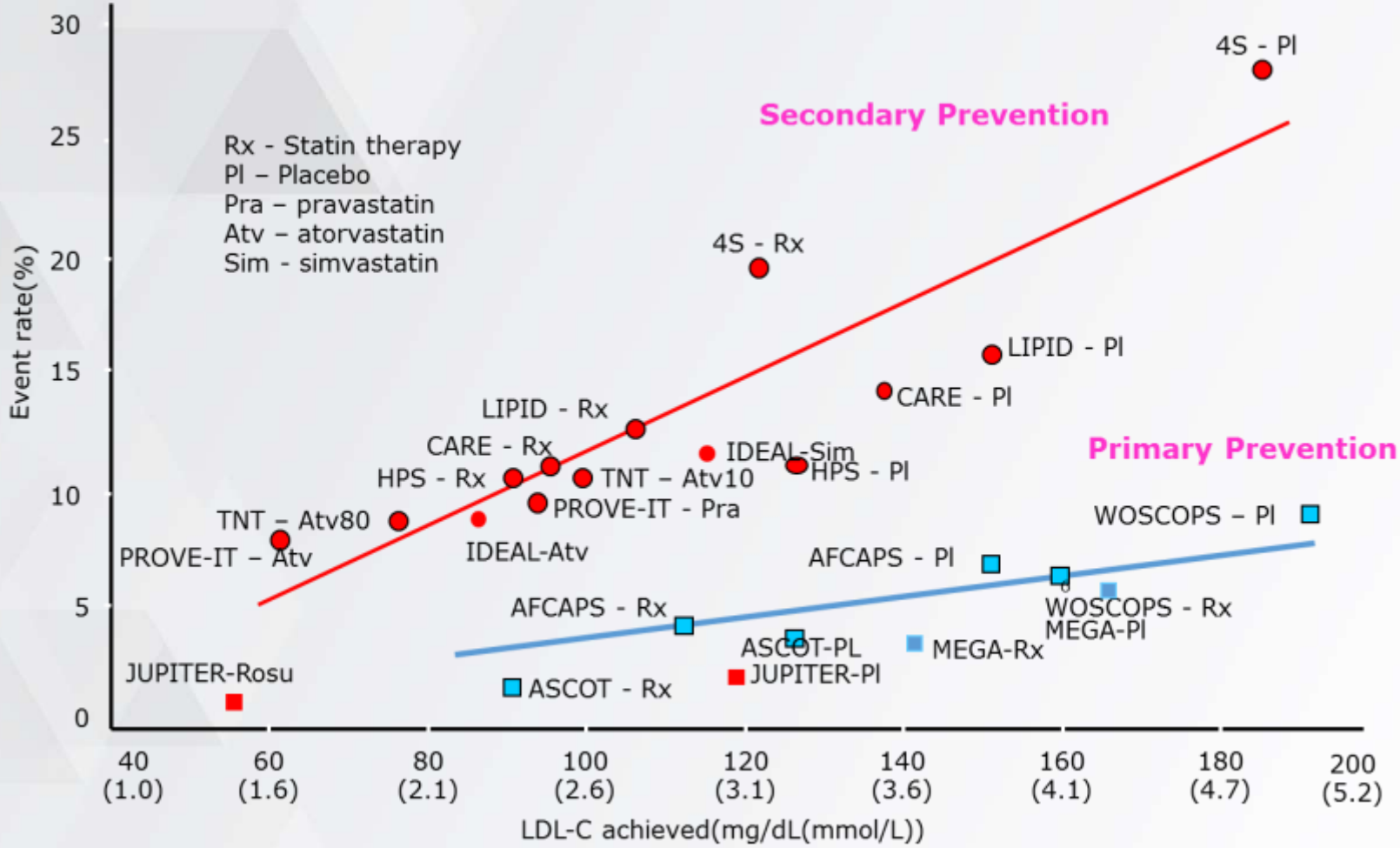


Risk factors	Atherosclerosis	Vascular disease
☑ Dyslipidemia	☑ Carotid artery	☑ Atherosclerotic Stroke
☑ DM	☑ Coronary artery	☑ Ischemic heart disease
☑ Hypertension	☑ Aorta	☑ Peripheral artery disease

Ref.> Dzau V, et al. *Am Heart J.* 1991;121(4 Pt 1):1244-1263.

The Lower, the better

<Relationship between LDL-C and CV incidence>



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

Dyslipidemia Fact Sheets in Korea (2020)

- **Definition and Diagnosis of Dyslipidemia**

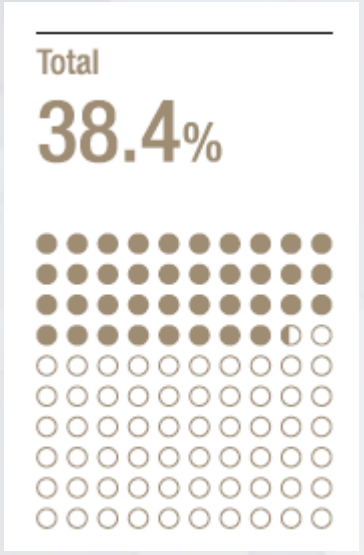
Hypercholesterolemia	**Total cholesterol ≥240mg/dL** or taking lipid-lowering drug
Hyper-LDL-C	**LDL-C ≥160mg/dL** or taking lipid-lowering drug
Hypertriglyceridemia	**TG ≥200mg/dL**
Hypo-HDL-C	**HDL-C <40mg/dL**

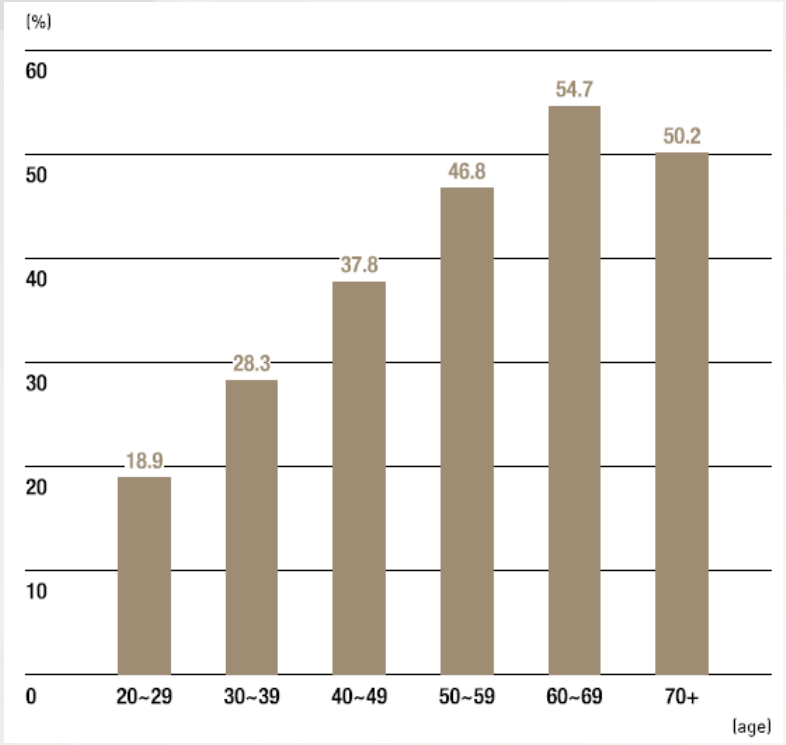
TC(=Total cholesterol)
LDL-C(=Low-density lipoprotein cholesterol)
HDL-C(=High-density lipoprotein cholesterol)
TG(=Triglycerides)

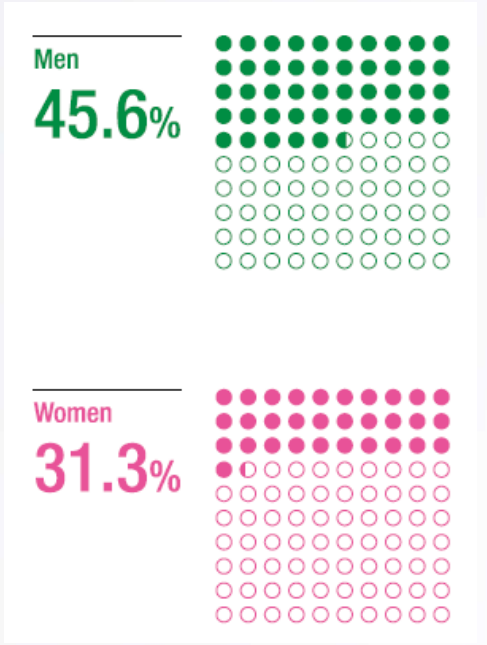
Ref.> Dyslipidemia Fact Sheets in Korea. Korean Society of Lipidology and Atherosclerosis. 2020.

Prevalence of Dyslipidemia

- **Four out of 10 adults aged 20 years or older had dyslipidemia.**
- **About 5 out of 10 men and 3 out of 10 women have dyslipidemia.**



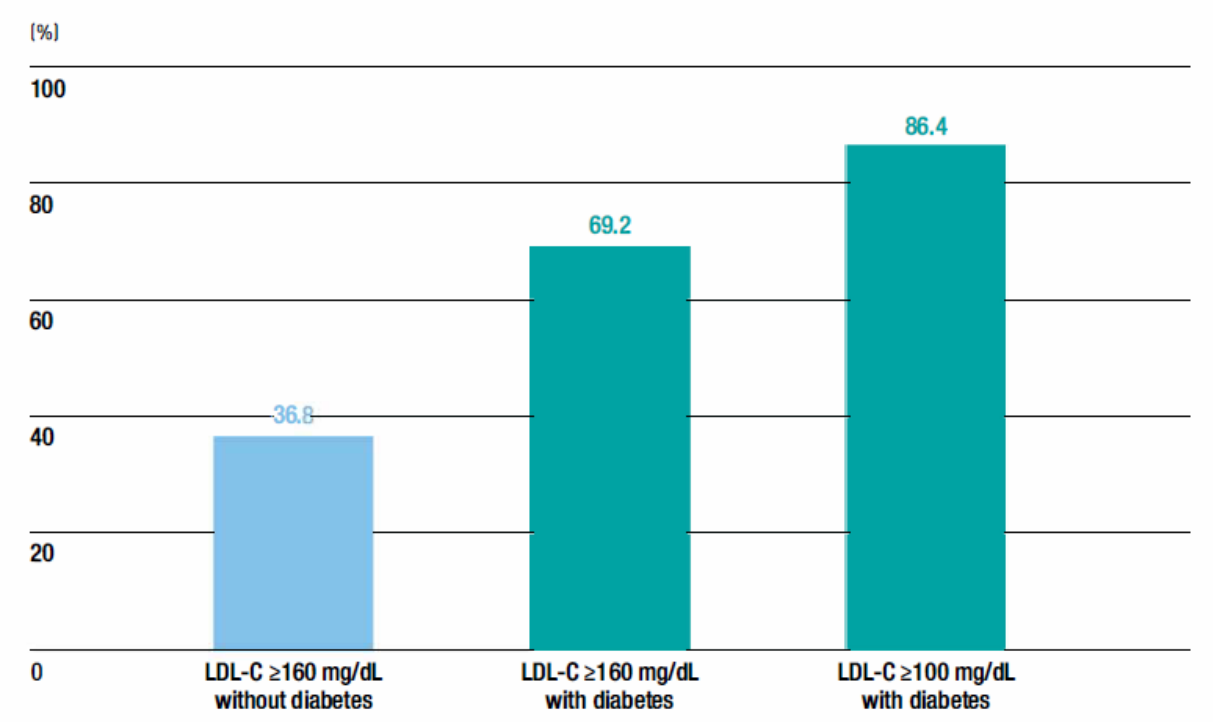




Ref.> Dyslipidemia fact sheets in Korea. Korean Society of Lipidology and Atherosclerosis.. 2020.

Diabetes and Dyslipidemia

- **The prevalence of dyslipidemia in adults with diabetes is <u>2 times higher</u> than that of the adults without diabetes.**
- **When the LDL-C cut-off value was strictly set to 100 mg/dL, more than <u>85% of people with diabetes</u> had dyslipidemia.**



Ref.> Dyslipidemia fact sheets in Korea. Korean Society of Lipidology and Atherosclerosis.. 2020.

NCEP ATP III

<LDL-C goals in different risk categories >

Risk Category	LDL-C Goal
High risk: **CHD* or CHD risk equivalents†** (10-year risk >20%)	**<100mg/dL** **(optional goal: <70mg/dL)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)	<130mg/dL
Moderate risk: 2+ risk factors‡ (10-year risk <10%)	<130mg/dL
Lower risk: 0-1 risk factor	<160mg/dL

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures(angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†**CHD risk equivalents** include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), **diabetes**, and 2+ risk factors with 10-year risk for hard CHD >20%.

‡Risk factors include cigarette smoking, hypertension (BP ≥140/90mmHg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥ 55years).

NCEP ATP III(=National Cholesterol Education Program Adult Treatment Panel III)

Ref.> Grundy SM, et al. *Circulation.* 2004;110(2):227-239.

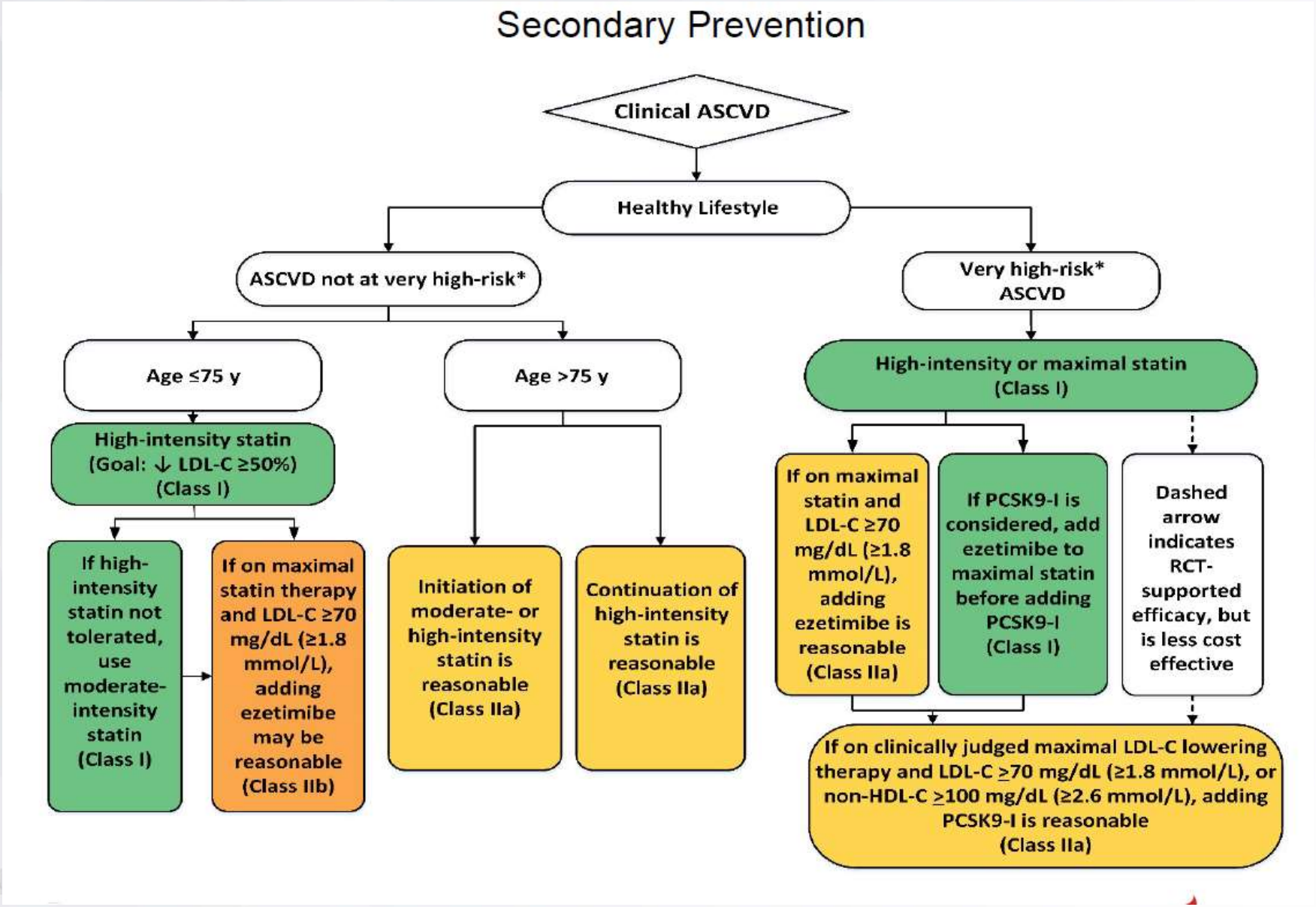
KSoLA Guideline 2018

Risk categories		LDL-C (mg/dL)	non-HDL-C (mg/dL)
Very high risk	Coronary artery disease	< 70	< 100
	Atherosclerotic Stroke and transient ischemic attack		
	Peripheral artery disease		
High risk	Carotid artery disease[1]	< 100	< 130
	Abdominal aortic aneurysm		
	Diabetes mellitus[2]		
Moderate risk	Major risk factors[3] ≥ 2	< 130	< 160
Low risk	Major risk factors[3] ≤ 1	< 160	< 190

1) In case of significant carotid artery stenosis (which has been shown to be strongly predisposed to clinical events)
2) Target goal can be lowered in patients who have target organ damage or major cardiovascular risk factors.
3) Age (men ≥ 45 years, women ≥ 55 years), family history of premature ASCVD, hypertension, smoking, and low HDL cholesterol level

LDL-C, low-density lipoprotein cholesterol ; non-HDL-C, non-high-density lipoprotein cholesterol ; ASCVD, atherosclerotic cardiovascular disease

2018 AHA/ACC Guideline on the Management of Blood Cholesterol - Secondary Prevention in Patients With Clinical ASCVD



Changes in ESC/EAS guideline

CV risk categories	Treatment goal for LDL-C (mg/dL)	
	2016	2019
Very-high-risk	<70 or LDL-C reduction of ≥50% from baseline	<55 and LDL-C reduction of ≥50% from baseline
High-risk	<100 or LDL-C reduction of ≥50% from baseline	<70 and LDL-C reduction of ≥50% from baseline
Moderate risk	<115	<100
Low risk		<116

※ ESC=European Society of Cardiology, EAS=European Atherosclerosis Society, LDL-C=low-density lipoprotein cholesterol

www.escardio.org/guidelines

Ref.> 1. Mach F, et al. Eur Heart J. 2019

2021 ADA Guideline

The addition of ezetimibe to maximally tolerated statin therapy has been shown to provide additional cardiovascular benefit.

<Recommendations for statin and combination treatment in people with diabetes>

Age	ASCVD risk factors	Recommended statin intensity*
Primary prevention		
20-39 years	ASCVD risk factor(s)** **-10-year ASCVD risk≥20%**	Initiate-High(multiple factors) **- Maximally tolerated statin plus ezetimibe**
40-75 years	None ASCVD risk factors **-10-year ASCVD risk≥20%**	Moderate High **- Maximally tolerated statin plus ezetimibe**
>75 years	None ASCVD risk factors	Moderate High
Second prevention		
ASCVD **ASCVD and LDL-C≥70mg/dL in patients with high-intensity statin therapy**		High **Maximally tolerated statin plus non-statin therapy** (ezetimibe may be preferred due to lower cost)

*In addition to lifestyle therapy.
**ASCVD risk factors include LDL cholesterol ≥100mg/dL(2.6mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

Ref.> American Diabetes Association. *Diabetes Care.* 2021;44(Suppl 1):S125-S150.

2021 ADA Guideline

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Lowers LDL Cholesterol by **≥50%**	Lowers LDL Cholesterol by **30-49%**
Atorvastatin 40–80mg **Rosuvastatin 20-40mg**	Atorvastatin 10-20mg **Rosuvastatin 5-10mg** Simvastatin 20-40mg Pravastatin 40-80mg Lovastatin 40mg Fluvastatin XL 80mg Pitavastatin 1-4mg

*Once-daily dosing.

※ **Low-dose statin therapy** is generally **not recommended** in patients with diabetes but is sometimes the only dose of statin that a patient can tolerate. For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used.

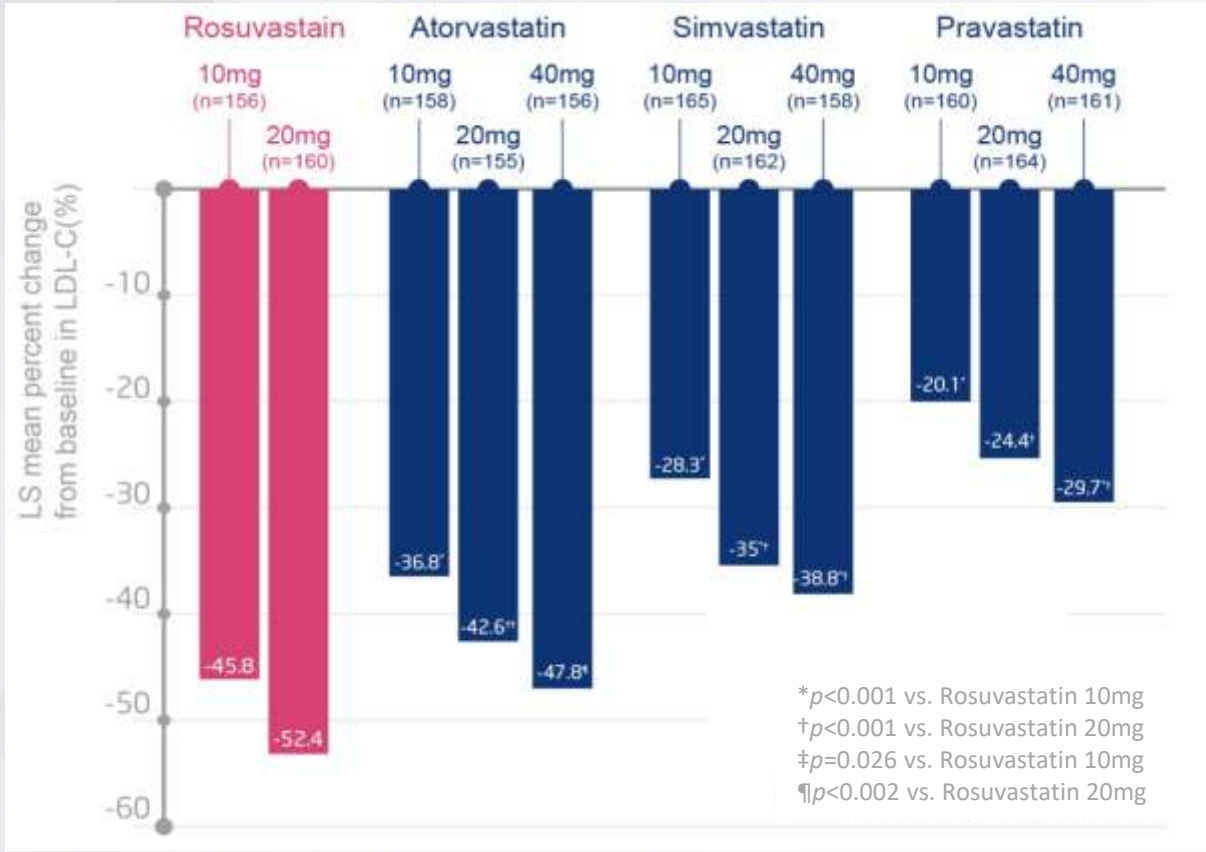
Ref.> American Diabetes Association. *Diabetes Care.* 2021;44(Suppl 1):S125-S150.

Contents

STELLAR: Reduction of LDL-C

Rosuvastatin produced numerically greater LDL-C reductions.

<Mean percent change from baseline in LDL-C>



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

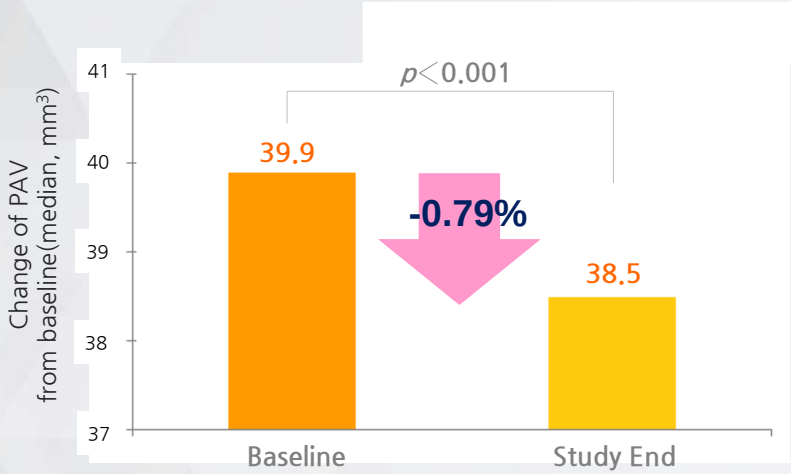
Ref.> Jones PH, et al. *Am J Cardiol*. 2003;92(2):152-160.

ASTEROID: Atheroma Volume Regression

Treatment of rosuvastatin for 24 months was associated With atherosclerosis regression.

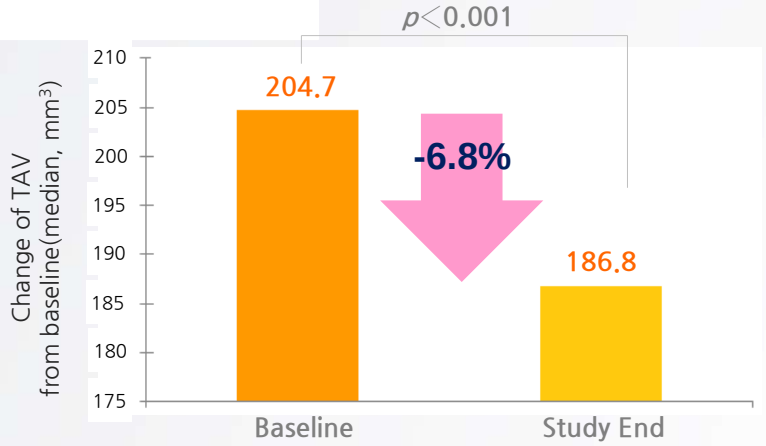
<Percent Atheroma Volume>

Atheroma volume/Blood vessel volume, n=349



<Total Atheroma Volume>

n=319



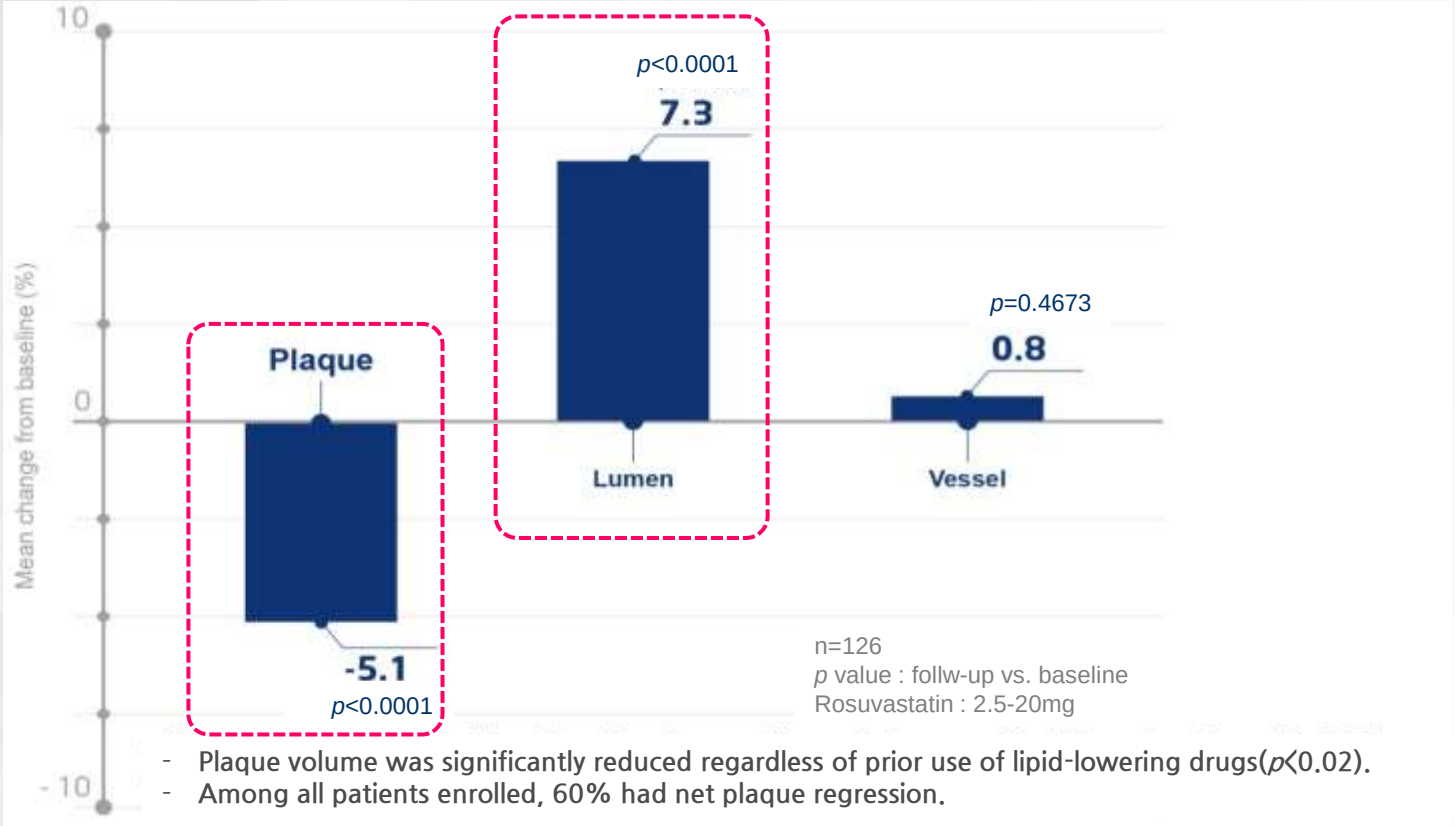
ASTEROID=A Study To Evaluate the Effect of ROsuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

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

COSMOS: Plaque Volume Regression

Rosuvastatin exerted significant regression of coronary plaque volume in Asian patients with stable CAD*.

<Percent change from baseline of plaque, lumen, and vessel volume>



- Plaque volume was significantly reduced regardless of prior use of lipid-lowering drugs(p<0.02).
- Among all patients enrolled, 60% had net plaque regression.

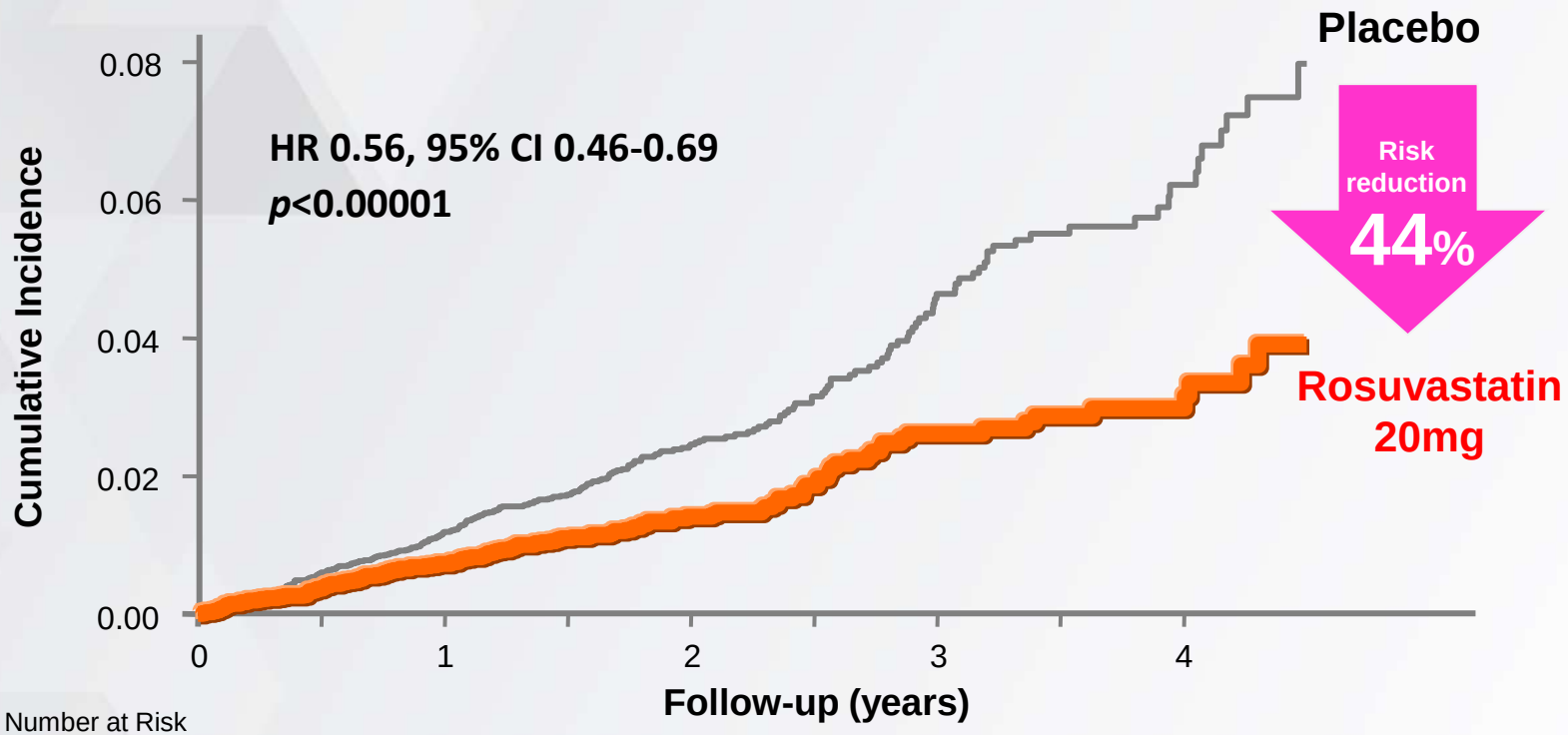
COSMOS=COronary atherosclerosis Study Measuring effects Of rosuvastatin using intravascular ultrasound in Japanese Subjects

*CAD=Coronary Artery Disease

Ref.> Takayama T, et al. *Circ J*. 2009;73(11):2110-2117.

JUPITER trial

<Cumulative incidence of primary end point*>



Number at Risk

Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	544	157
Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	534	174

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

*Primary end point: Occurrence of a first major cardiovascular event
(nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes)

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

HOPE-3

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

HOPE-3=Heart Outcomes Prevention Evaluation

Rosuvastatin 10mg	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;374:2021-31.

HOPE-3

- **Outcomes**

1st Co-primary Outcome

- Composite of death from CV cause, nonfatal MI, nonfatal stroke

2nd Co-primary Outcome

- Composite 1 + resuscitated cardiac arrest, heart failure, revascularization

Ref.> Yusuf S, et al. N Engl J Med 2016;374:2021-31.

HOPE-3 : Results ①

- **Baseline Characteristics of the Participants**

Characteristic	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)
Age — yr	65.8±6.4	65.7±6.3
Female sex — no. (%)	2951 (46.4)	2923 (46.1)
Cardiovascular risk factors — no. (%)		
Elevated waist-to-hip ratio	5540 (87.1)	5494 (86.6)
Recent or current smoking	1740 (27.4)	1784 (28.1)
Low HDL cholesterol level	2344 (36.8)	2244 (35.4)
Impaired fasting glucose or impaired glucose tolerance	809 (12.7)	807 (12.7)
Early diabetes mellitus	374 (5.9)	357 (5.6)
Family history of premature coronary heart disease	1675 (26.3)	1660 (26.2)
Early renal dysfunction	169 (2.7)	181 (2.9)
Hypertension	2403 (37.8)	2411 (38.0)
Presence of 2 risk factors	3002 (47.2)	2924 (46.1)
Presence of ≥3 risk factors	1545 (24.3)	1523 (24.0)
Blood pressure — mm Hg		
Systolic	138.04±14.92	138.06±14.62
Diastolic	81.85±9.38	81.90±9.26

Ref.> Yusuf S, et al. N Engl J Med 2016;374:2021-31.

HOPE-3 : Results ②

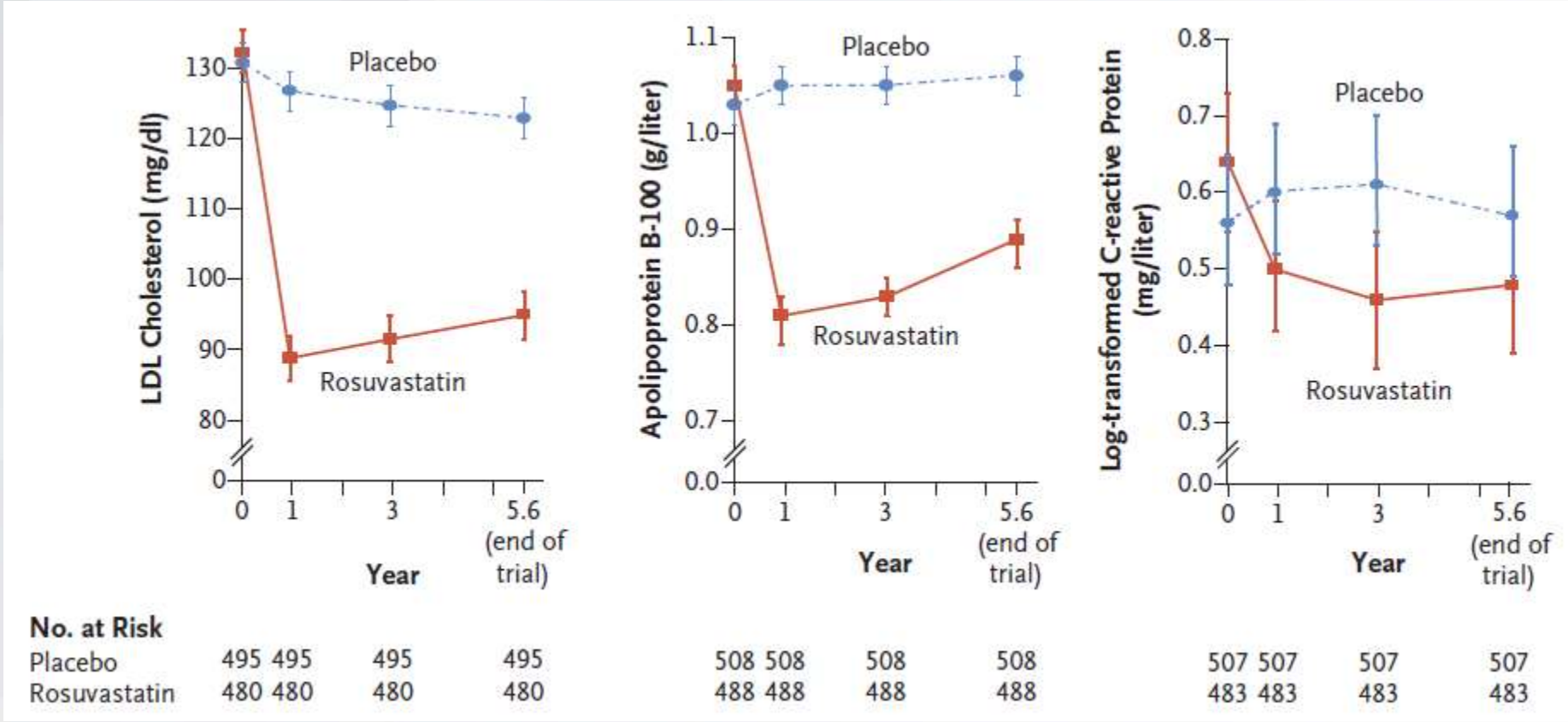
- **Baseline Characteristics of the Participants(continued)**

Characteristic	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)
Race or ethnic group — no. (%)¶		
Chinese	1854 (29.1)	1837 (29.0)
Hispanic	1744 (27.4)	1752 (27.6)
White	1286 (20.2)	1260 (19.9)
South Asian	927 (14.6)	927 (14.6)
Other Asian	341 (5.4)	355 (5.6)
Black	113 (1.8)	112 (1.8)
Other	96 (1.5)	101 (1.6)

Ref.> Yusuf S, et al. N Engl J Med 2016;374:2021-31.

HOPE-3 : Results ③

<Levels of LDL-C, ApoB, and C-Reactive Protein>



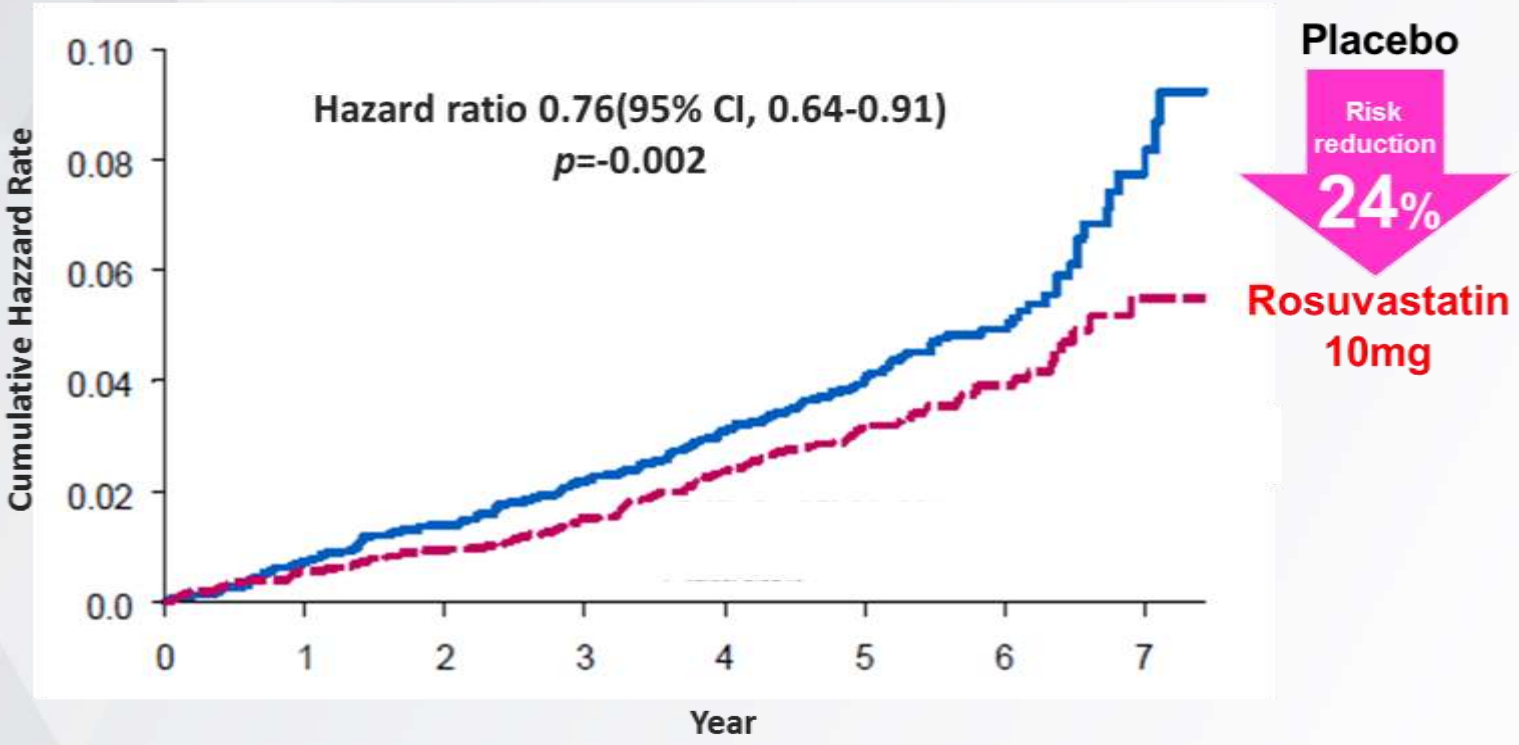
No. at Risk												
Placebo	495	495	495	495	508	508	508	508	507	507	507	507
Rosuvastatin	480	480	480	480	488	488	488	488	483	483	483	483

Ref.> Yusuf S, et al. N Engl J Med 2016;374:2021-31.

HOPE-3 : Results ④

- **1st Co-primary Outcome**

<CV Death, MI, Stroke>



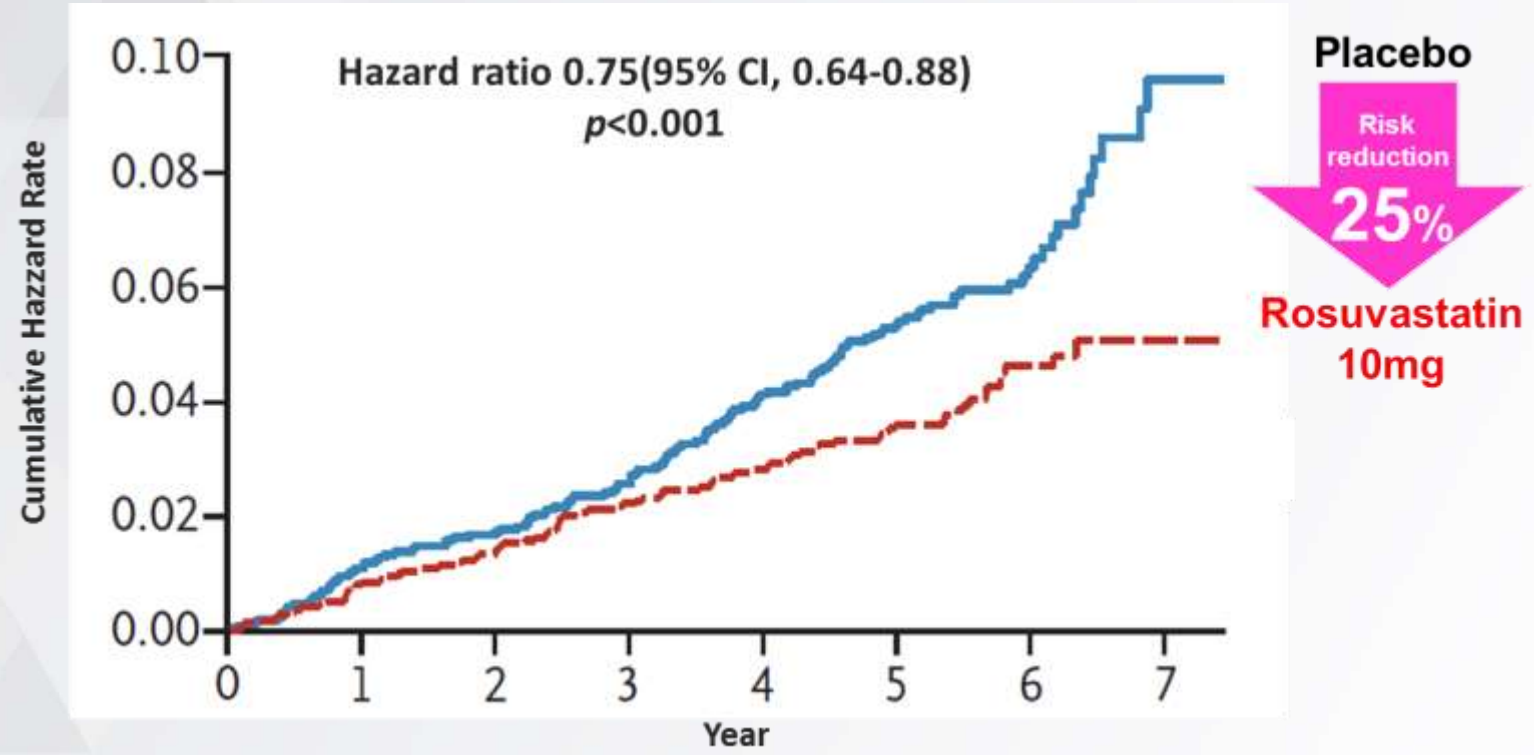
No. at Risk								
Placebo	3,185	3,140	3,097	3,054	2,987	2,488	1,041	244
Rosuvastatin	3,168	3,137	3,112	3,079	3,019	2,524	1,056	265

Ref.> Yusuf S, et al. *N Engl J Med.* 2016 Apr 2. [Epub ahead of print].

HOPE-3 : Results ⑤

- **2nd Co-primary Outcome**

<CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure>



No. at Risk								
Placebo	2,118	2,083	2,055	2,018	1,967	1,638	674	164
Rosuvastatin	2,117	2,091	2,068	2,034	1,999	1,662	694	165

Ref.> Yusuf S, et al. N Engl J Med 2016;374:2021-31.

HOPE-3: Conclusions

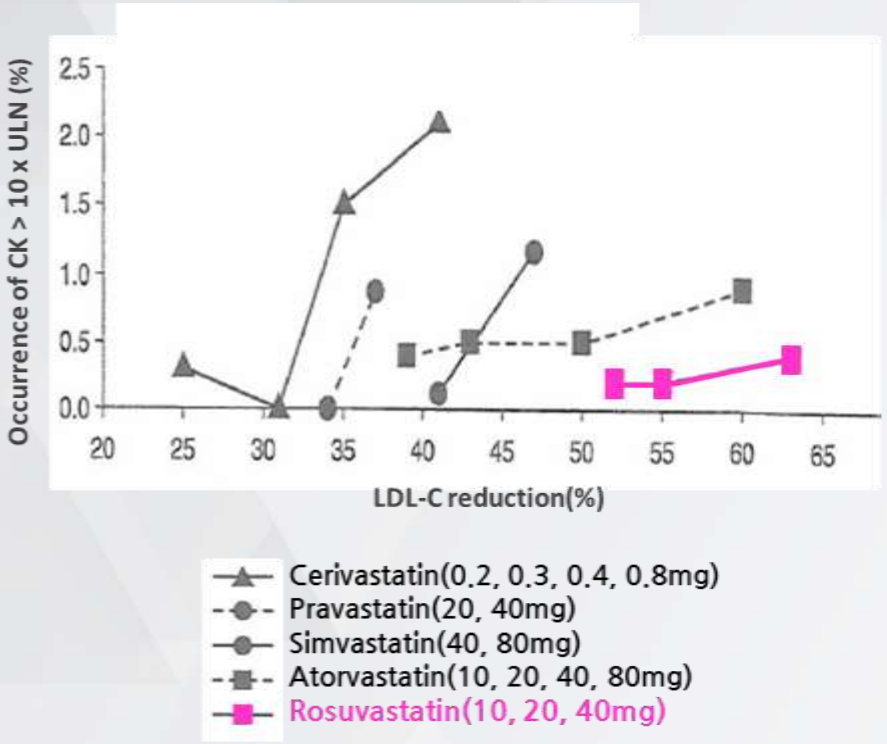
- **Treatment with rosuvastatin at dose 10mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease.**

Ref.> Yusuf S, et al. N Engl J Med 2016;374:2021-31.

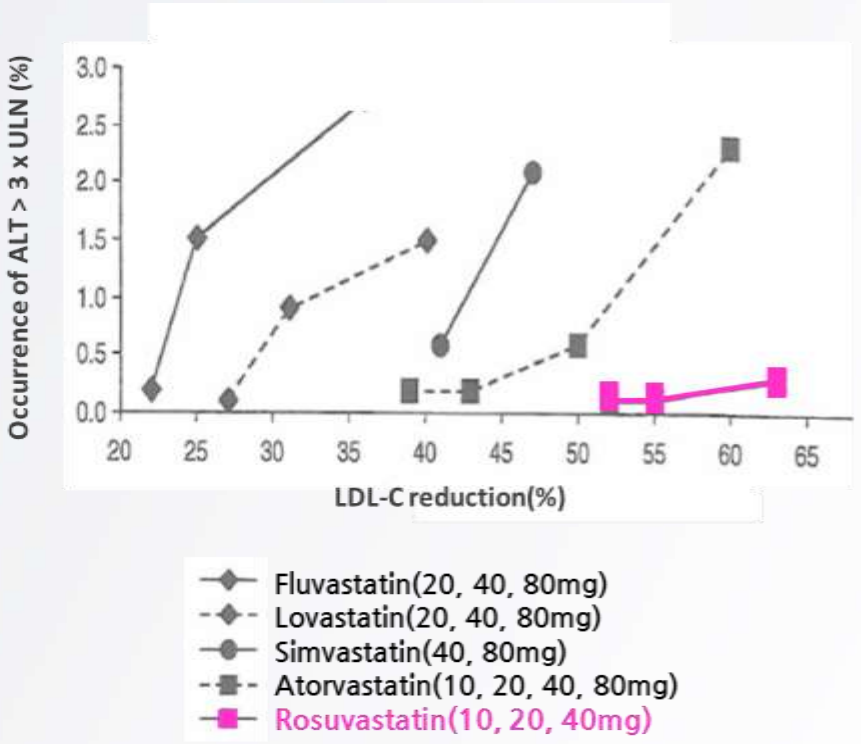
Concern about High Dose Statin

Highest doses statin was associated with increased muscle injury and LFT abnormalities.

Myopathy/Muscle injury (CK > 10X ULN)



LFT abnormalities (ALT >3X ULN)

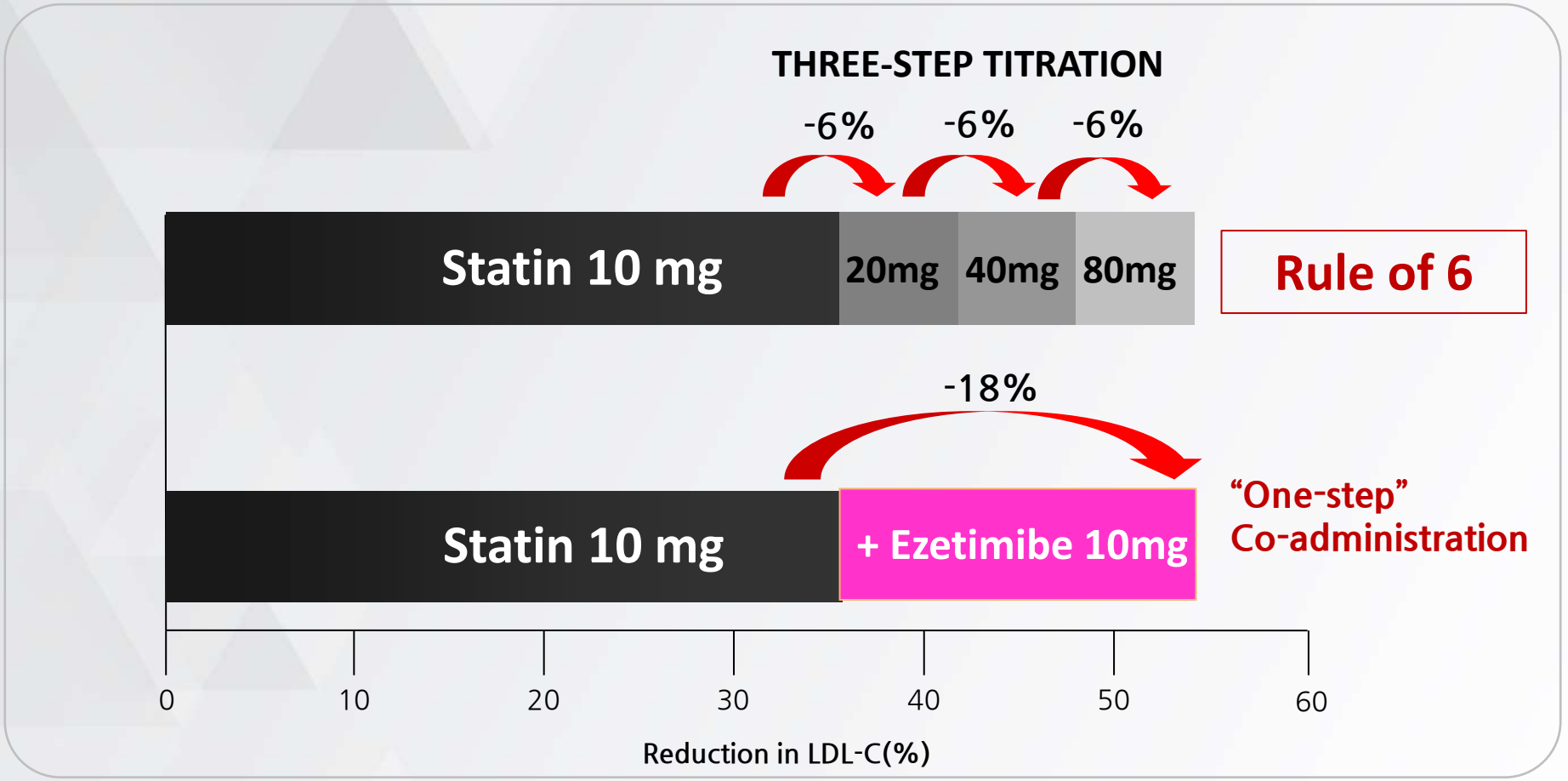


Ref.> Brewer HB Jr. *Am J Cardiol*. 2003;92(4B):23K-29K.

Ezetimibe add-on vs. Statin doubling

Statin up-titration has limitation on LDL-C reduction.

<New role for combination therapy for lipid management>

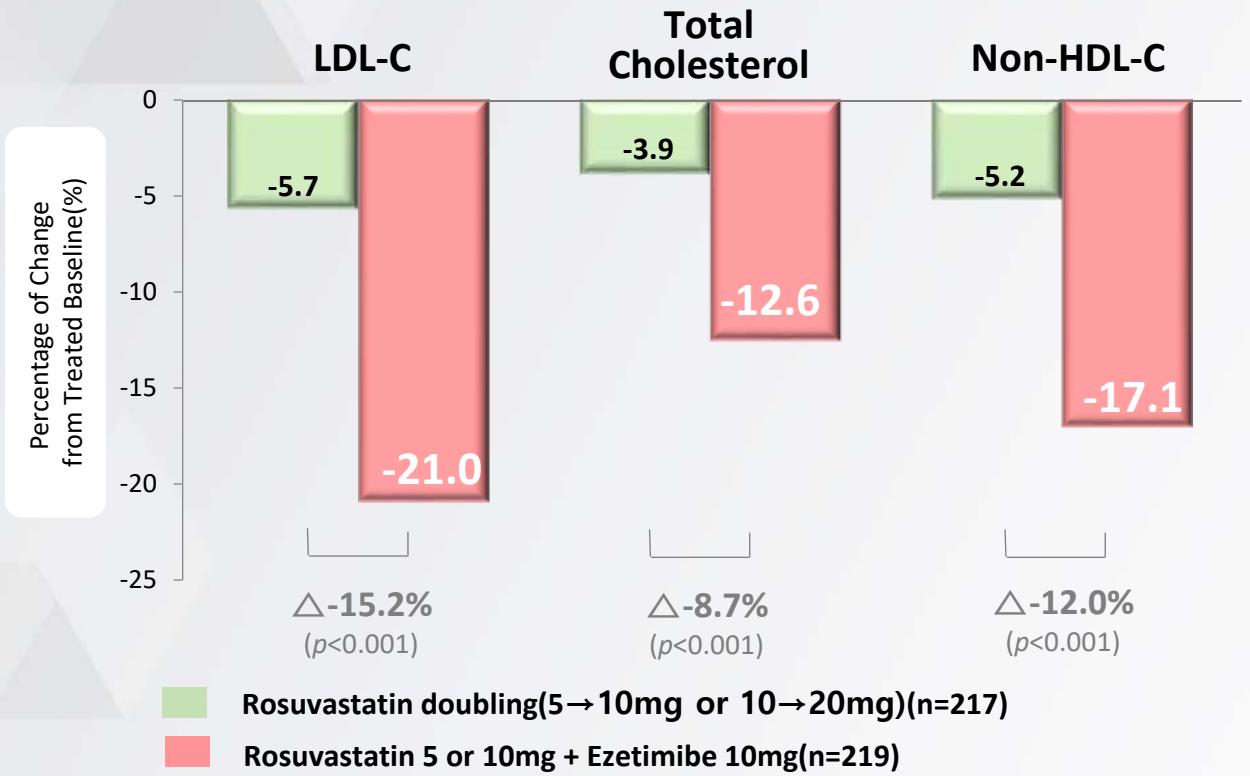


Ref.〉 Bays H, et al. *Expert Opin Pharmacother*. 2003;4(5):779-790.

ACTE: Ezetimibe add-on vs. Statin doubling

Ezetimibe added to stable rosuvastatin produced greater improvements in many lipid parameters.

<Percent change from treated baseline in lipid parameters>

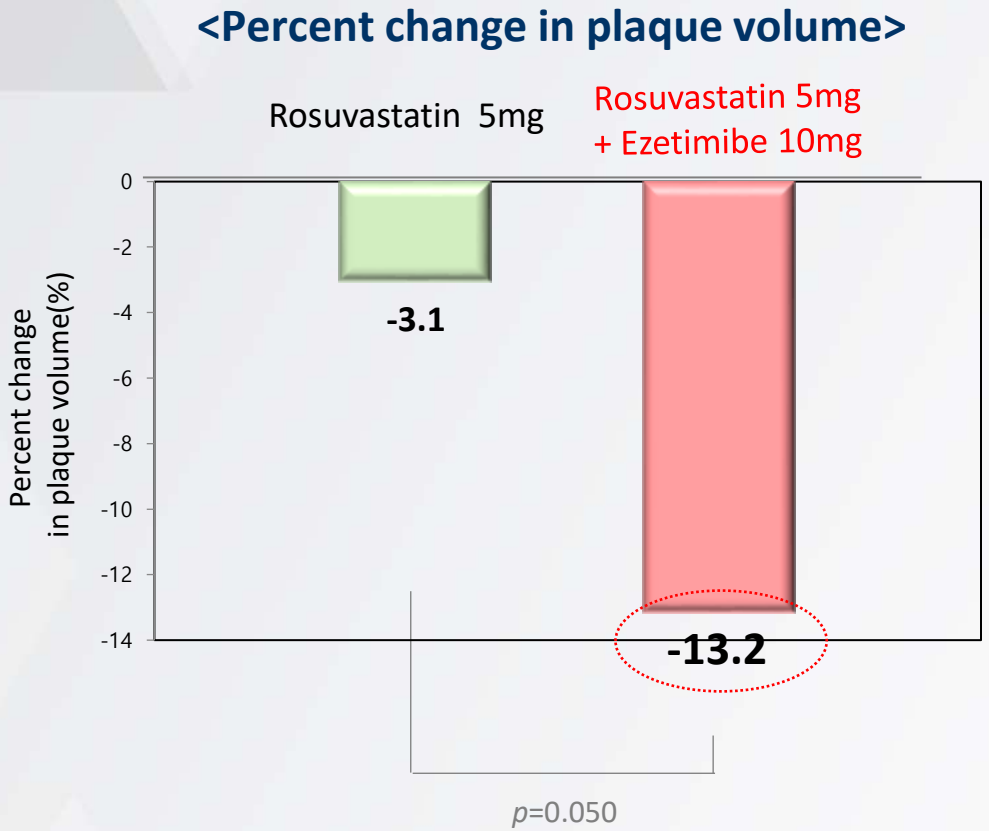


ACTE=Effic**AC**y and Safe**T**y of **E**zetimibe Added on to Rosuvastatin Versus Up Titration of Rosuvastatin in Hypercholesterolemic Patients at Risk for Coronary Heart Disease

Ref.〉Bays HE, et al. *Am J Cardiol.* 2011;108(4):523-530.

Regression of Coronary Atherosclerosis
: Ezetimibe add-on vs. Statin monotherapy

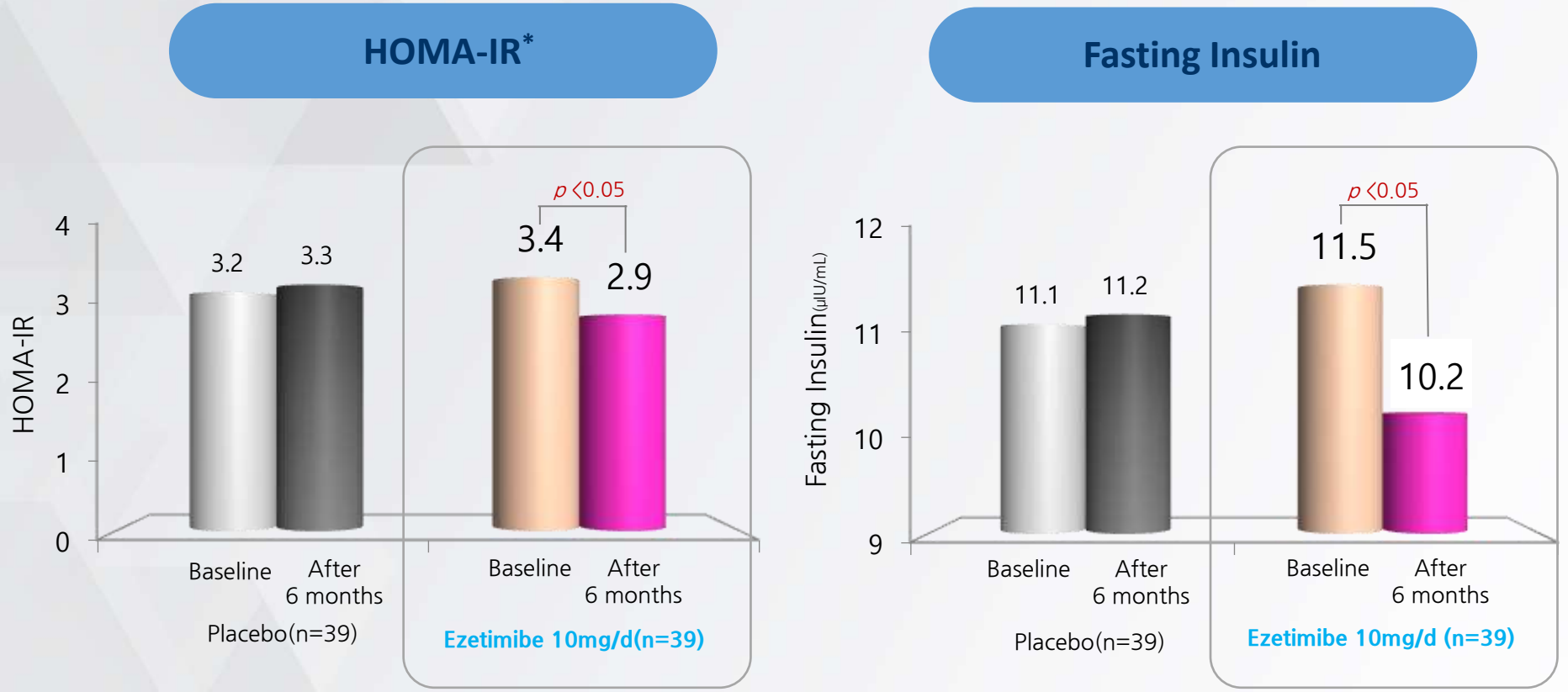
Ezetimibe added to statin may provide significant incremental reduction in coronary plaques compared with statin monotherapy.



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

Ezetimibe: Improvement of Insulin Resistance

Ezetimibe reduced fasting insulin and HOMA-IR.



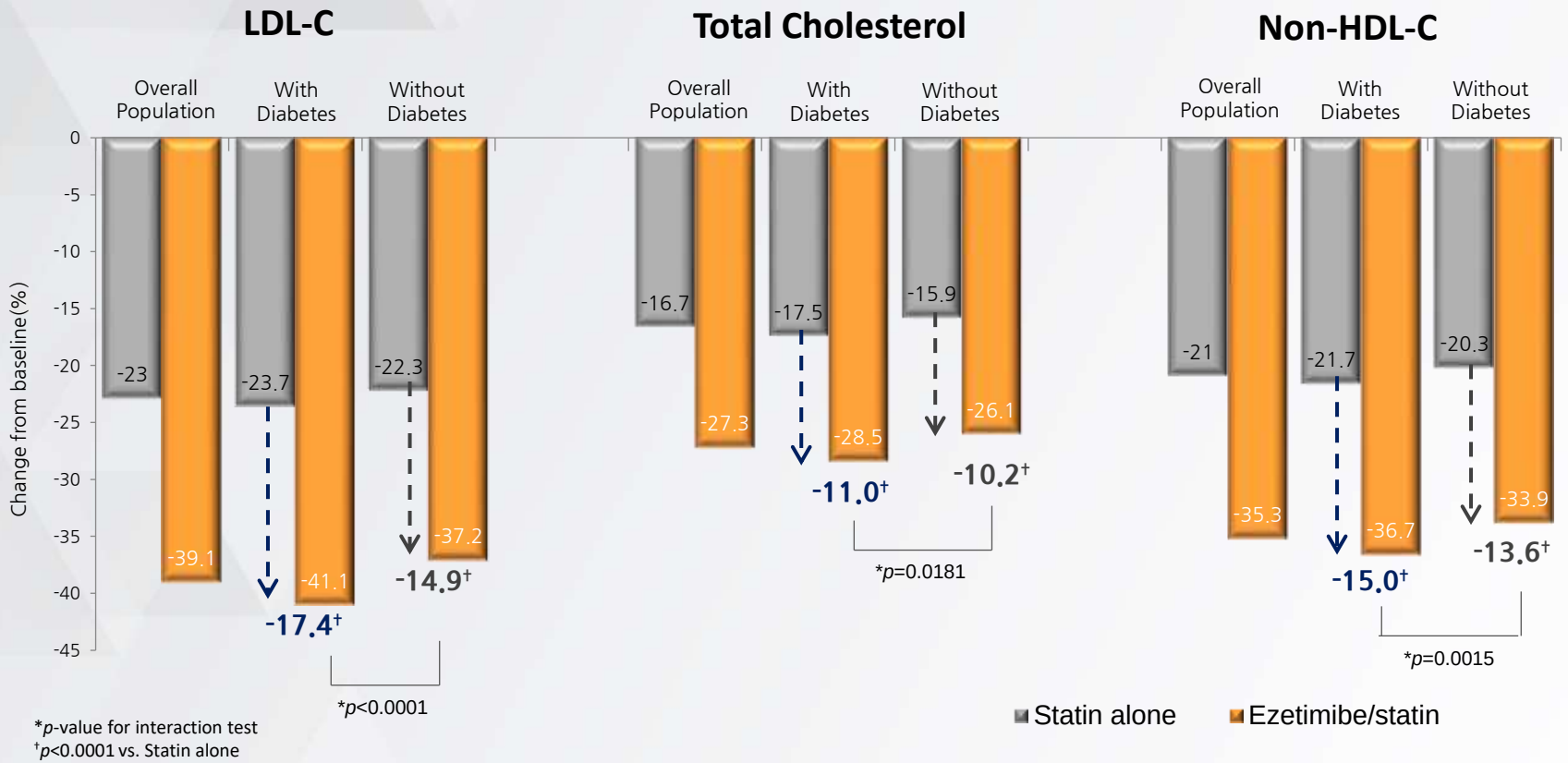
*HOMA-IR(=Homeostasis Model Assessment of Insulin Resistance)

Ref.> Takase H, et al., *Eur J Clin Invest.* 2012;42(12):1287-1294.

Lipid-altering efficacy of Ezetimibe/Statin in patients with and without Diabetes

Treatment with Ezetimibe/statin provided significantly larger reductions in LDL-C, total cholesterol and non-HDL-C in patients with diabetes than in patients without diabetes.

<Percent changes from baseline in lipid parameters>



*p-value for interaction test
†p<0.0001 vs. Statin alone

Ref.〉 Leiter LA, et al. *Diabetes Obes Metab.* 2011;13(7):615-628.

Contents

Phase III Clinical Trial

Object

: Efficacy and safety of Crezet®(Rosuvastatin/ezetimibe) versus rosuvastatin in primary hypercholesterolemia patients

Patients

: **379 primary hypercholesterolemia patients** ≥19 years of age (LDL≤250mg/dL, TG≤350mg/dL)

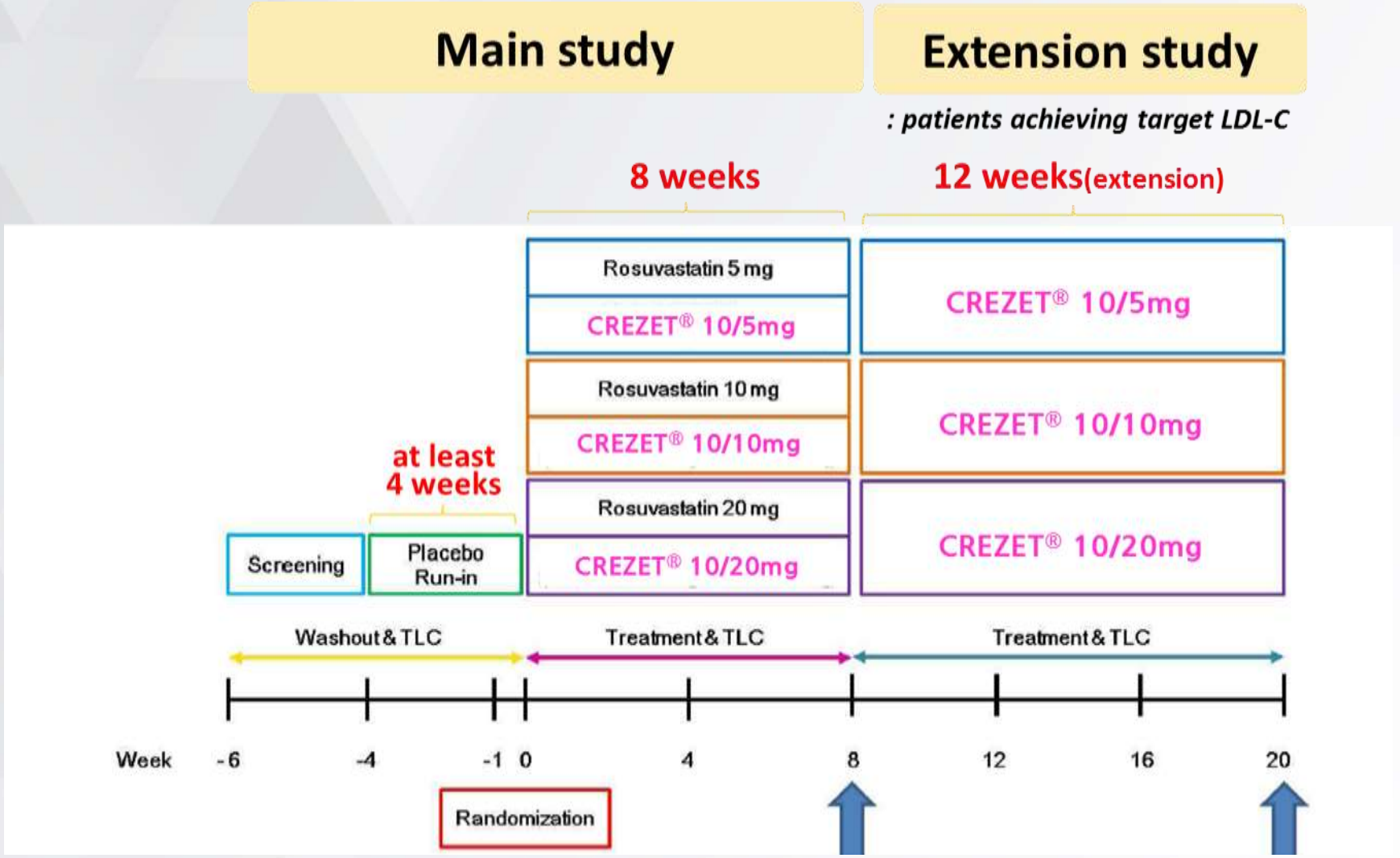
Study Design

: Multi-centers, randomized, double-blind, parallel study
After run-in period of 4 weeks, patients were randomized to receive Crezet® (n=191) or Rosuvastatin(n=188) once daily for 8 weeks.
-**Primary end point: the percentage reduction in LDL-C from baseline after 8 weeks of treatment.**
-Secondary end point: the percentage reduction in each lipid profile from baseline after 4 weeks and 8 weeks of treatment , the percentage of patients reaching treatment goal for LDL-C (NCEP ATP III) at 4 weeks and 8 weeks of treatment

*NCEP ATP III(=National Cholesterol Education Program Adult Treatment Panel III)

Ref.> Data on file, Daewoong, DW_DP-CRT207-02.

Study design

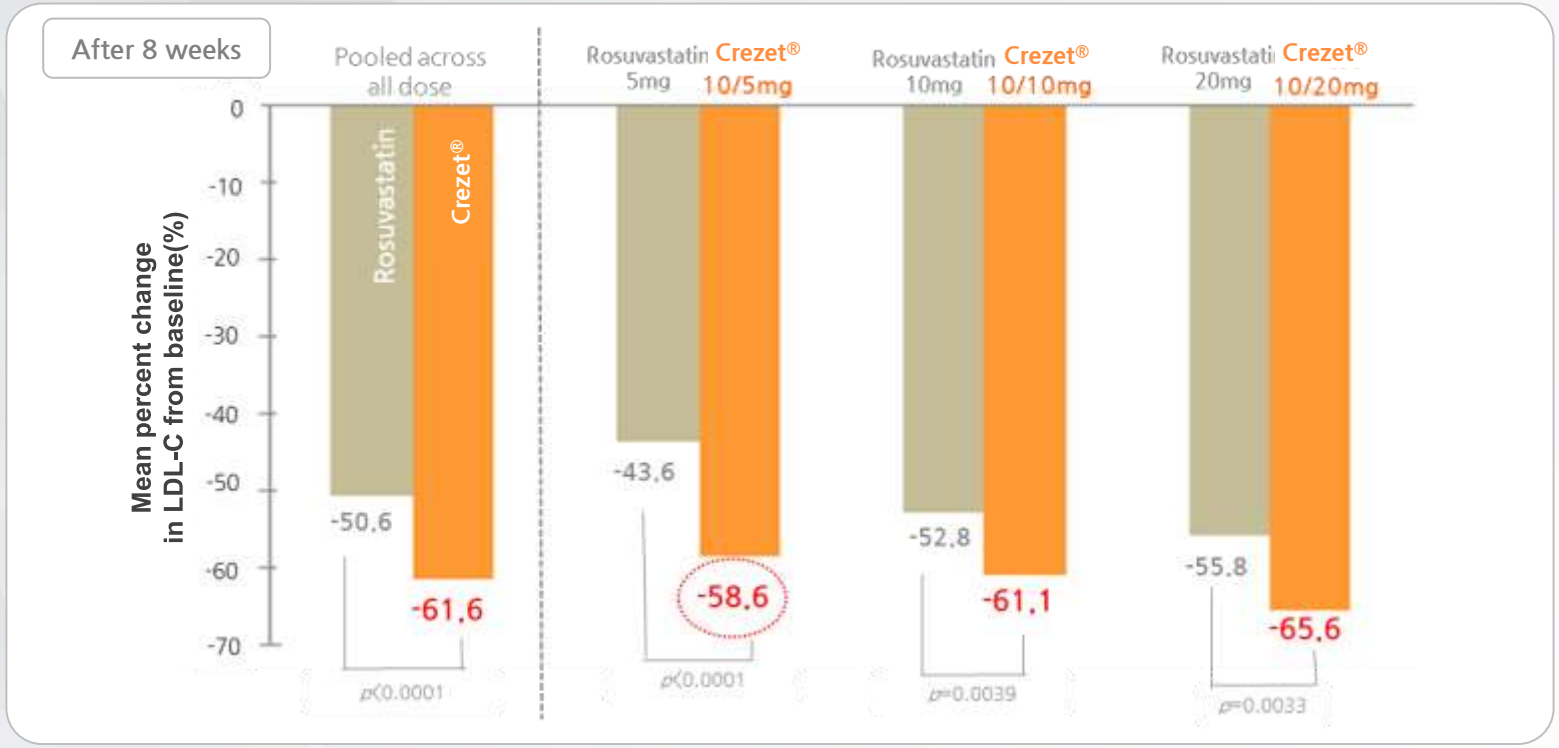


Ref.> Data on file, Daewoong, DW_DP-CRT207-02.

Study Result –LDL-C lowering effect

■ Primary endpoint: (%) Change of LDL-C (8 weeks)

Crezet® provided **significantly greater LDL-C reduction** compared with corresponding Rosuvastatin doses in phase III clinical study for Korean.



Initial dose of **Crezet®** provided the **LDL-C reduction of ≥50%** from baseline.

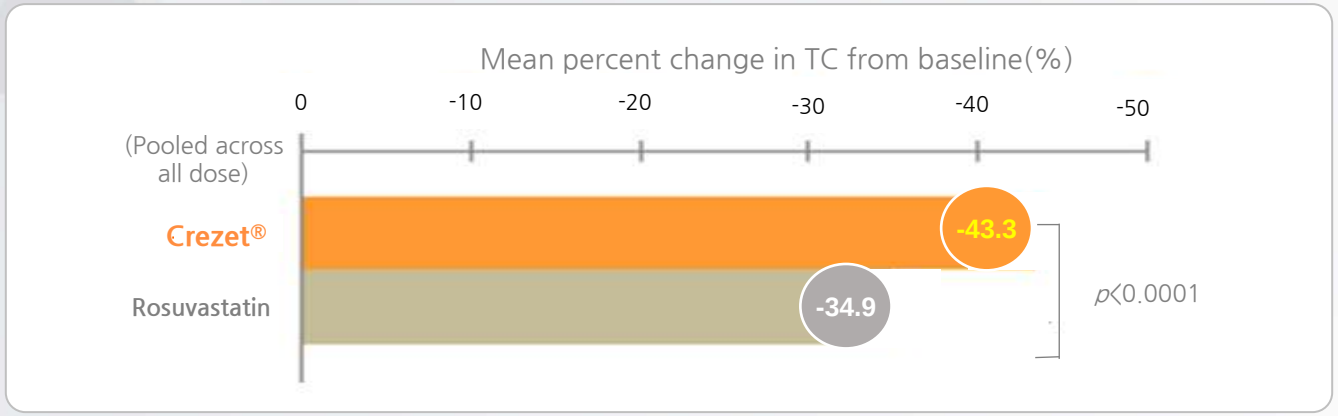
Ref.> Data on file, Daewoong, DW_DP-CRT207-02.

Study Result – Improvement of lipid profile ①

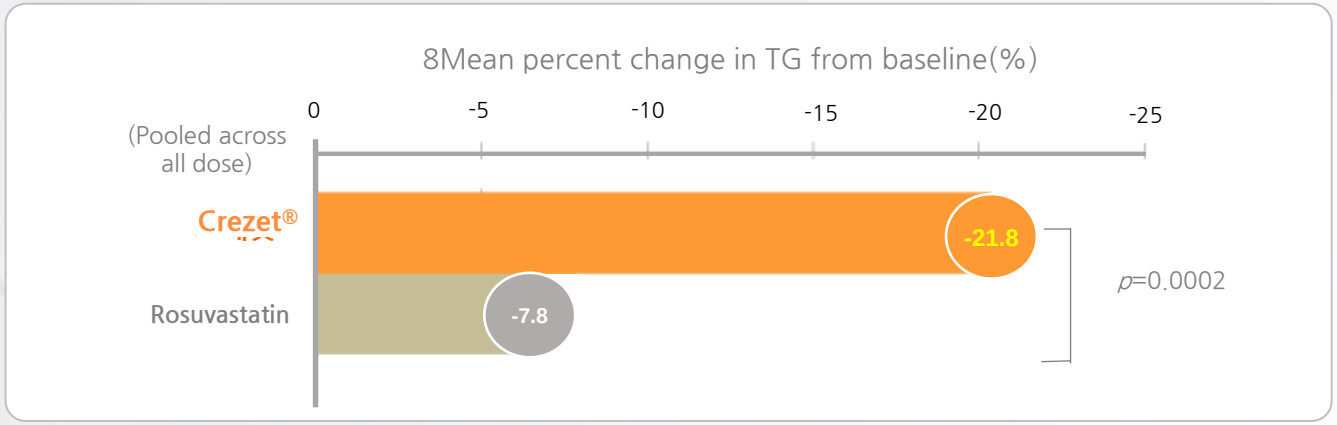
■ Total Cholesterol and Triglyceride

Crezet® provided **significantly greater TC and TG reduction** compared with Rosuvastatin monotherapy.

Total cholesterol (TC)



Triglyceride (TG)

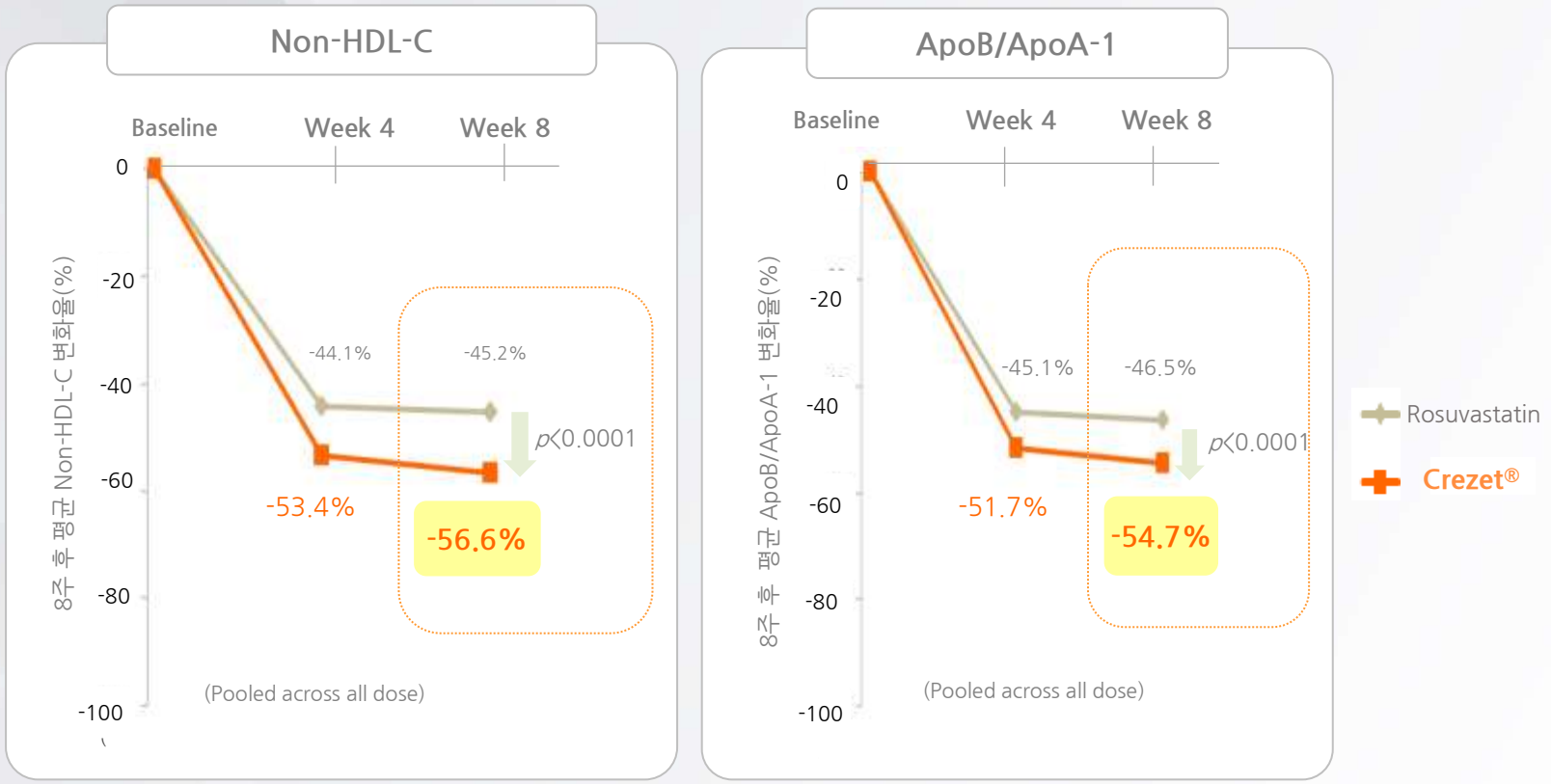


Ref.> Data on file, Daewoong, DW_DP-CRT207-02.

Study Result - Improvement of lipid profile ②

■ Non-HDL-C, ApoB/ApoA-1

Crezet® significantly improved **Non-HDL-C and ApoB/ApoA-1 reduction** compared with Rosuvastatin monotherapy.



Ref.> Data on file, Daewoong, DW_DP-CRT207-02.

Study Result - Safety

Crezet® was **well tolerated** in phase III clinical trial for Korean.

Reported adverse events

	Rosuvastatin (N=187)			Crezet® (N=190)			Overall
Adverse Reaction	5mg (N=62) N	10mg (N=62) N	20mg (N=63) N	10/5mg (N=63) N	10/10mg (N=64) N	10/20mg (N=63) N	(N=377) N(%)
Nasopharyngitis	2	0	1	4	1	4	12(3.2%)
Dyspepsia	0	1	1	1	2	1	6(1.6%)
ALT elevations	0	1	0	0	1	3	5(1.3%)
Edema	1	1	0	0	0	2	4(1.1%)
Myalgia	1	0	1	0	2	0	4(1.1%)

Ref.> Data on file, Daewoong, DW_DP-CRT207-02.

Conclusion (1)

- High prevalence rate of dyslipidemia in diabetes
- Recommendation of cholesterol management in guidelines
- Effect of Rosuvastatin on LDL-C reduction and CV prevention (STELLAR, ASTEROID, COSMOS, JUPITER, HOPE-3)
- Concerns for high dose statin (e.i. Myopathy, ALT elevations)
- Additional benefits from ezetimibe in patients with and without diabetes

Conclusion (2)

- Benefits of CREZET

  - Dual action of Rosuvastatin/Ezetimibe combination

  - Significantly reduced LDL-C and improved lipid parameters more than statin monotherapy

  - Low CYP3A4-mediated metabolism

  - Improved patient compliance with once-daily dosing regardless of time

Thank you