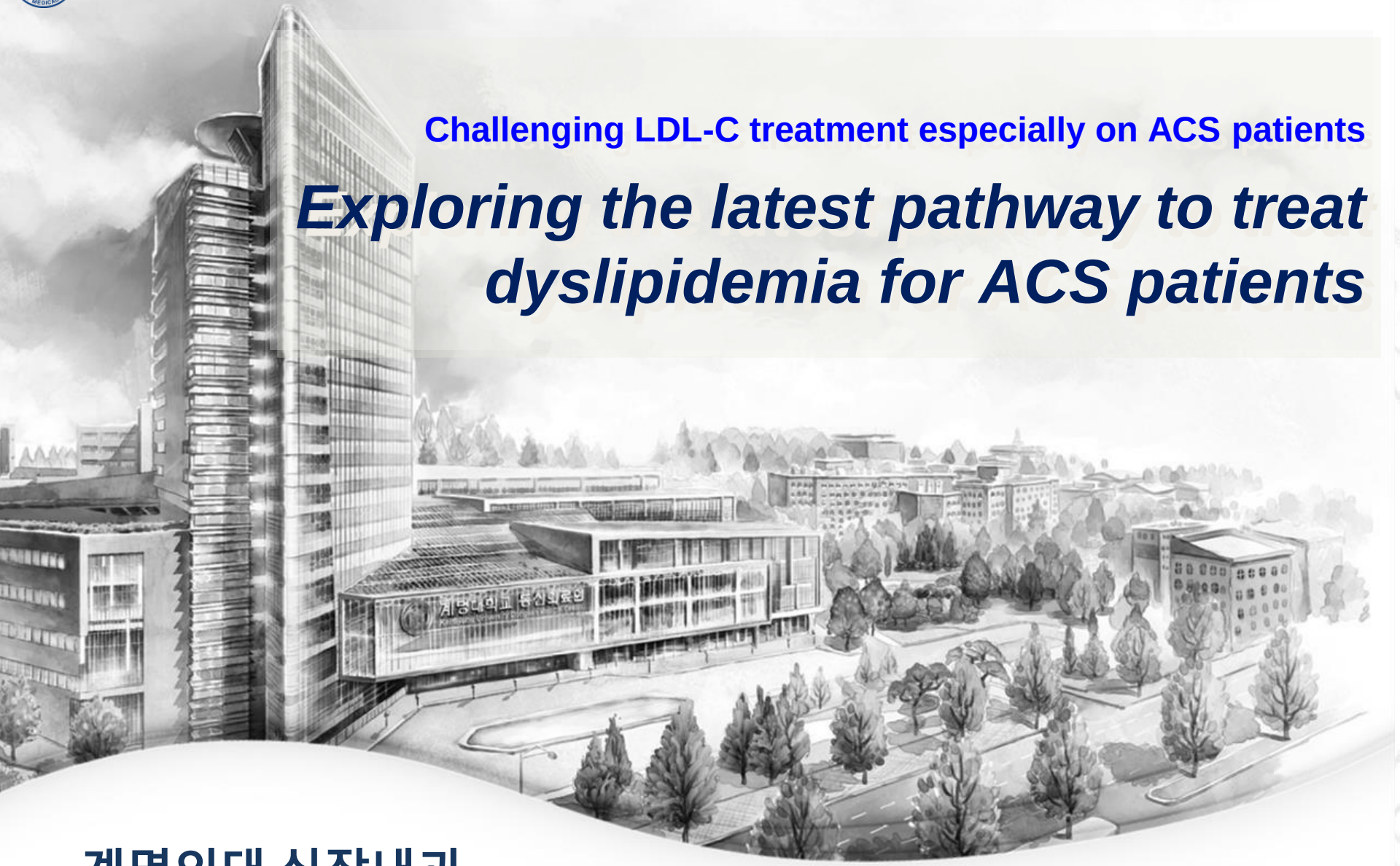
계명대학교 동산의료원
Keimyung University Dongsan Medical Center



Challenging LDL-C treatment especially on ACS patients

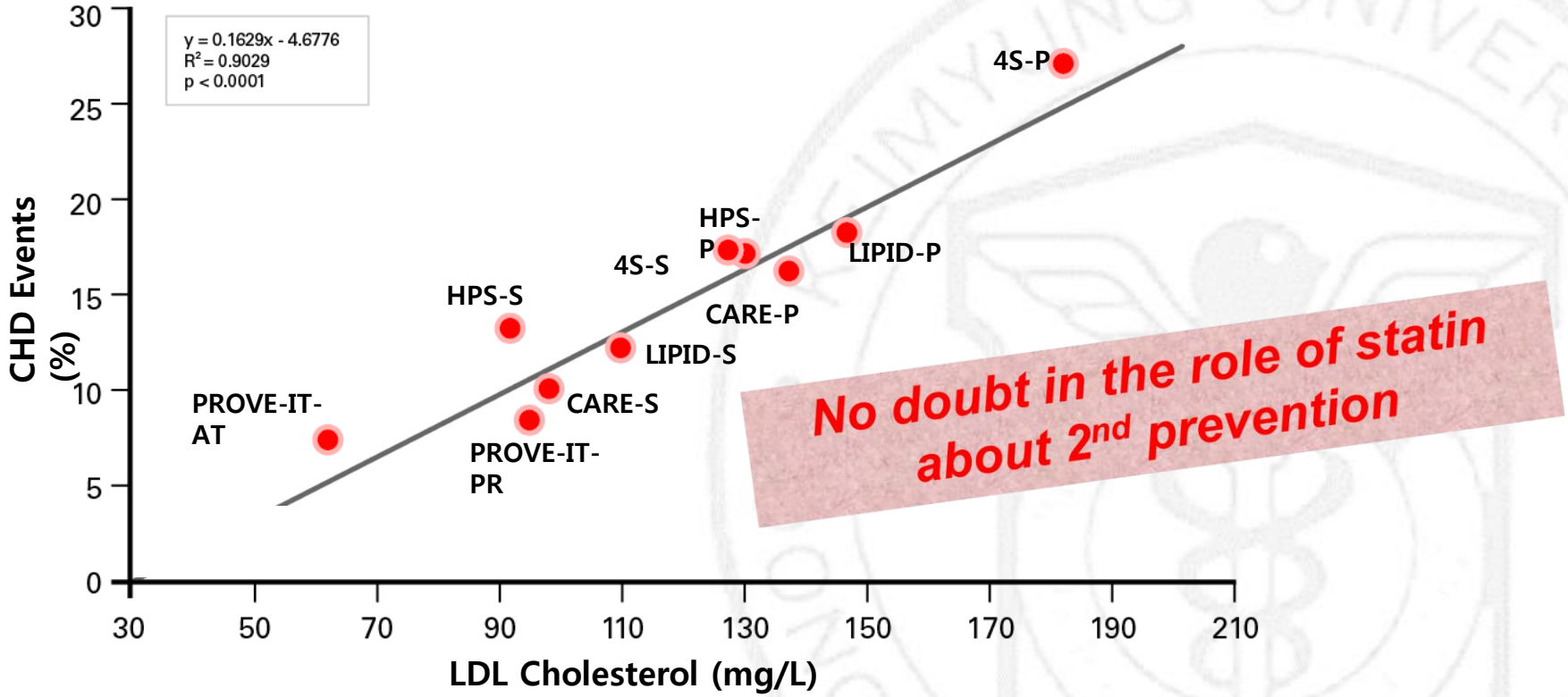
Exploring the latest pathway to treat dyslipidemia for ACS patients

계명의대 심장내과
남창욱

OVERVIEW

- **Clinical Unmet Needs**
- **Benefit of Ezetimibe Combination Therapy**

CHD event rates in secondary prevention trials



AT = atorvastatin; S = simvastatin; P = placebo ; PR = pravastatin ; 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol And Recurrent Events trial; HPS = Heart Protection Study; LIPID = Long-term Intervention with Pravastatin In Ischemic Disease trial; PROVE-IT = PRavastatin Or atorVastatin Evaluation and Infection Therapy trial.

1. O'Keefe JH, et al. *J Am Coll Cardiol* 2004;43:2142–6

2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS

1 Four Statin Benefit Groups

- Individuals with clinical atherosclerotic cardiovascular disease (ASCVD) – acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin – without New York Heart Association (NYHA) class II-IV heart failure or receiving hemodialysis.

- Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dl.

- Individuals 40-75 years of age with diabetes, and LDL-C 70-189 mg/dl without clinical ASCVD.

- Individuals without clinical ASCVD or diabetes, who are 40-75 years of age with LDL-C 70-189 mg/dl, and have an estimated 10-year ASCVD risk of 7.5% or higher.

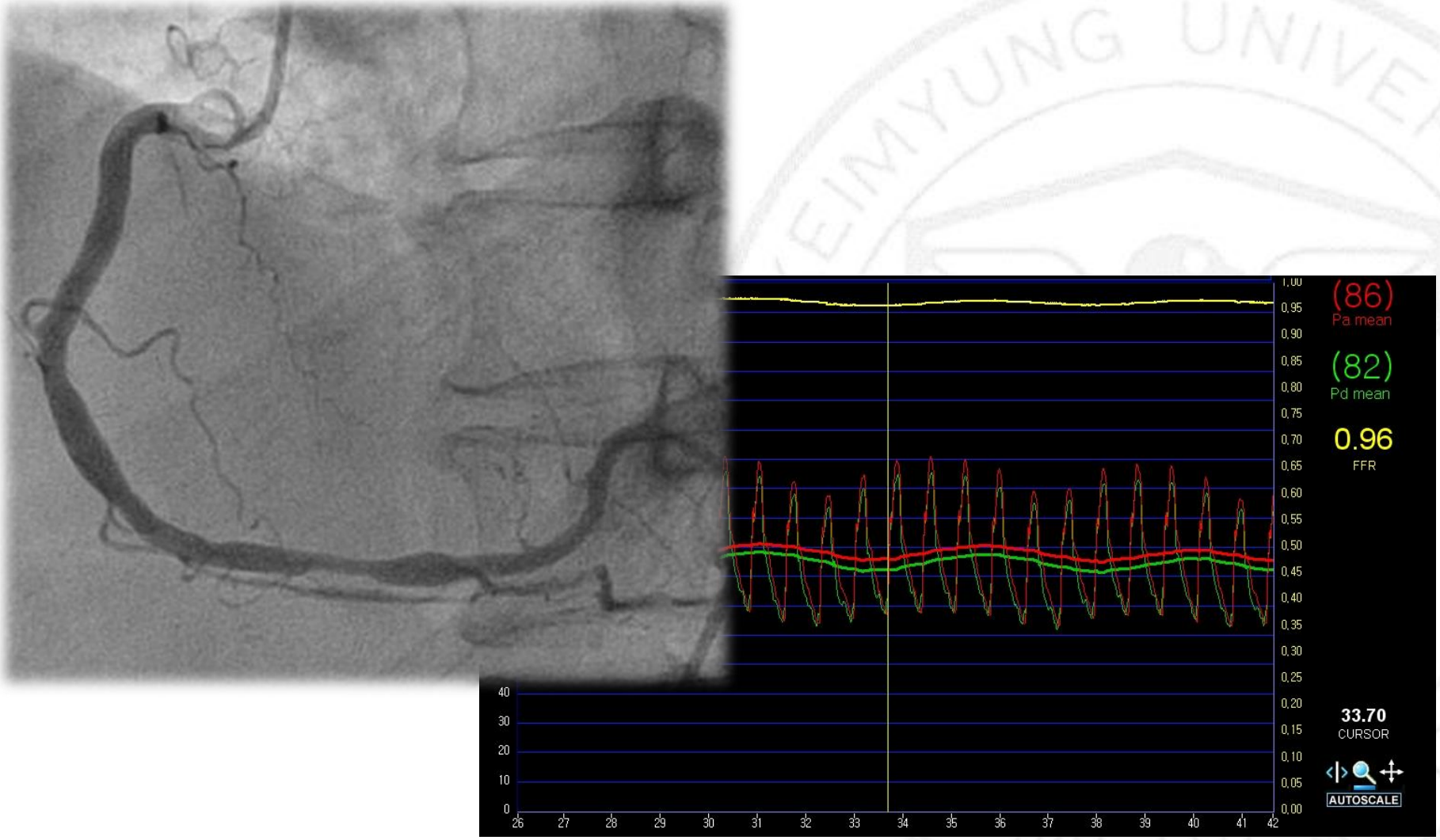
Both ACC/AHA 2013 and ESC/EAS 2011 Guidelines recommend **50% reduction in LDL-C** for CHD patients including **MI and ACS**

ACC/AHA (2013) Guideline		ESC/EAS (2011) Guidelines	
Clinical risk categories	**Treatment**	**Clinical risk categories**	**Treatment**
Those with clinical **ASCVD** ASCVD includes coronary heart disease **(CHD)**, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin	**High-intensity statin therapy**. If **50% reduction** is not reached drug combination may be considered	Those with CVD Documented **CVD**, previous **MI, ACS**, coronary or other arterial revascularization, ischemic stroke, PAD, type 2 diabetes or type 1 diabetes with target organ damage, moderate to severe CKD, or a calculated 10 year risk **SCORE ≥10%**	**LDL-C <**1.8 mmol/L **(70mg/dL)** or **50% reduction** in LDL-C

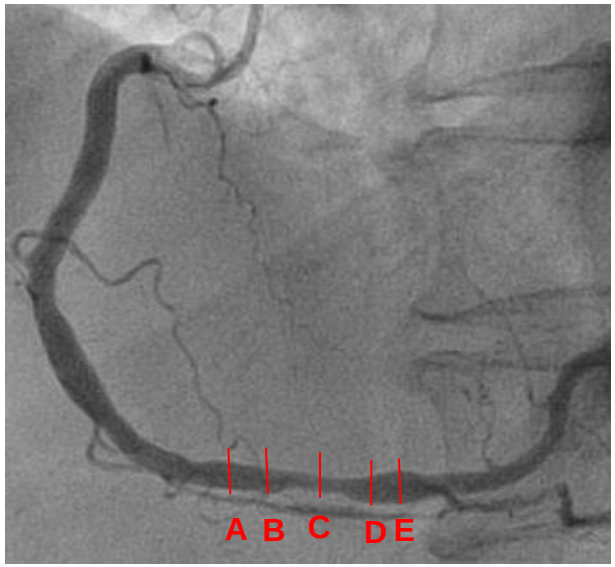
ACC: American College of Cardiology. AHA: American Heart Association. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society. ASCVD: atherosclerotic cardiovascular disease. CVD: cardiovascular disease. LDL-C: low-density lipoprotein cholesterol. LDL: low-density lipoprotein. FCH: familial combined hyperlipidaemia. FH: familial hypercholesterolaemia.

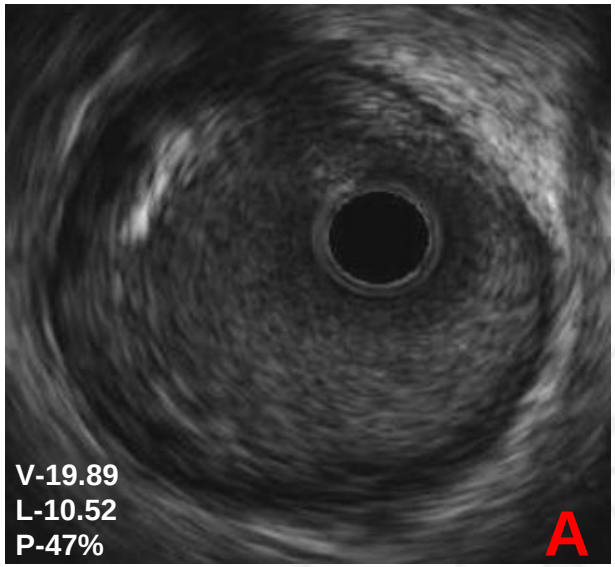
1. Ray KK et al. *Eur Heart J*. 2014 Mar 17. [Epub ahead of print]. doi:10.1093/eurheartj/ehu107.

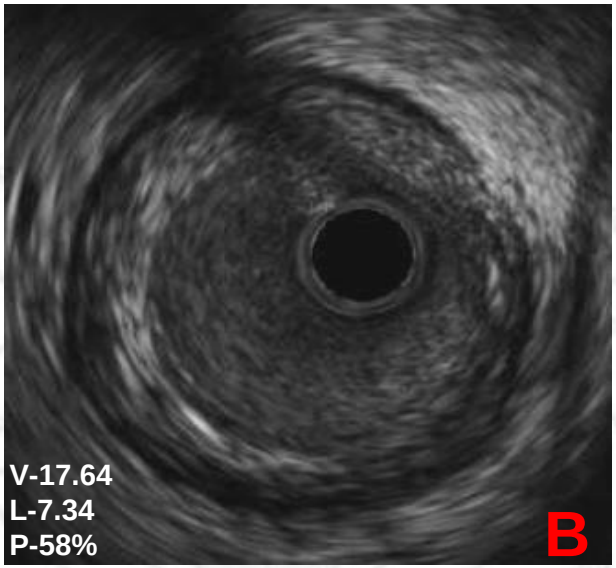
- **68 YO / Female**
- **UA**
- **CV risk factor: HTN, hyperlipidemia**

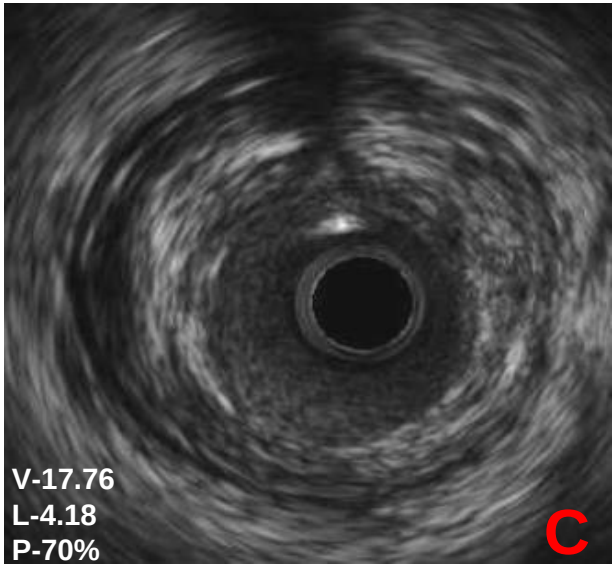


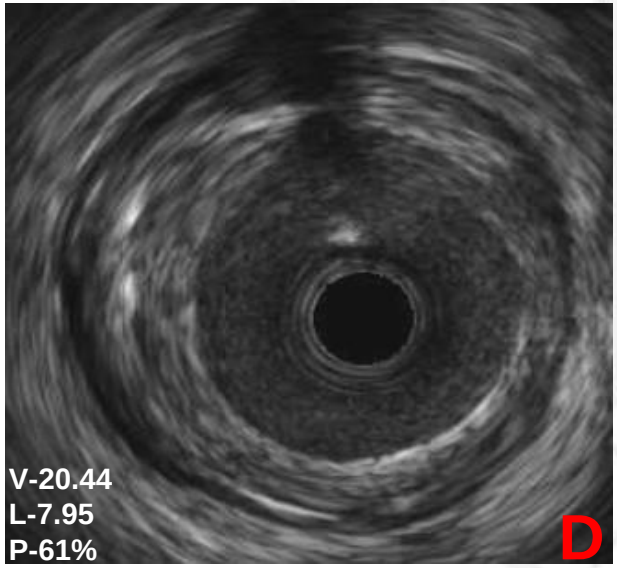
Intravascular Ultrasound

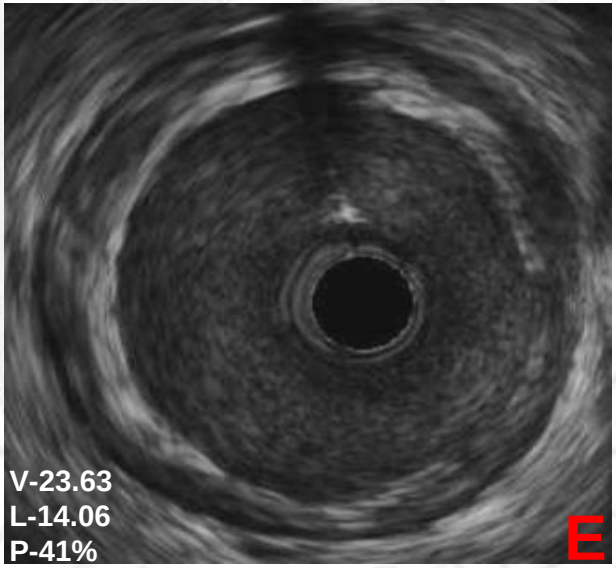












Medical Therapy

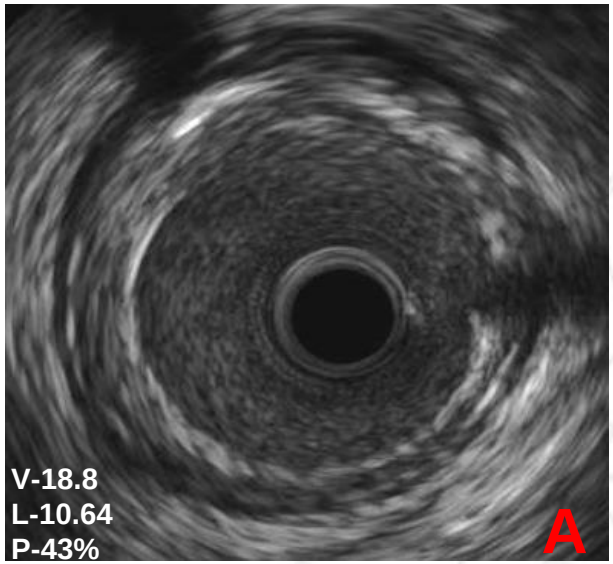
- **AntiPLT, Antiangina drugs, Statin (dose-up)**
- **Lab:**

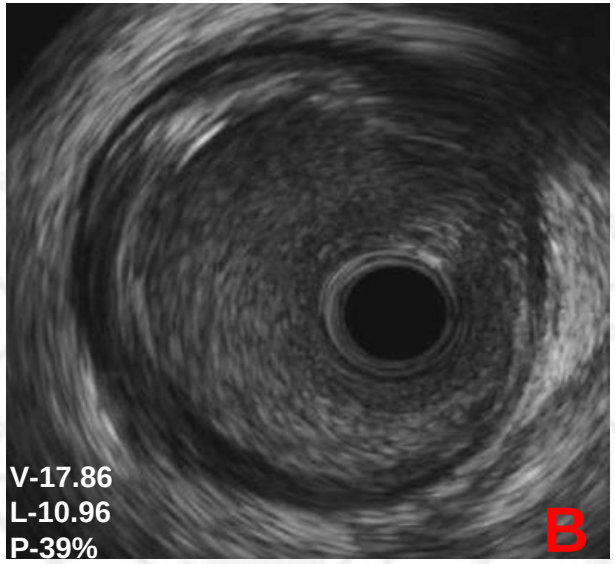
  TC 202 / TG 388 / HDL 29 / LDL 108
- **1 year later, Lab:**

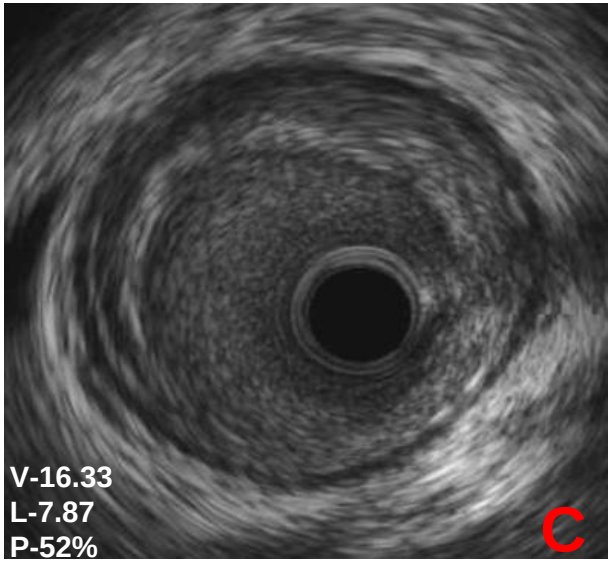
  TC 121 / TG 224 / HDL 55 / LDL 49

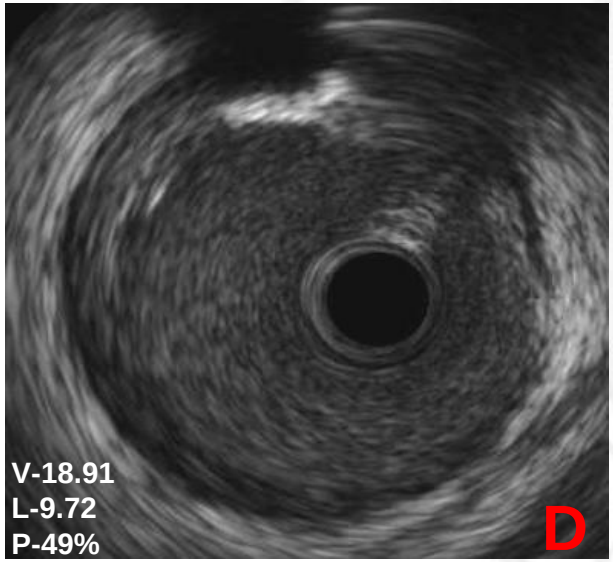
1 year later…

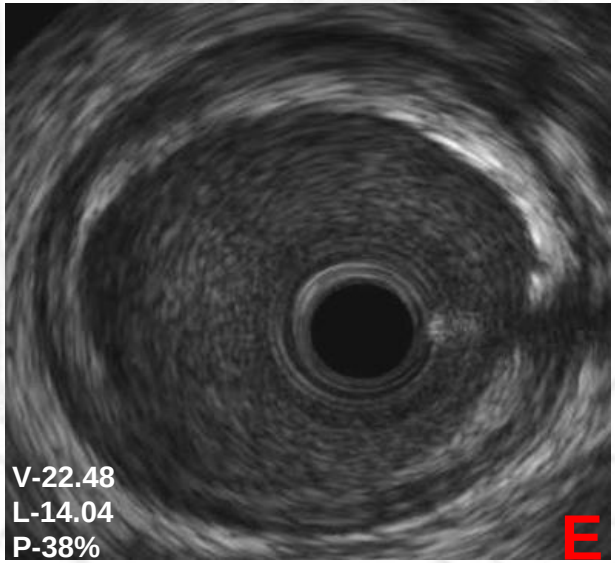

A B C D E


V-18.8
L-10.64
P-43%
A

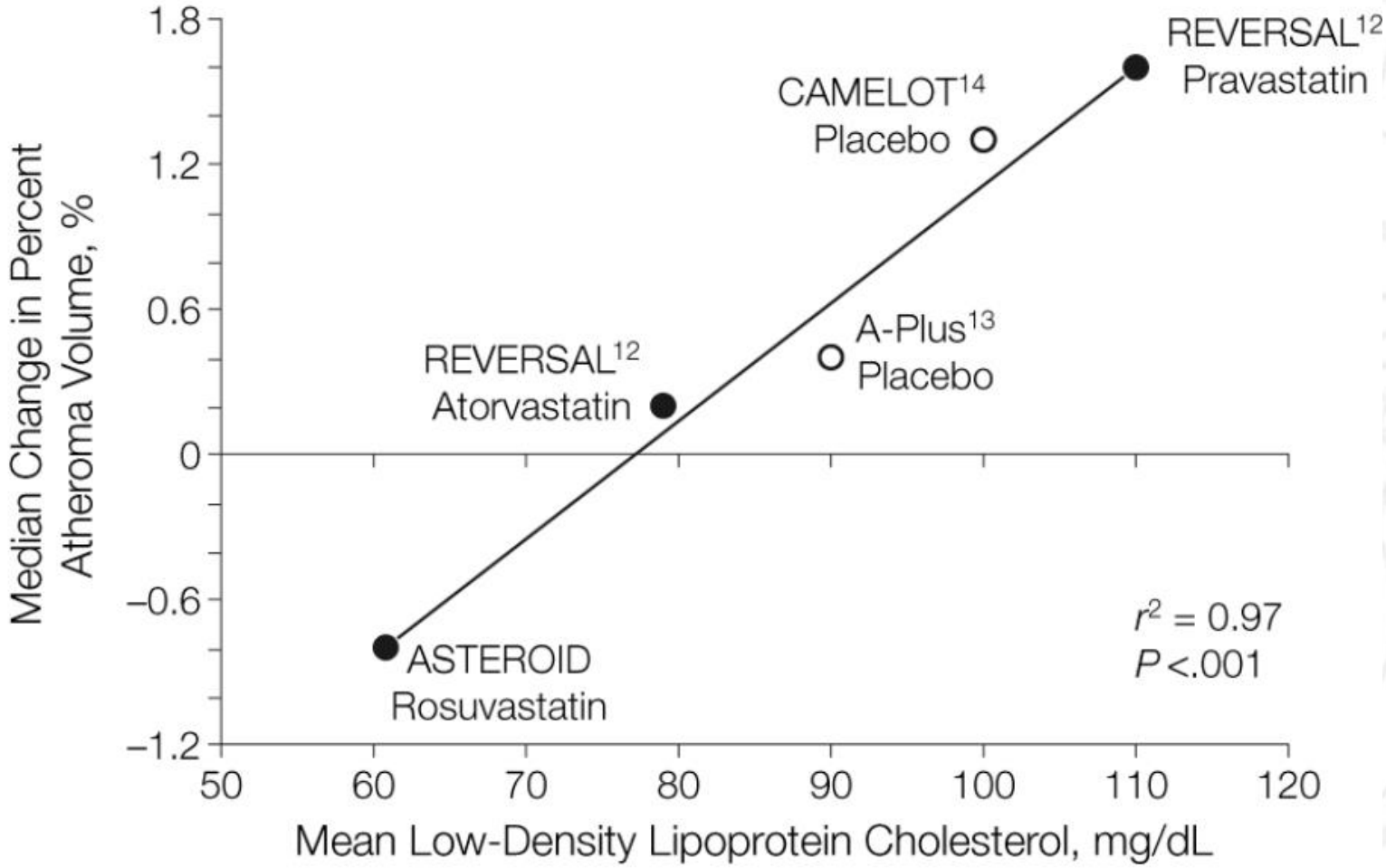

V-17.86
L-10.96
P-39%
B


V-16.33
L-7.87
P-52%
C


V-18.91
L-9.72
P-49%
D


V-22.48
L-14.04
P-38%
E

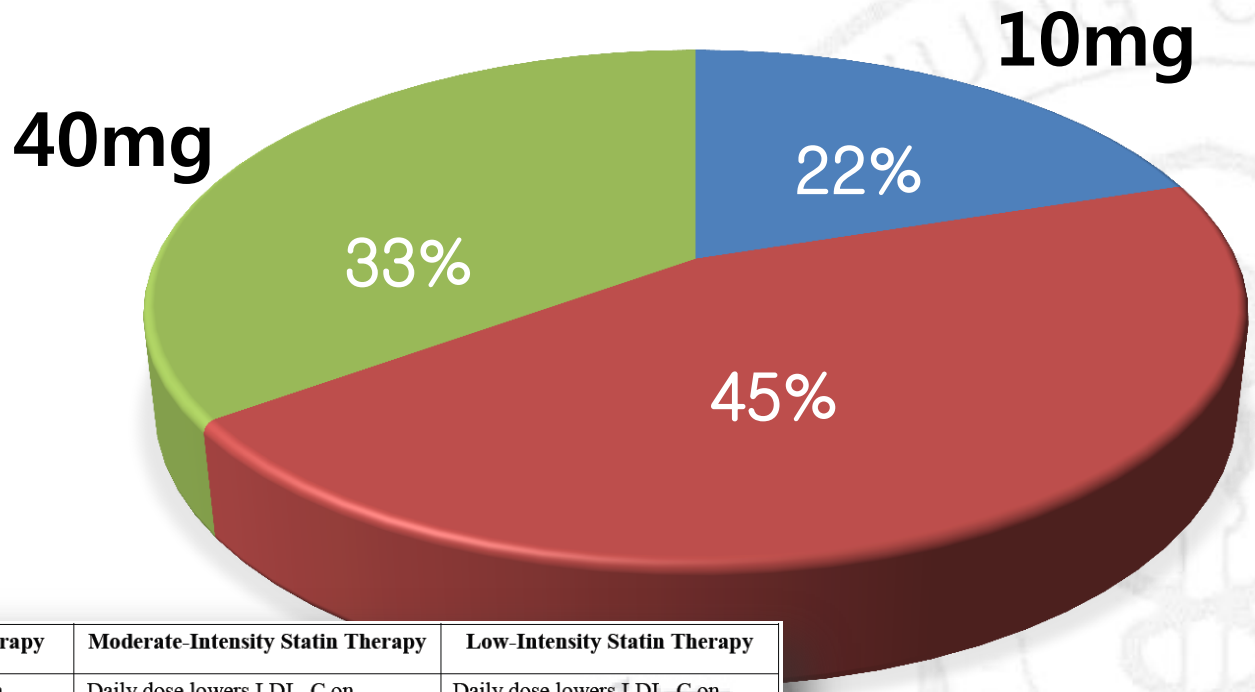
Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis



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

Real world practice of statin therapy

Initial dose selection of atorvastatin in patients with ACS

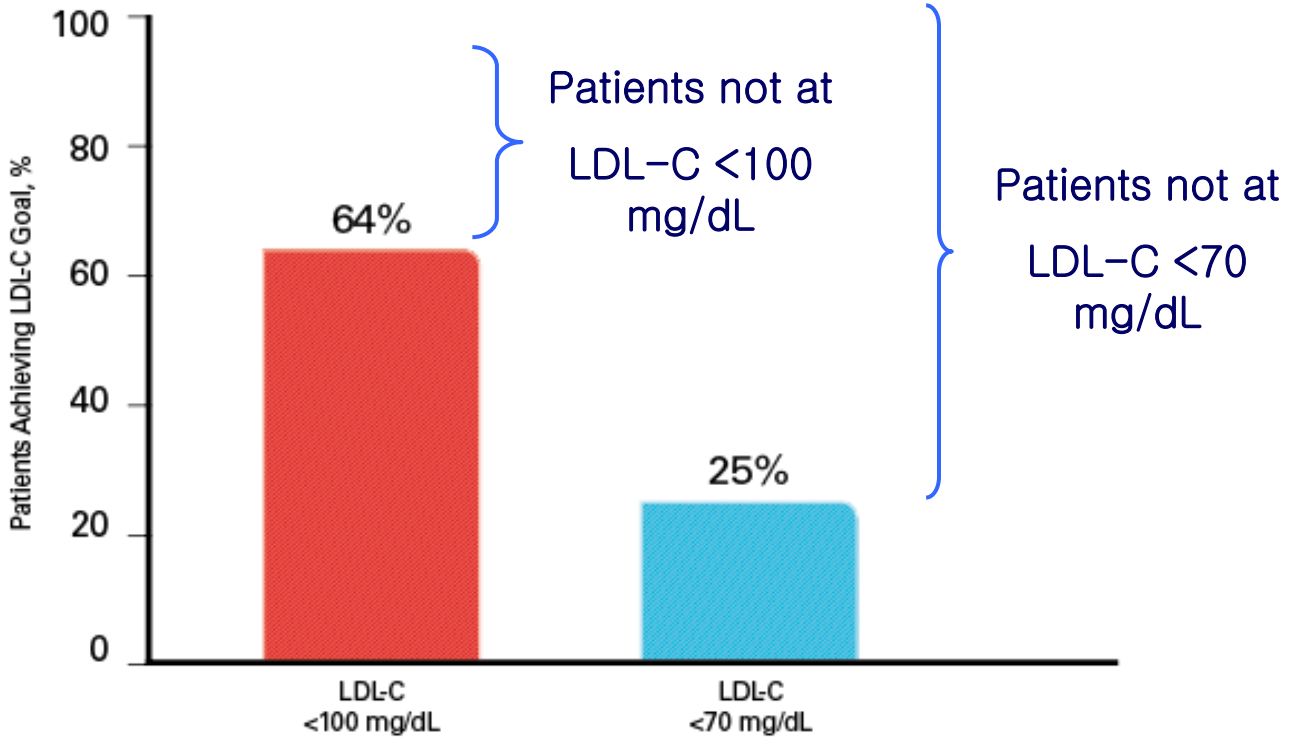


High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Unpublished data from Keimyung univerisity

Patients on Lipid-Lowering Therapy Prior to Hospitalization for CHD—Percentage at LDL-C <100 mg/dL or <70 mg/dL[1]

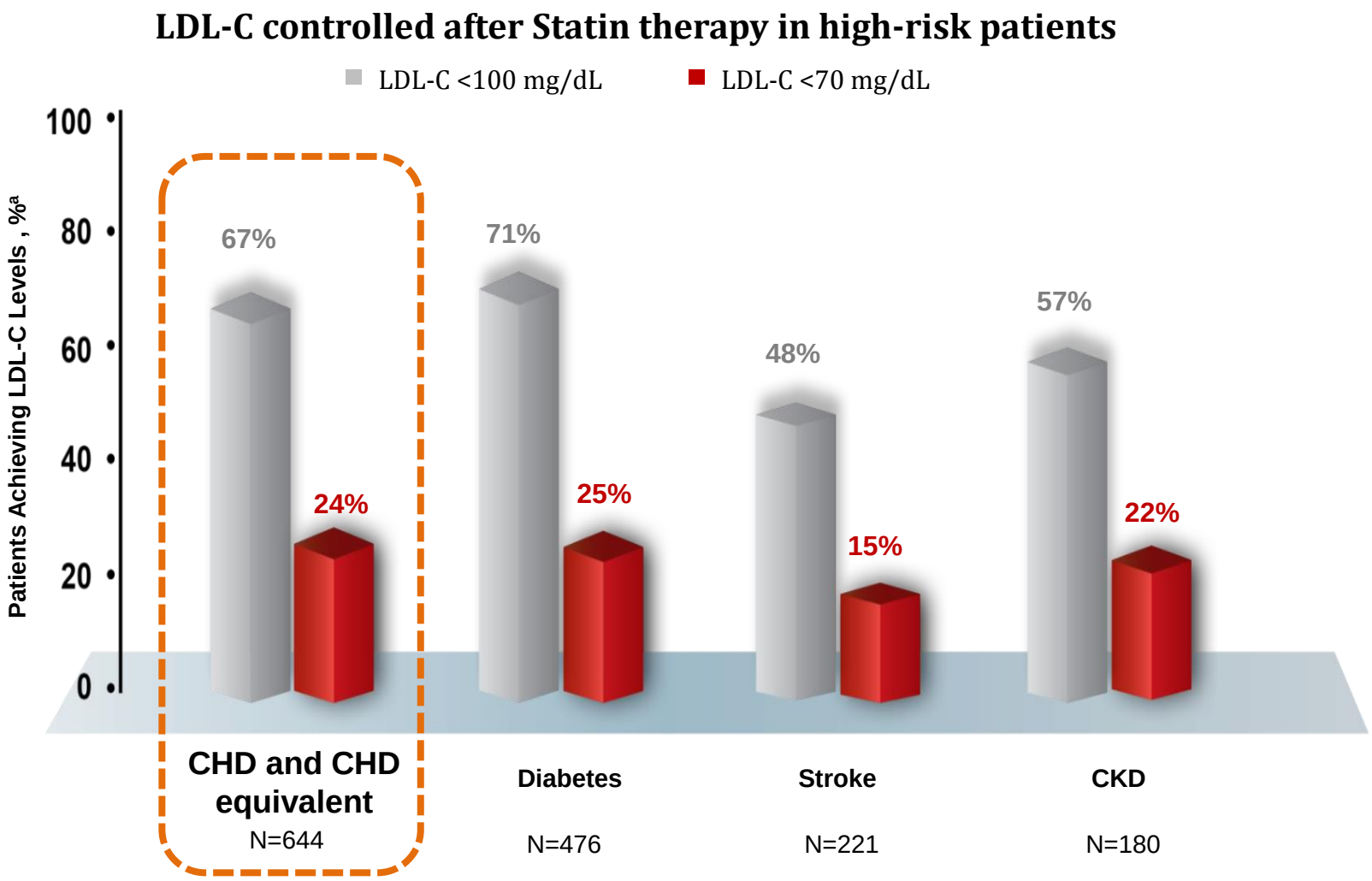
- Study population included patients with ACS, stable CAD hospitalized for revascularization, and patients with documented CAD hospitalized for reasons other than heart failure



GWTG = Get With The Guidelines; ACS = acute coronary syndrome; CAD = coronary artery disease. [a]Patients on lipid-lowering therapy prior to hospitalization (n=28,944).

1. Sachdeva A et al. *Am Heart J.* 2009;157:111–117.e2

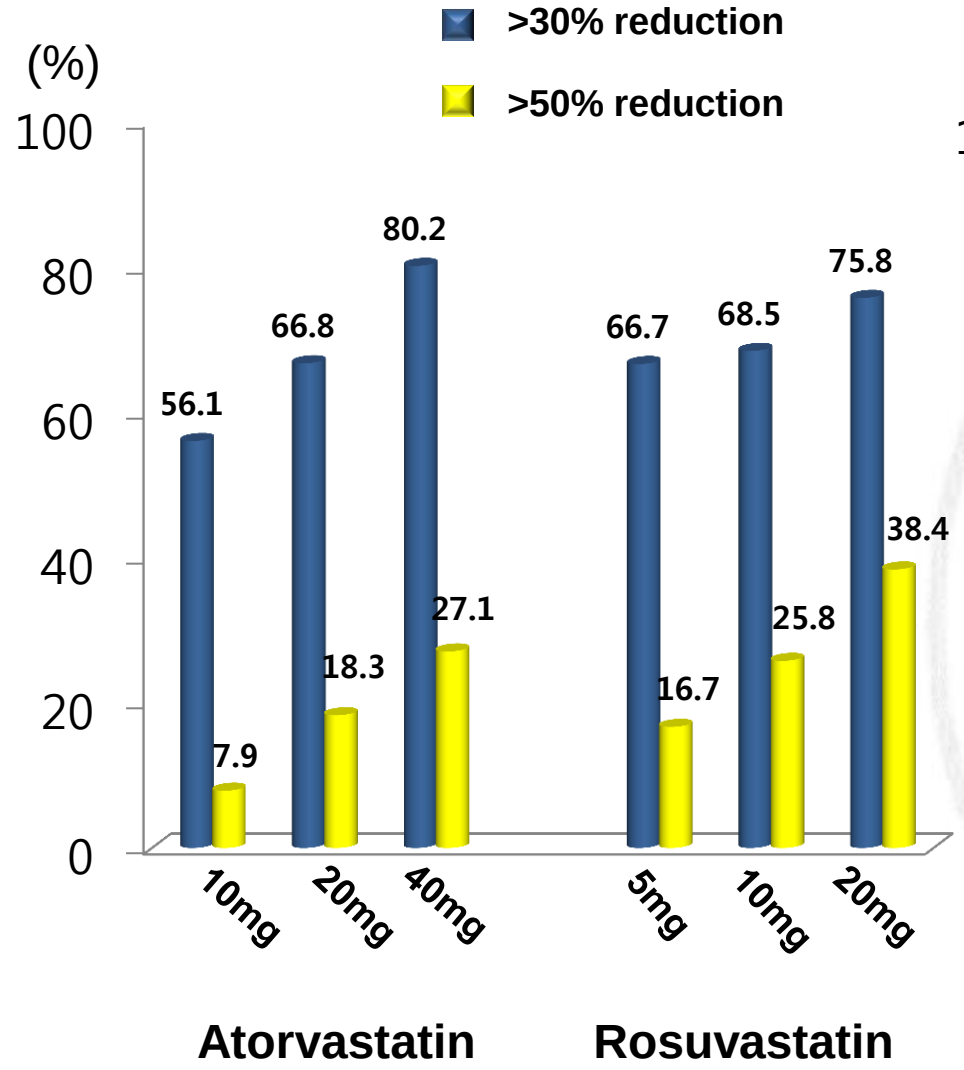
Many High-Risk Patients Did Not Achieve LDL-C <100 mg/dL or <70 mg/dL in Korea[1]

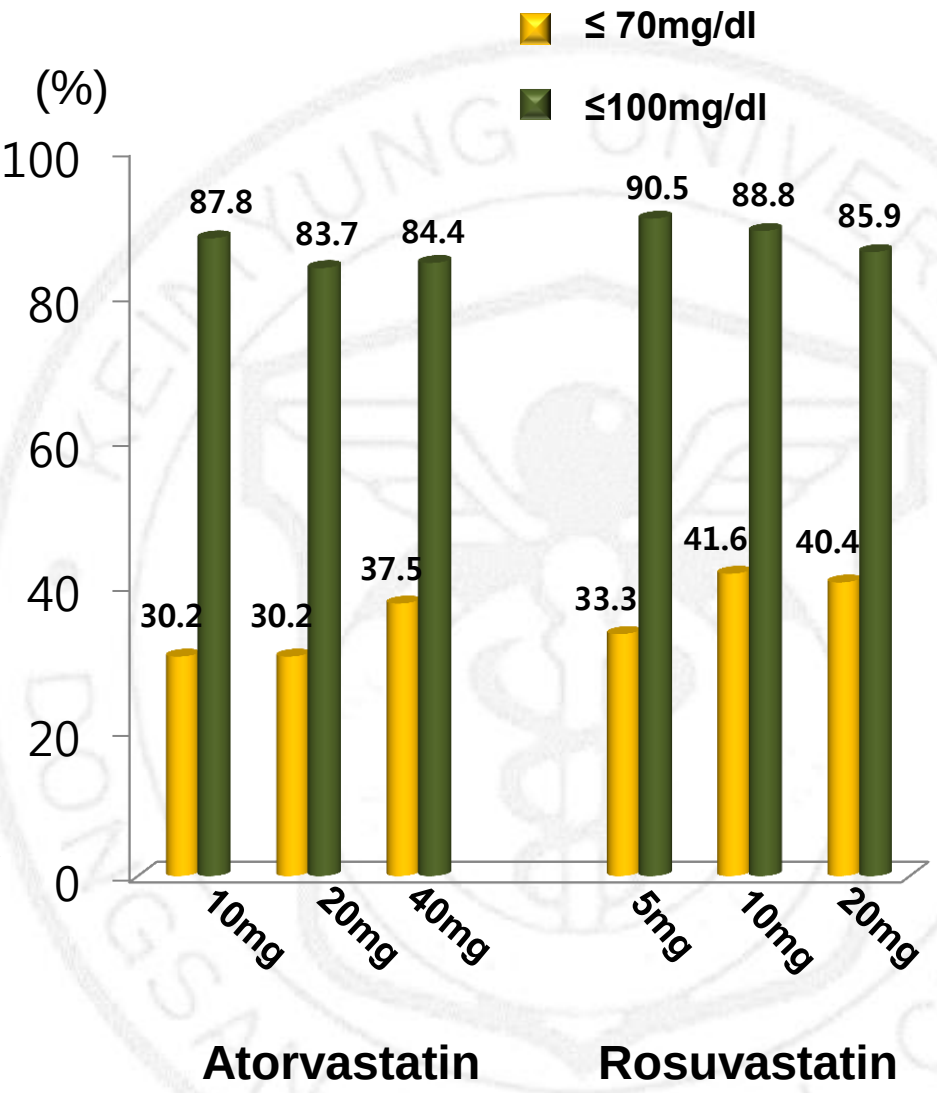


LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; CKD, chronic kidney disease.

1. Data on file, MSD Korea (Market Research for understanding CKD risk and LDL-C control level of statin Rx. Patients by Ipsos, 2011)

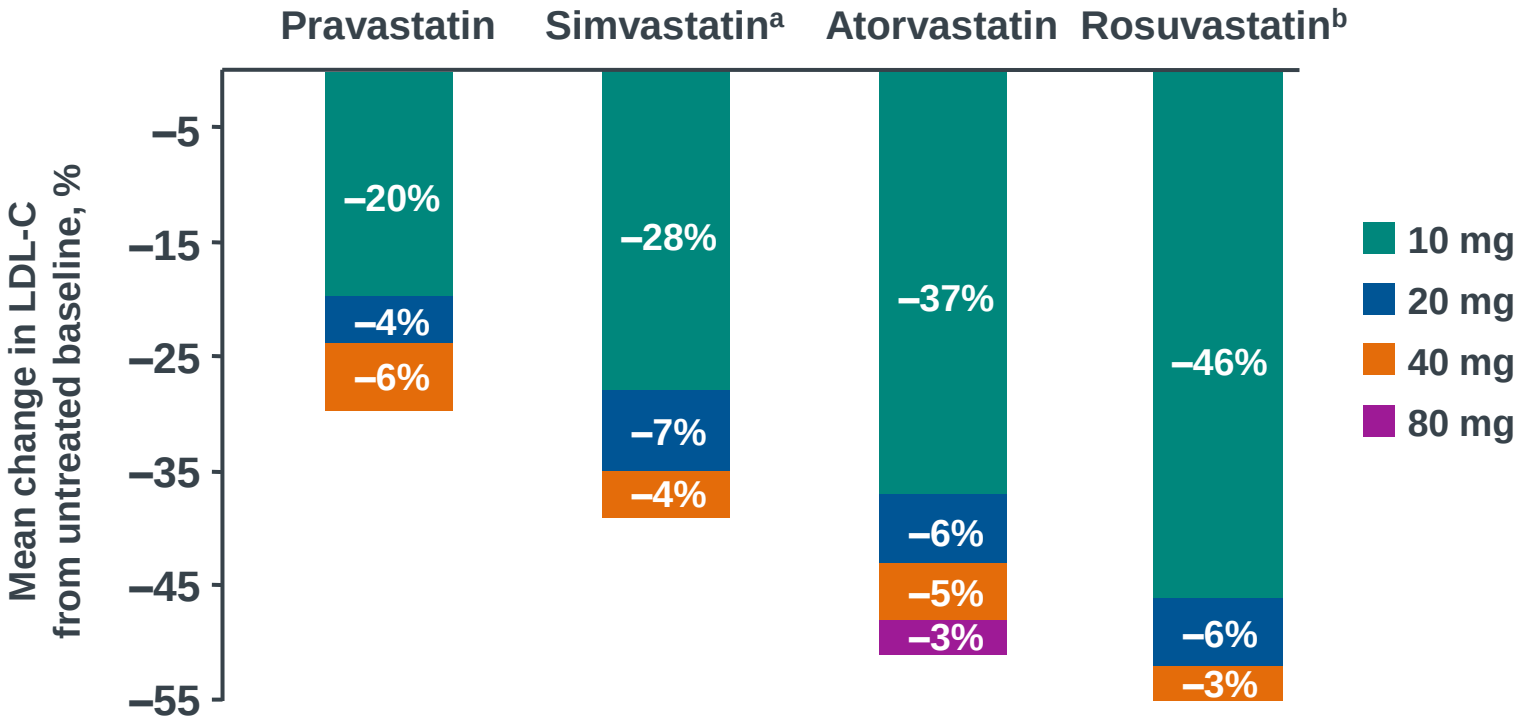
Real world practice of statin therapy





Unpublished data from Keimyung univerisity

STELLAR:LDL-C Reductions With Statin Monotherapy[1]



A 6-week, parallel-group, open-label, randomized, multicenter study comparing LDL-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.

[a]Mean change in LDL-C from untreated baseline after 6 weeks for simvastatin 80 mg was 46%.[1] The 80-mg dose of simvastatin is only recommended in patients at high CV risk who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the risks.[2]

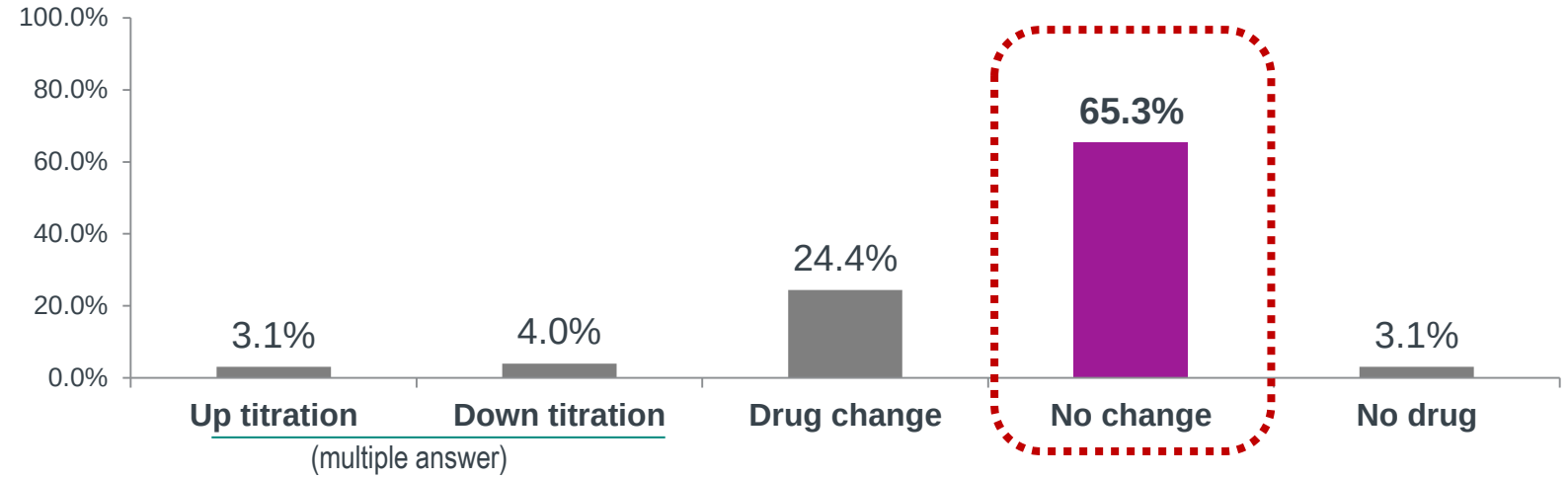
[b]Across the dose range: *P*<0.001 for the difference between rosuvastatin vs pravastatin, simvastatin, and atorvastatin.[1]

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

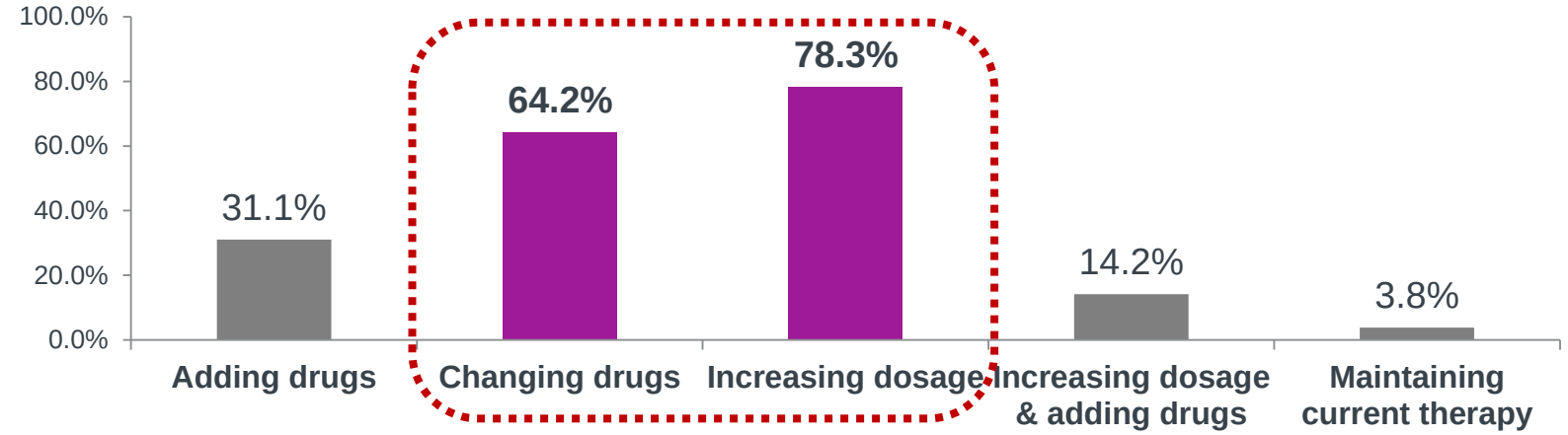
1. Jones PH et al. Am J Cardiol. 2003;92:152–160. **2.** 아토젯정 제품설명서

Many physicians do not change treatment strategies for patients not achieving LDL-C goal

Physician treatment strategies to achieve target goals analyzed by chart review



Physician's answer for treatment strategies to achieve target goals



Hwang JY, Jung CH, Lee WJ, Park CY, Kim SR, Yoon KH, Lee MK, Park SW, Park JY. *Diabetes Metab J* 2011;35:628-636

About 10% of hyperlipidemic patients suffer from muscular symptoms with high dose statin

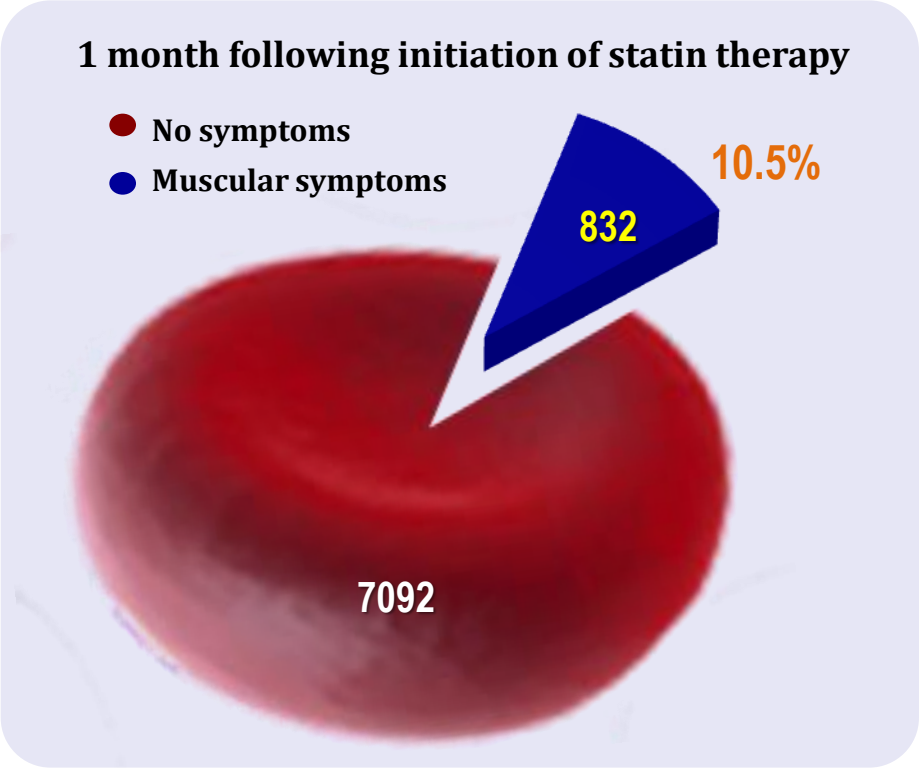
PRIMO study: mild to moderate muscular symptoms with high dosage statin therapy in hyperlipidemic patients

Objective: To characterization the risk factors, rate of occurrence, onset, nature and impact of mild to moderate muscular symptoms with high dose statin.

Design: Observational survey, 7924 hyperlipidemic pts.

Risk factors of muscle pain

- **Unexplained cramps (OR 4.14)**
- **History of CK (OR 2.04)**
- **Hypothyroidism (OR 1.71)**
- **Duration of statin treatment more than 3 month (OR 0.28)**

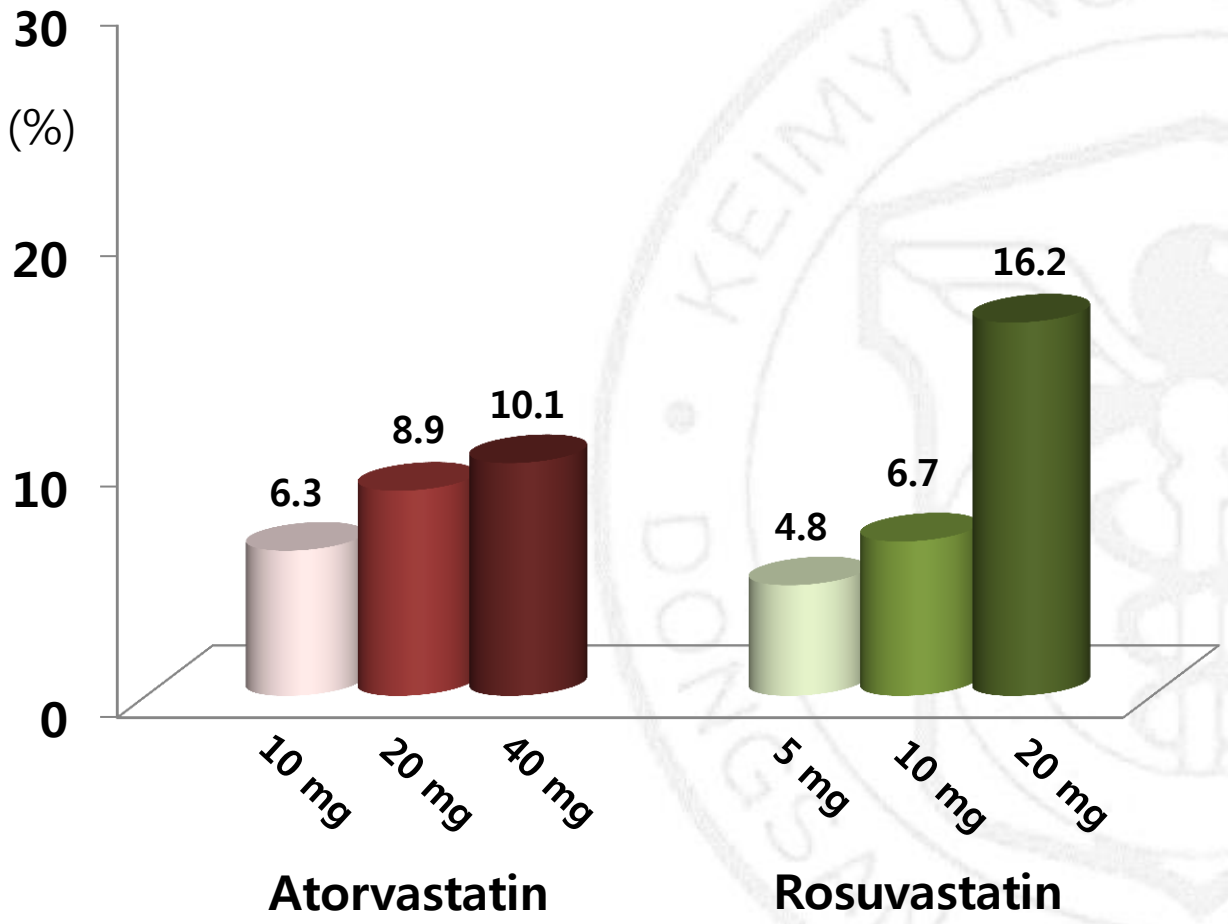


pts, patients; CK, cardiac kinase.

1. Bruckert et. al, Cardiovascular Drugs and Therapy, 2005;19:403-414

Real world practice of statin therapy

Incidence of any side effect after statin therapy



Unpublished data from Keimyung univerisity

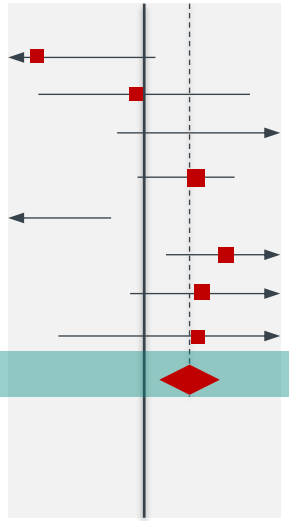
The risk of new onset diabetes of higher potency statin therapy

Higher potency statin therapy was associated with a 15% increased risk for new-onset diabetes compared with lower potency agents in the first two years of regular statin use.

The risk increase seemed to be highest (26%) in the first four months of use.[1]

Rate ratios for new onset diabetes within 120 days of starting higher potency or lower potency statins after a major CV event or procedure (as-treated analysis)

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



Test for heterogeneity: $x^2=15.22$, df=7, $p=0.03$, $I^2=54\%$

Test for overall effect: z=2.84, p=0.04

Study design; 8 population based cohort studies and a meta-analysis was conducted in 136 966 patients aged ≥40 years newly treated with statins . Within each cohort of patients newly prescribed a statin after hospitalisation for a major cardiovascular event or procedure, This was performed as-treated, nested case-control analyses to compare diabetes incidence in users of higher potency statins with incidence in users of lower potency statins. This was to evaluate the incremental increase in new onset diabetes from higher potency statins compared with lower potency statins when used for secondary prevention.

1. Dormuth CR et al. *BMJ* 2014;348:g3244

Features of the metabolic syndrome are predictive of new-onset T2DM

Prediction of new-onset T2DM across the 3 trials

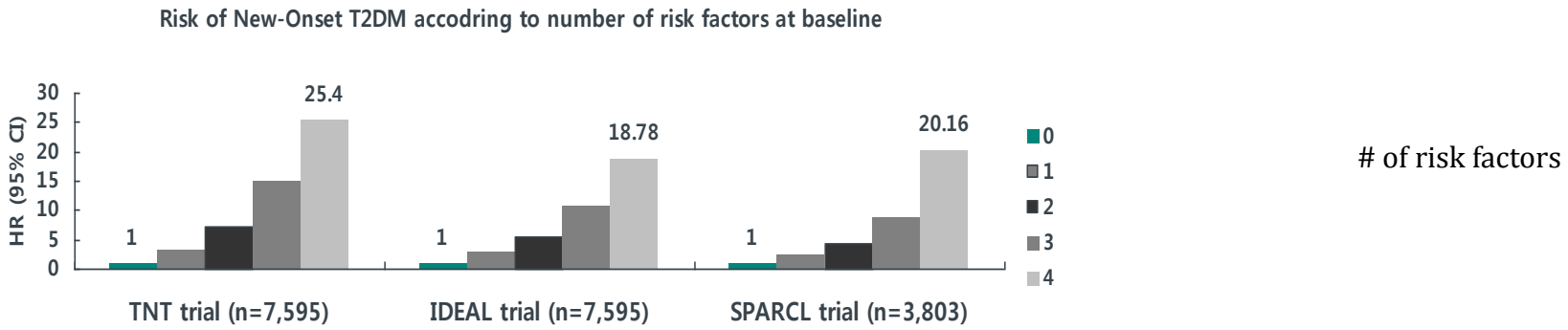
Risk Factors:

1) baseline **fasting glucose** > 100 mg/dl

2) **fasting triglycerides** > 150 mg/dl

3) **BMI** >30 kg/m^2

4) History of **hypertension**



Baseline fasting glucose level and features of the MS are predictive of new-onset T2DM.

T2DM= type 2 diabetes mellitus; BMI= body mass index; DM= diabetes mellitus; MS= metabolic syndrome.

1. Waters DD. et al. *J Am Coll Cardiol*. 2011;57(14):1535-1545. doi:10.1016/j.jacc.2010.10.047

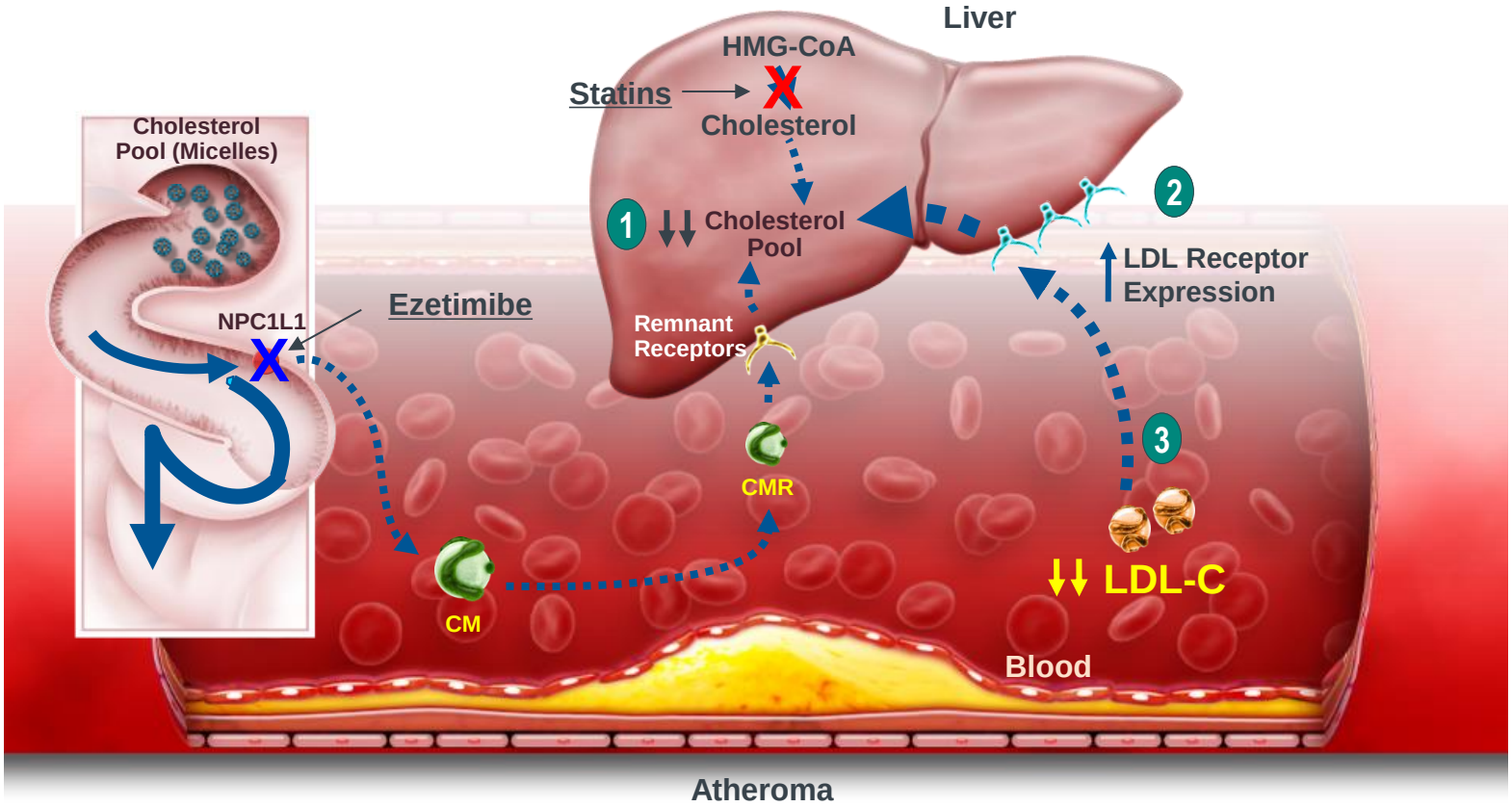
Overview

- Clinical Unmet Needs
- Benefit of Ezetimibe Combination Therapy

Ezetimibe and Statins Have Complementary Mechanisms of Action[1]

Together, ezetimibe in combination with a statin provides:

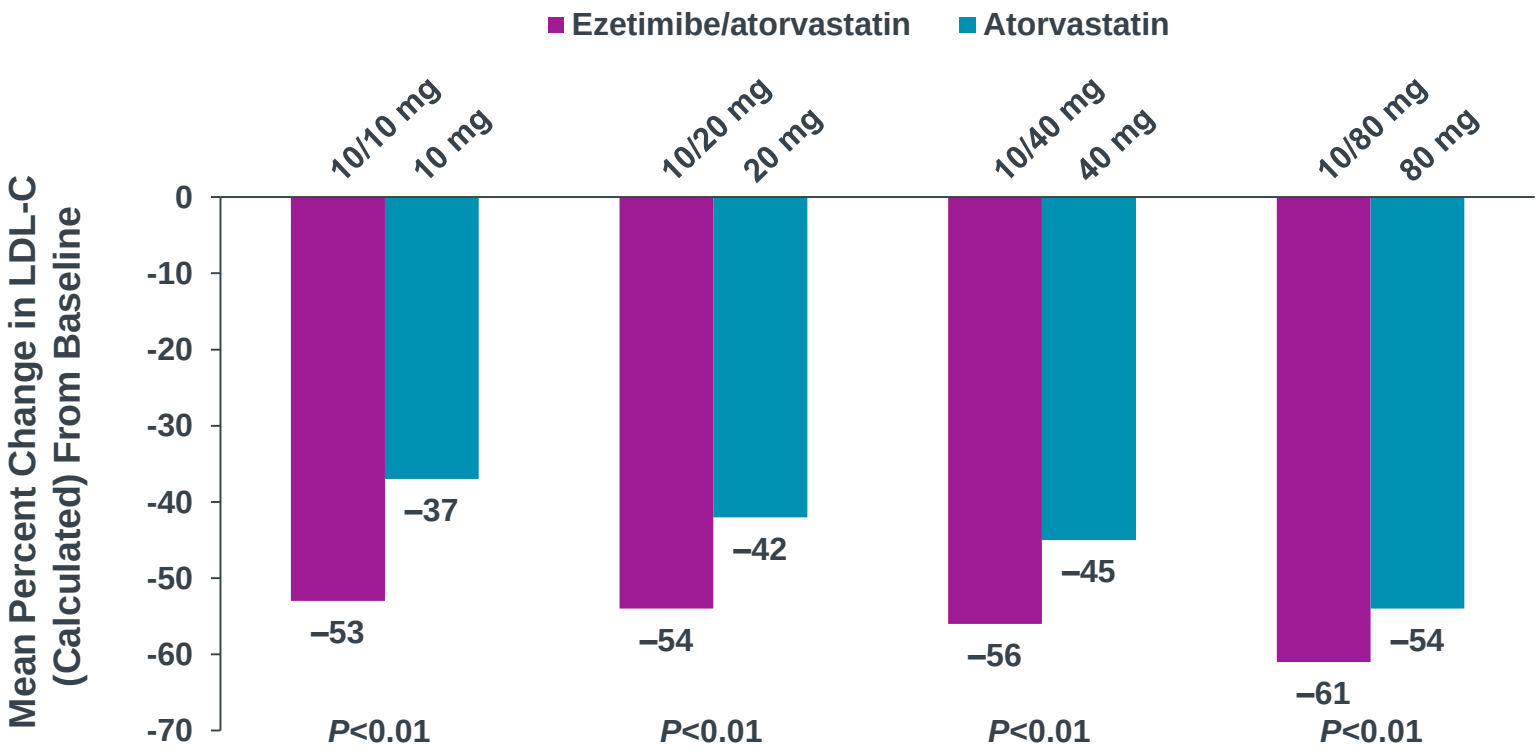
1. Reduction of hepatic cholesterol
2. Increased LDL receptor expression
3. Increased clearance of plasma LDL-C



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

1. Grigore L et al. *Vas Health Risk Manag*. 2008;4:267–278.

Ballantyne 2003: Ezetimibe/Atorvastatin Provided Significantly Greater LDL-C Reduction Compared With Corresponding Atorvastatin Doses[1]

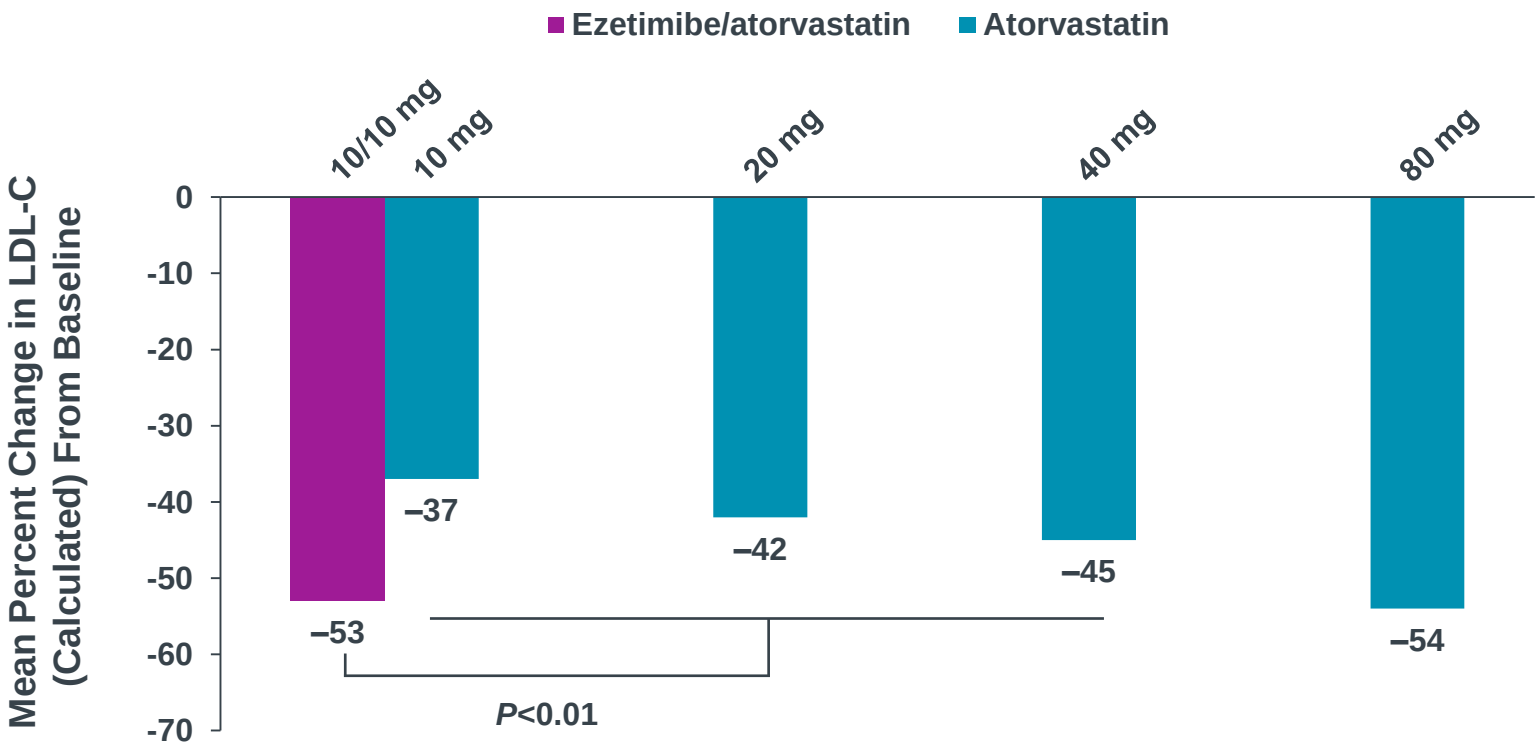


Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe/atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).

Adapted with permission from Ballantyne CM et al.[1]

1. Ballantyne CM et al. *Circulation*. 2003;107:2409–2415.

Ballantyne 2003: Ezetimibe/Atorvastatin 10/10 mg Provided Significantly Greater LDL-C Reduction Compared With Atorvastatin 10, 20, and 40 mg[1,2]



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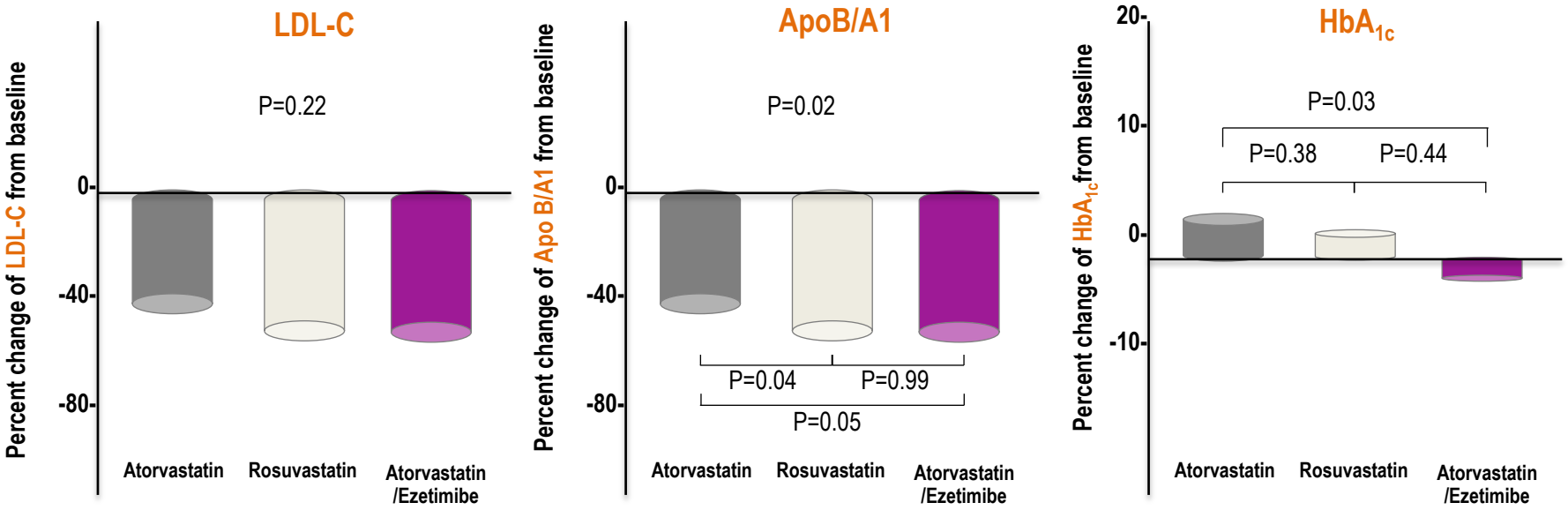
Adapted with permission from Ballantyne CM et al.[1]

1. Ballantyne CM et al. *Circulation*. 2003;107:2409–2415.

Effects of ezetimibe/atorvastatin on lipoproteins and glucose metabolism

Ezetimibe/atorvastatin 5 mg/5 mg was more efficacious in improving Apo B/A1 ratio than atorvastatin 20 mg after comparable LDL-C reduction. On the other hand, atorvastatin 20 mg showed greater increase in HbA_{1c} than ezetimibe/atorvastatin 5 mg/5 mg.[1]

Change of LDL-C and the glucose metabolism-related parameters (n=76) at week 8



Atorvastatin 20 mg (n=25)**, Rosuvastatin 10 mg** (n=25), **Atorvastatin/Ezetimibe 5 mg/5 mg** (n=26)

This clinical result is based on sources including off-label indications

Study design; This 12-week (4-week dietary lead-in period followed by 8 weeks of drug treatment), randomized, open-label, single center study was conducted in 90 hypercholeserolemic patients to 1 of 3 treatment groups : atorvastatin 20 mg, rosuvastatin 10 mg, or atorvastatin/ezetimibe 5 mg/5 mg. The primary end point was the percentage changes in the apolipoprotein B/A1 ratio and hemoglobin A1c from baseline to week 8 of drug treatment.

HbA_{1c}=glycosylated hemoglobin, LDL-C=low-density lipoprotein cholesterol, Apo=apolipoprotein

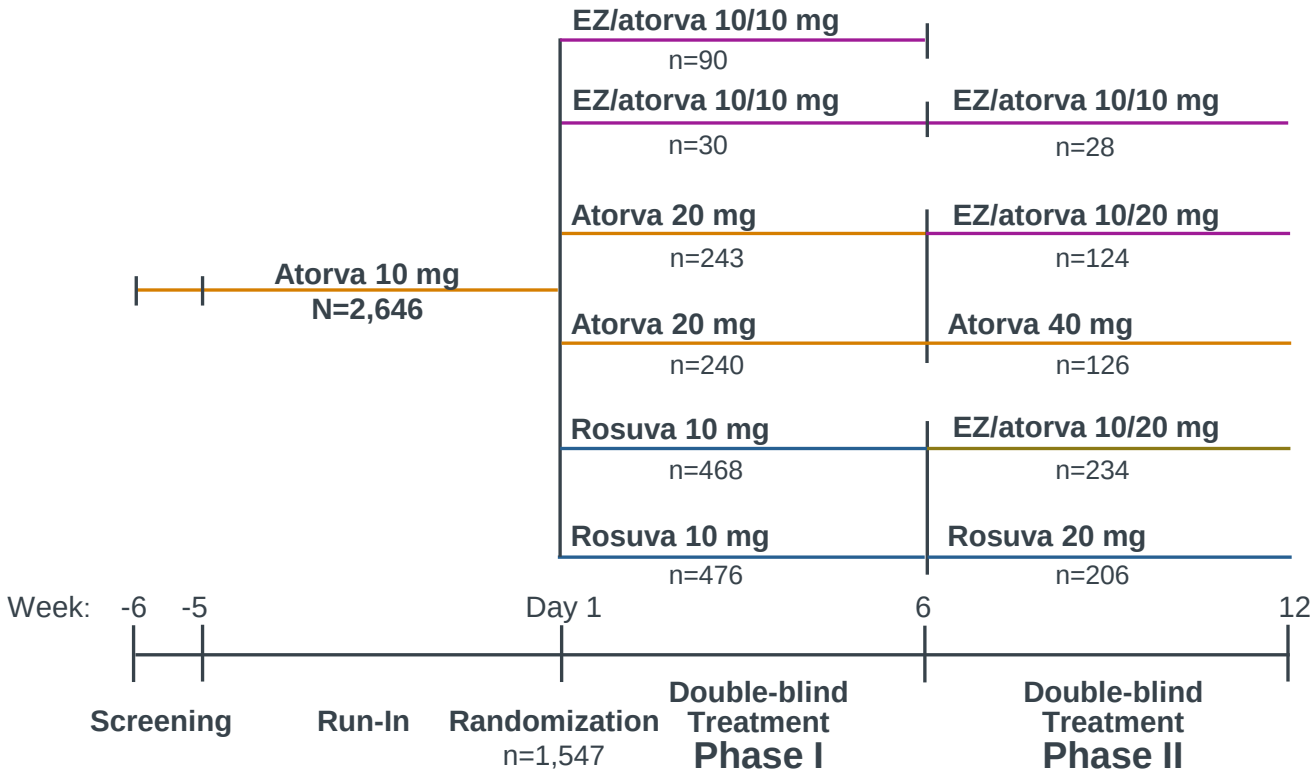
1.Her AY et al. J Cardiovascular Pharm and Therapeutics 2010;15 167–174

Clinical Data for Ezetimibe/Atorvastatin: Efficacy and Safety of Ezetimibe Added to Atorvastatin Versus Atorvastatin Uptitration or Switching to Rosuvastatin in Patients With Primary Hypercholesterolemia (PACE Study)

Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE: Efficacy of Ezetimibe/Atorvastatin vs Atorvastatin Uptitration or Switching to Rosuvastatin (Study Design)[1]

High-risk patients[a] with hypercholesterolemia not at LDL-C <100 mg/dL (~2.6 mmol/L) on atorvastatin 10 mg



Adapted with permission from Bays HE et al.[1]

[a]High risk of CHD was defined as: 1) subjects without CVD who had type 2 diabetes, or ≥2 risk factors and a 10-year risk for CHD >20% as determined by the Framingham calculation, or 2) subjects with CVD, including established coronary or other atherosclerotic vascular disease.

PACE = a randomized, double-blind, active-controlled, multicenter study of patients with **P**rimary hypercholesterolemia and high cardiovascular risk who are not adequately controlled with **A**torvastatin 10 mg: a **C**omparison of the efficacy and safety of switching to coadministration **E**zetimibe and atorvastatin versus doubling the dose of atorvastatin or switching to rosuvastatin;

EZ = ezetimibe; Atorva = atorvastatin; Rosuva = rosuvastatin; CHD = coronary heart disease; CVD = cardiovascular disease.

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE Phase I: Ezetimibe/Atorvastatin 10/10 mg Resulted in Greater Attainment of LDL-C <100 mg/dL (~2.6 mmol/L) vs Doubling Atorvastatin to 20 mg or Switching to Rosuvastatin 10 mg[1]

High-risk Patients Reaching LDL-C <100 mg/dL (~2.6 mmol/L) at 6 weeks, as a Result of Greater LDL-C Reduction

Ezetimibe/atorvastatin 10/10 mg
(n=119)

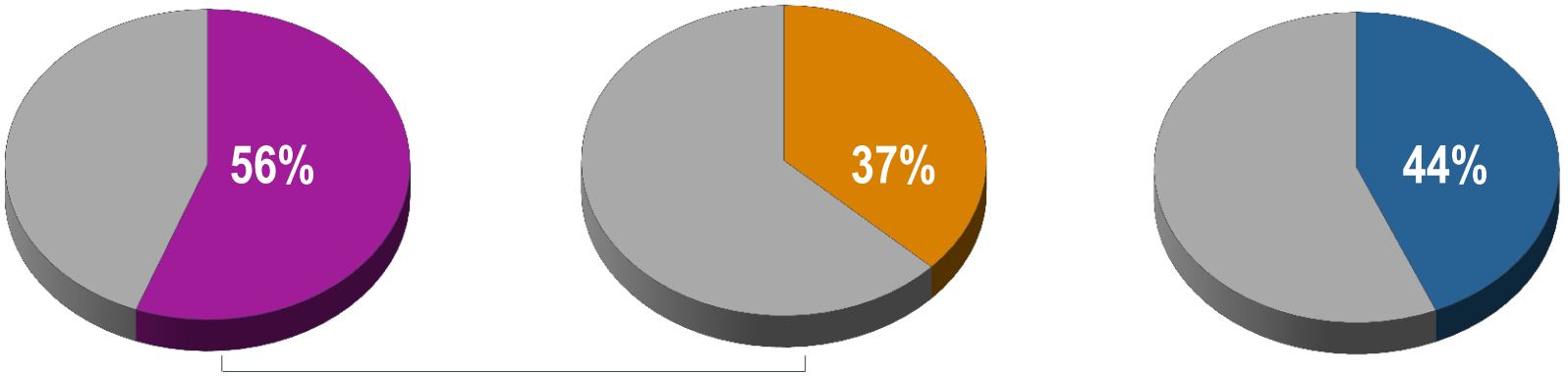
Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)

Atorvastatin 20 mg
(n=471)

Mean treated baseline LDL-C:
120 mg/dL (~3.1 mmol/L)

Rosuvastatin 10 mg
(n=915)

Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)



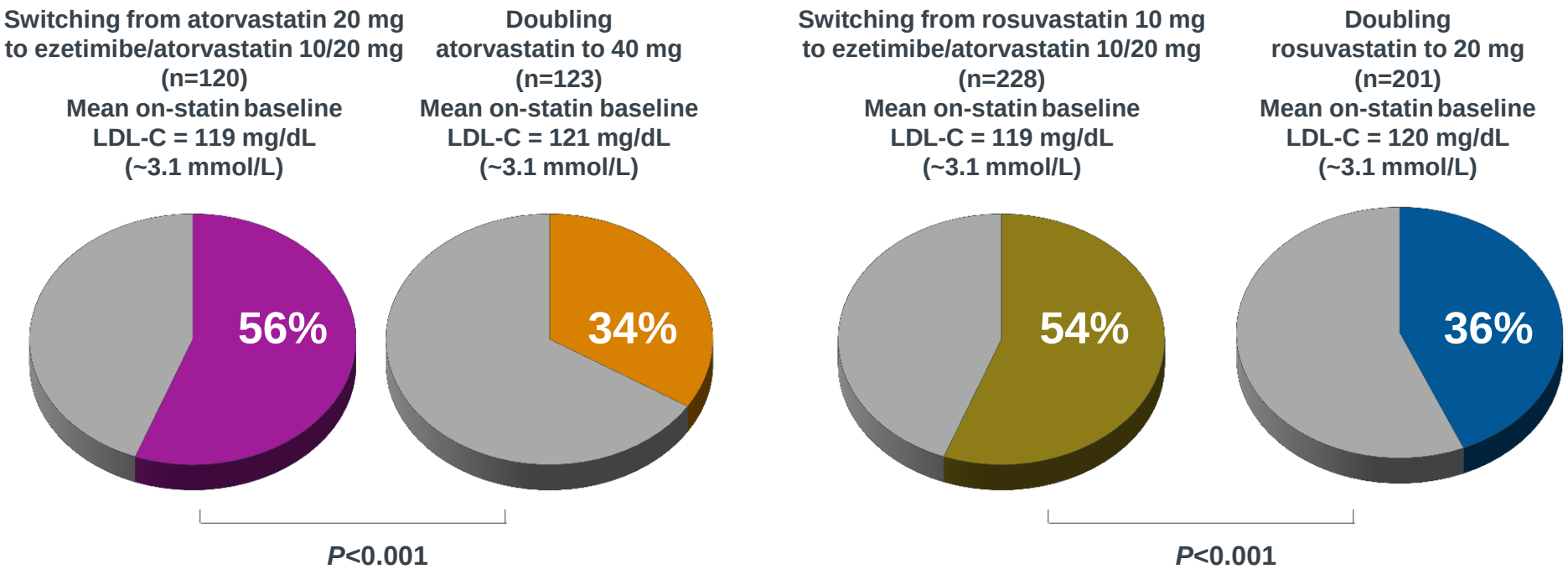
The IRLS mean decrease in LDL-C from statin-treated baseline was 22% with ezetimibe + atorvastatin 10 mg compared with 10% with atorvastatin 20 mg and 13% with rosuvastatin 10 mg; *P*<0.001 for each comparison vs ezetimibe + atorvastatin 10 mg.

IRLS = iteratively reweighted least squares.

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE Phase II: Greater Attainment of LDL-C <100 mg/dL With Ezetimibe/Atorvastatin 10/20 mg[1]

High-risk Patients Reaching LDL-C <100 mg/dL (~2.6 mmol/L) as a Result of Greater LDL-C Reduction

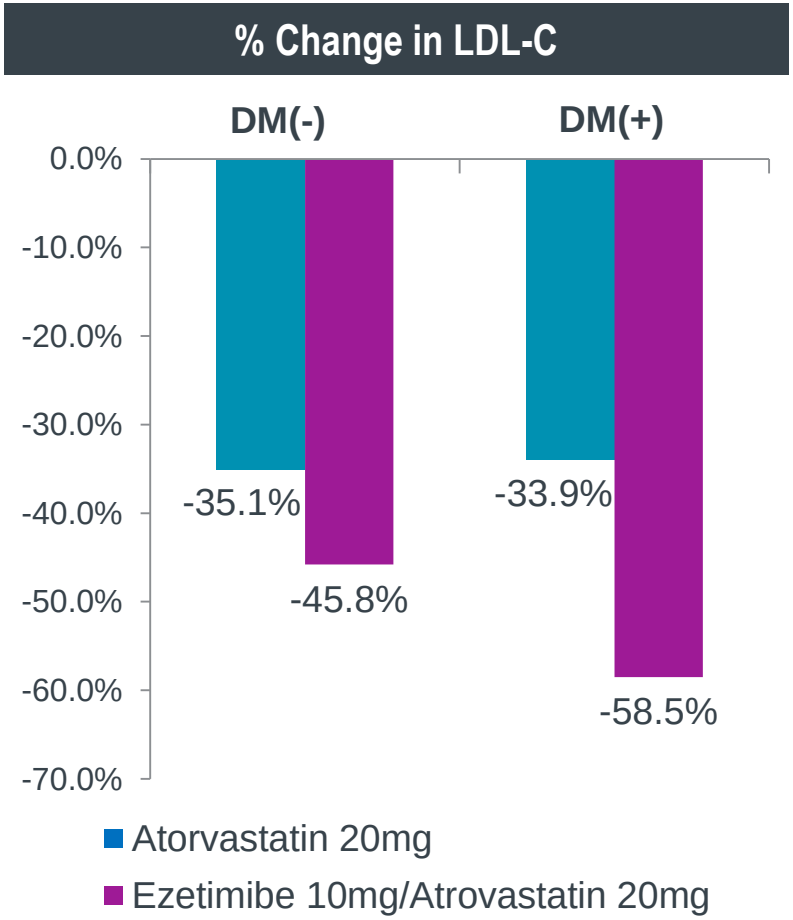


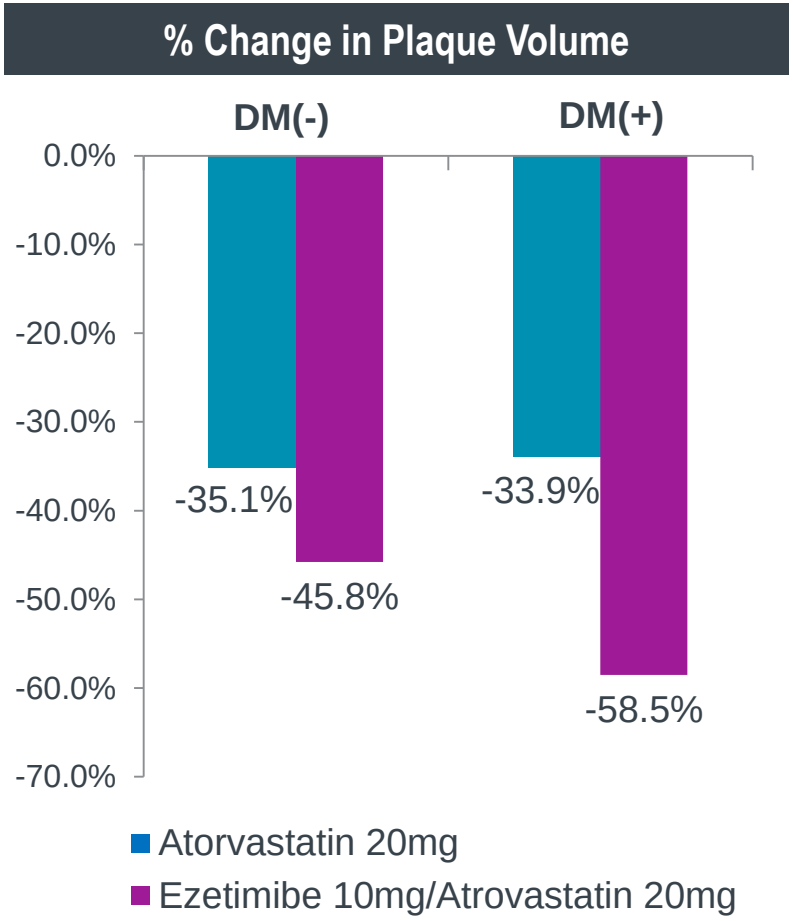
The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

IRLS = iteratively reweighted least squares.

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

Effect of combination of ezetimibe and a statin on coronary plaque regression in patients with acute coronary syndrome





Methods: Prospective serial intravascular ultrasound (IVUS) of non-culprit lesions of the target vessel was performed in 95 patients with ACS. Of these, 50 patients were administered combination of atorvastatin 20 mg/day and ezetimibe 10 mg/day. 45 subjects treated by atorvastatin 20 mg/day alone were the control group. At the beginning and 24 weeks after PCI, quantitative PV was accessed by IVUS. The primary end point was the percentage change in non-culprit coronary PV.

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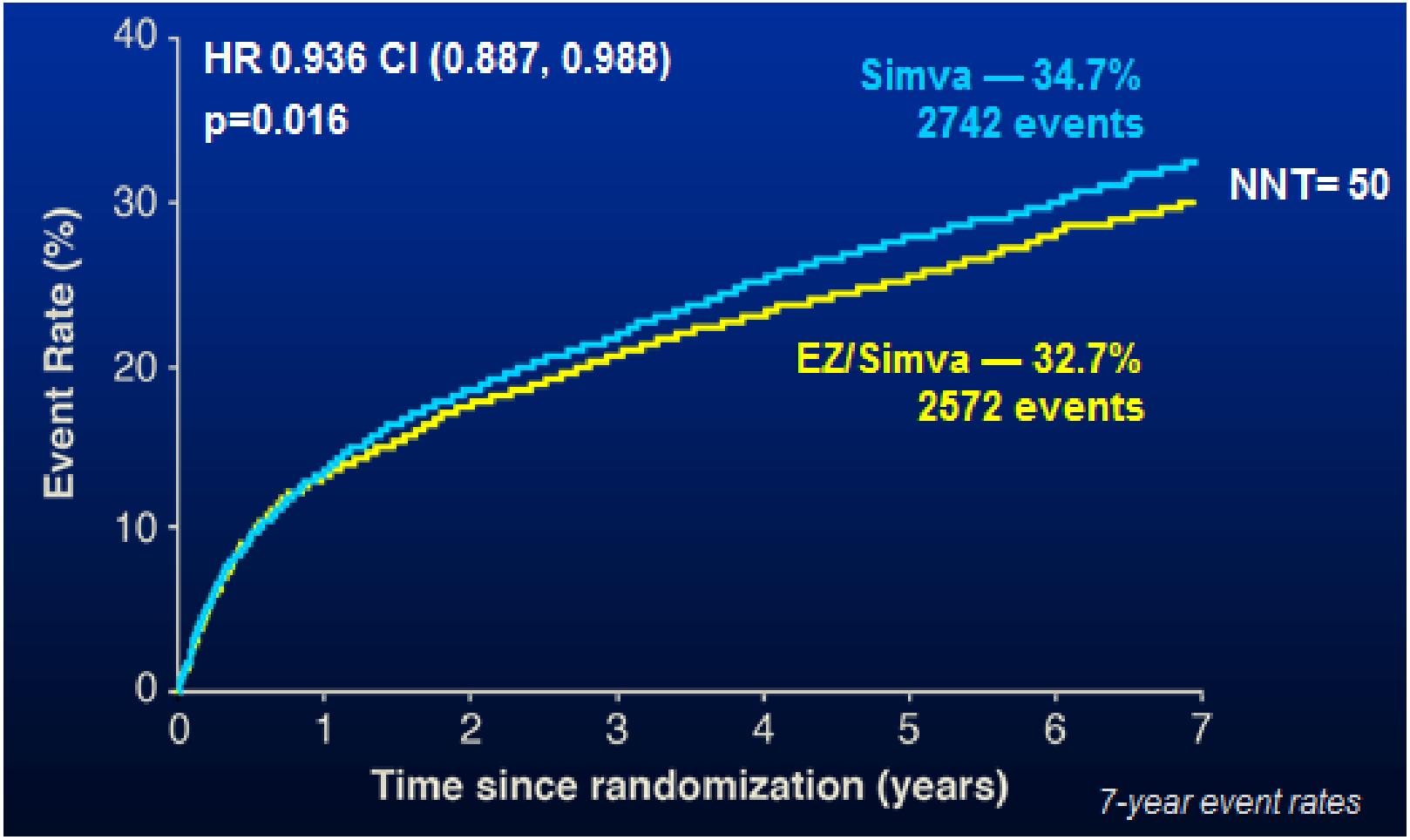
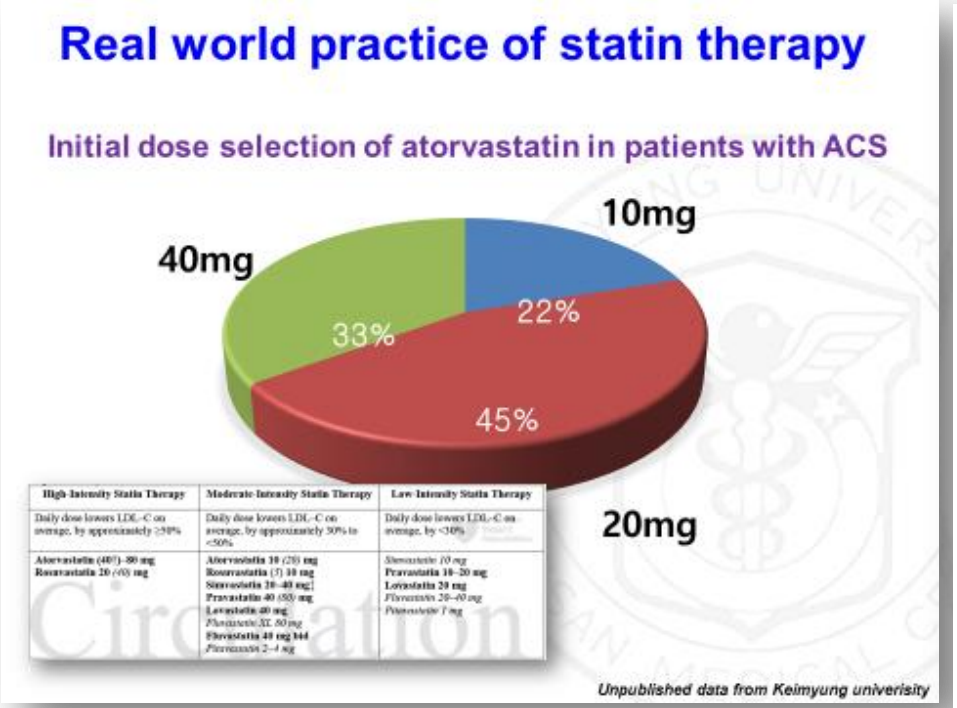
IMPROVE-IT: Ezetimibe can reduce cardiovascluar event for ACS patients

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

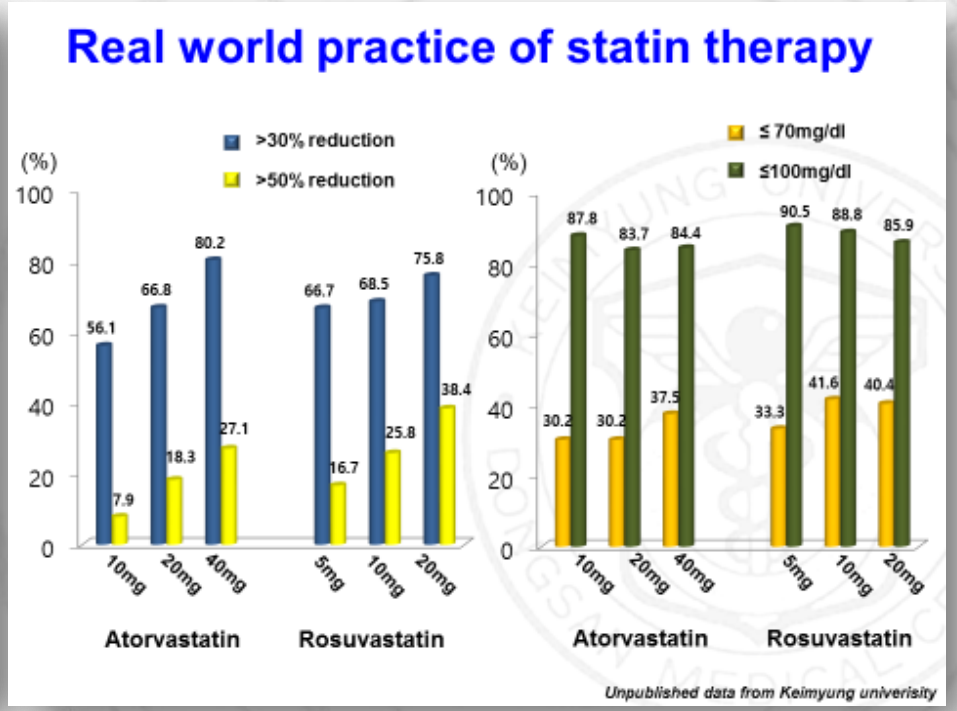


Which side?

Statin Believer



LDL Believer



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Invited commentary

IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy"?

Luis Masana [a], Juan Pedro-Botet [b], Fernando Civeira [c, *]

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Classification of cholesterol-lowering therapy according to LDL cholesterol reduction intensity.

Low-intensity cholesterol-lowering therapy (LICLT) ↓ LDLc < 30%	Mild-intensity cholesterol-lowering therapy (MICLT) ↓ LDLc 30–49%	High-intensity cholesterol-lowering therapy (HICLT) ↓ LDLc 50–60%	Very-high-intensity cholesterol-lowering therapy (VHICLT) ↓ LDLc > 60%
Simvastatin 10 mg	Atorvastatin 10–20 mg	Atorvastatin 40–80 mg	Atorvastatin 40–80 mg + Ezetimibe 10 mg
Pravastatin 10–20 mg	Rosuvastatin 5–10 mg	Rosuvastatin 20–40 mg	Rosuvastatin 20–40 mg + Ezetimibe 10 mg
Lovastatin 10–20 mg	Simvastatin 20–40 mg	Simvastatin 20–40 mg + Ezetimibe 10 mg	
Fluvastatin 40 mg	Pravastatin 40 mg	Pravastatin 40 mg + Ezetimibe 10 mg	
Pitavastatin 1 mg	Lovastatin 40 mg	Lovastatin 40 mg + Ezetimibe 10 mg	
Ezetimibe 10 mg	Fluvastatin XL 80 mg	Fluvastatin 80 mg + Ezetimibe 10 mg	
	Pitavastatin 2–4 mg	Pitavastatin 2–4 mg + Ezetimibe 10 mg	
	Simvastatin 10 mg + Ezetimibe 10 mg	Atorvastatin 10–20 mg + Ezetimibe 10 mg	
	Pravastatin 20 mg + Ezetimibe 10 mg		
	Lovastatin 20 mg + Ezetimibe 10 mg	Rosuvastatin 5–10 mg + Ezetimibe 10 mg	
	Fluvastatin 40 mg + Ezetimibe 10 mg		
	Pitavastatin 1 mg + Ezetimibe 10 mg		

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Challenging LDL-C treatment especially on ACS patients

Exploring the latest pathway to treat dyslipidemia for ACS patients

계명의대 심장내과
남창욱

경청에 감사 드립니다.

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