How do we achieve lower for longer LDL-C levels for patients

INHA University Hospital

Cardiovascular center

Sang-Don Park

Unmet need of statin

Lipids: LDLc

Statin

Intolerable

- Myopathy
- Liver function deterioration
- New onset DM

Inadequate LDL lowering

- Residual CV risk
- Unable to > 50% LDL reduction

Add on or Switch therapy
Ezetimibe
PCSK9 inhibitor
Bempedoic acid

Contents

Several questions and up-to-date evidence for ezetimibe combination therapy

1. Would adding ezetimibe on statin really improve CV outcomes?

2. Is there any benefit of adding ezetimibe on moderate intensity satin compared to high-dose statin therapy?

3. Which approach provides more benefit: high-intensity statin strategy or treat-to-target strategy?

Several questions and up-to-date evidence for ezetimibe combination therapy

1. Would adding ezetimibe on statin to lower LDL-C improve CV outcomes?

- **Evidence: Compared to Simvastatin alone, Ezetimibe add-on therapy reduced LDL-C (IMPROVE-IT Trial)**

2. Is there any benefit of moderate-intensity statin+ezetimibe therapy compared to high-dose statin therapy?

3. Which approach provides more benefit: high-intensity statin strategy or treat-to-target strategy?

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial[1]

Compared to Simvastatin alone, Ezetimibe add-on therapy reduced LDL-C by 24%, with **NNT of 50**.[1]

This study was conducted with ezetimibe and simvastatin.

Stain + Ezetimibe

A double-blind, randomized trial, 18,144 patients stabilized post ACS ≤ 10 days: LDL-C 50–125* mg/dL (or 50–100** mg/dL if prior lipid-lowering therapy)

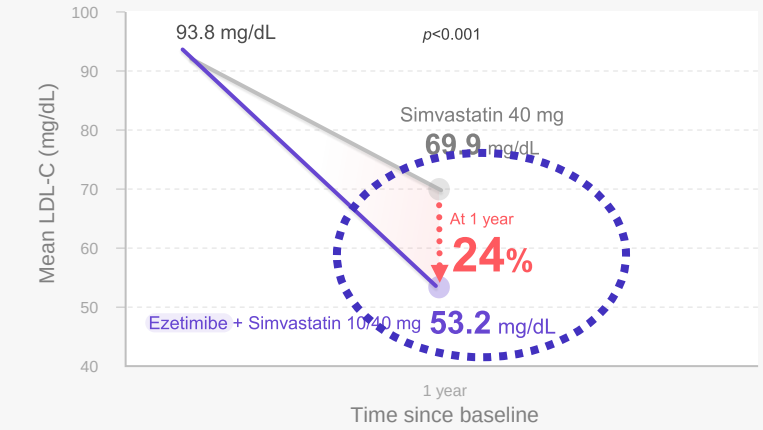
- **Simvastatin 40 mg** (n=9,077)
- **Ezetimibe/simvastatin 10/40 mg** (n=9,067)

Primary Endpoint:

CV death, Nonfatal MI, Hospital admission for UA, Coronary revascularization (≥ 30 days after randomization)**, or Nonfatal stroke**

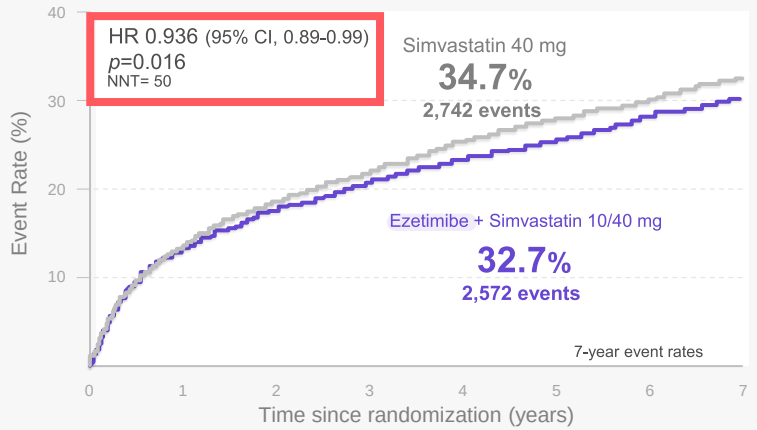
Duration: Minimum 2½--year follow-up (at least 5,250 events)
The median follow-up was 6 years.

Change of LDL-cholesterol[1]



Adapted from Cannon CP, *et al.*[1]

Primary Endpoint[1]



Adapted from Cannon CP, *et al.*[1]

* 3.2 mM[1] ** 2.6 mM[1]

ACS : Acute coronary syndrome, **MI :** Myocardial infarction, **HR :** Hazard ratio, **UA :** Unstable angina, **LDL-C :** Low-density lipoprotein cholesterol, **CI :** Confidence interval, **NNT :** Number needed to be treated, **CV :** Cardiovascular, **LDL :** Low-density lipoprotein

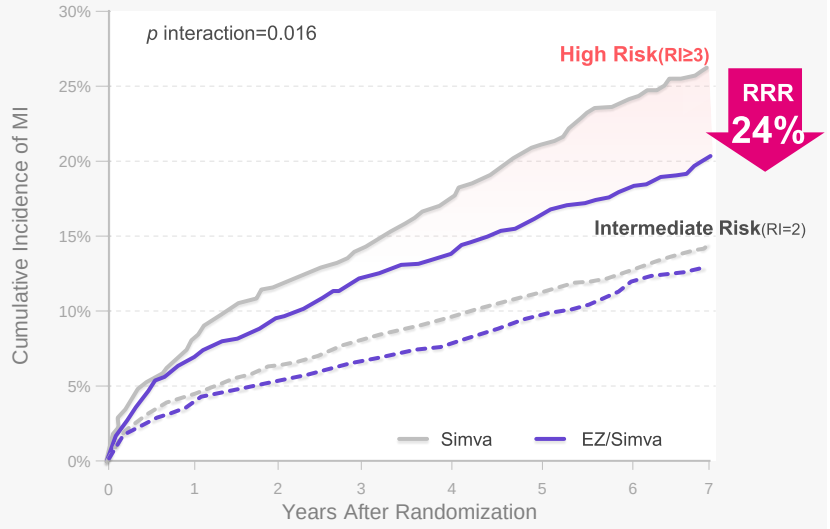
1. Cannon CP, Blazing MA, Giugliano RP, *et al*; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397.

IMPROVE-IT: Stroke sub-analysis

Ezetimibe demonstrated an additional risk reduction of 24% in MI & 32% in Ischemic Stroke when added to statin therapy in high-risk patients.[1]

Stain + Ezetimibe

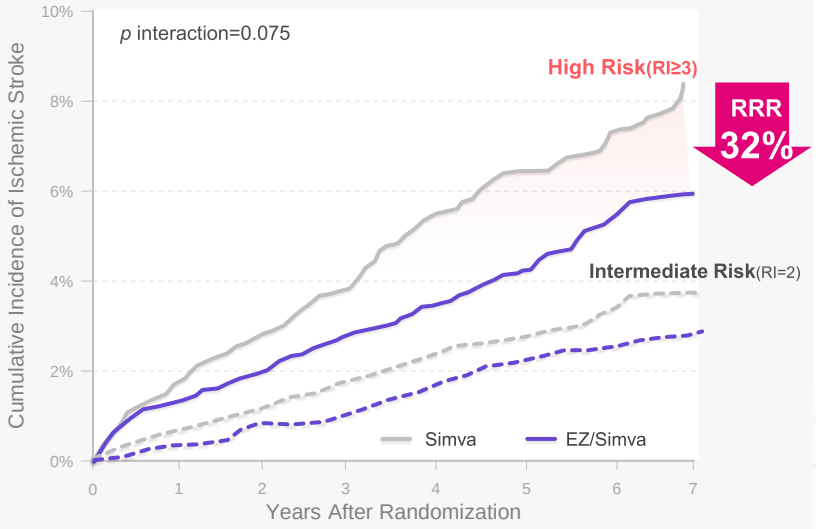
Outcomes by Risk Category and Randomized Treatment : MI[1]



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

Adapted from Bohula EA, *et al.*[1]

Outcomes by Risk Category and Randomized Treatment : Ischemic stroke[1]



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

Adapted from Bohula EA, *et al.*[1]

IMPROVE-IT : Improved Reduction of Outcomes: Vytorin Efficacy International Trial, **MI :** Myocardial infarction, **RI :** Risk indicators, **RRR :** Relative risk reduction, **KM :** Kaplan-Meier, **ARR :** Absolute risk reduction, **HR :** Hazard ratio, **EZE/Simva :** Ezetimibe/Simvastatin

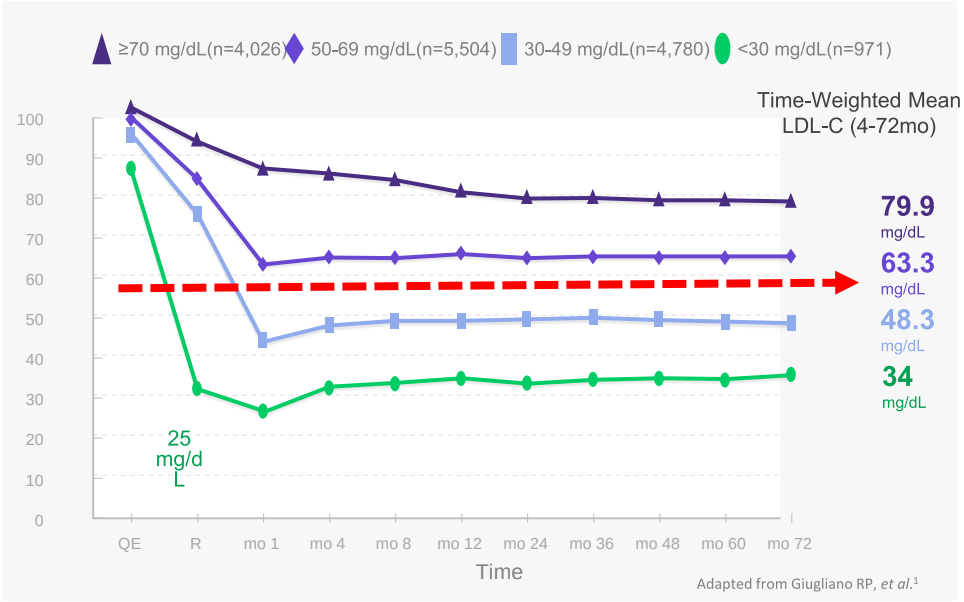
1. Bohula EA, *et al.* Atherothrombotic risk stratification and Ezetimibe for secondary prevention. *J Am Coll Cardiol.* 2017 Feb 28;69(8):911-921.

IMPROVE-IT subgroup analysis: Long-term Safety and Efficacy

The median LDL-C level at 1 month was 25 mg/dL and their time-weighted average LDL-C level after randomization was 34 mg/dL over a median of 6 years' follow-up.[1]

Stain + Ezetimibe

Median low-density lipoprotein cholesterol(LDL-C) level at 1 Month[1]



Adapted from Giugliano RP, *et al.*[1]

Safety Events by Achieved LDL-C Level at 1 Month[1,a]

Prespecified Safety End Points	Achieved LDL-C Level (mg/dL) at 1 mo, No. (%) of Patients				*P* Value for Trend
	<30 (n=971)	30-49 (n=4,786)	50-69 (n=5,504)	≥70 (n=4,026)	
Adverse event leading to drug discontinuation	92 (9.5)	451 (9.4)	470 (8.5)	354 (8.8)	.21
Rhabdomyolysis, myopathy, or myalgias with CK elevation >5 times ULN[b]	4 (0.4)	30 (0.6)	26 (0.5)	25 (0.6)	.81
Rhabdomyolysis or myopathy[b]	0	13 (0.3)	9 (0.2)	15 (0.4)	.12
Rhabdomyolysis[b]	0	6 (0.1)	7 (0.1)	8 (0.2)	.16
AST or ALT above 3 times ULN	21 (2.2)	97 (2.0)	97 (1.8)	84 (2.1)	.88
Gall bladder adverse event	35 (3.6)	155 (3.2)	200 (3.6)	145 (3.6)	.48
Neurocognitive adverse events	20 (2.1)	121 (2.5)	158 (2.9)	91 (2.3)	.95
Short-term[c]	12 (1.2)	61 (1.3)	91 (1.7)	48 (1.2)	.98
Longer-term[d]	8 (0.8)	60 (1.3)	67 (1.2)	43 (1.1)	.89
Hemorrhagic stroke[b]	3 (0.3)	41 (0.9)	23 (0.4)	25 (0.6)	.50
Hospitalization for heart failure	45 (4.6)	200 (4.2)	189 (3.4)	148 (3.7)	.06
Noncardiovascular death[b]	56 (5.8)	244 (5.1)	310 (5.6)	197 (4.9)	.50
Cancer[b]	87 (9.0)	413 (8.6)	477 (8.7)	300 (7.5)	.04

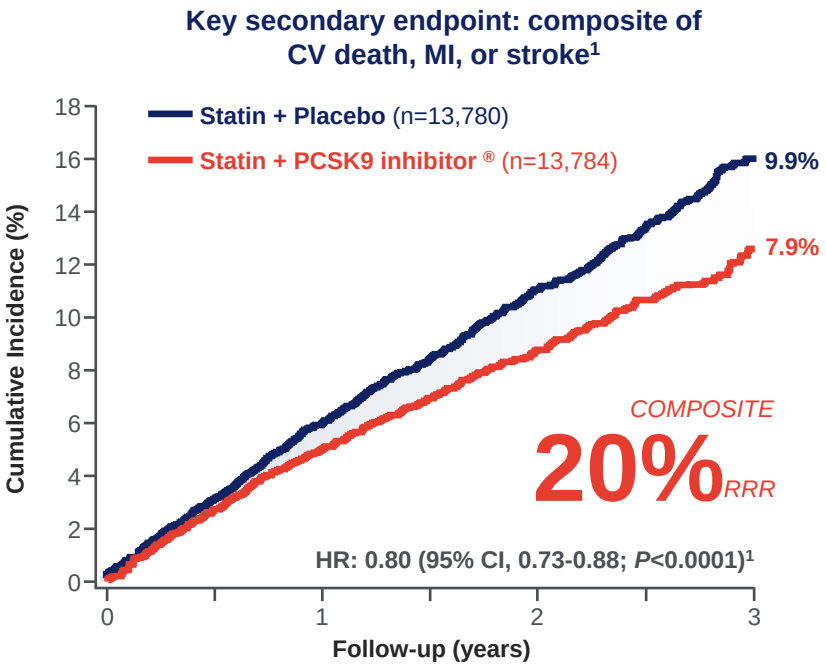
IMPROVE-IT : Improved Reduction of Outcomes: Vytorin Efficacy International Trial, **LDL-C :** Low-density lipoprotein cholesterol, **QE :** Qualifying event (at time of admission), **R :** Randomization

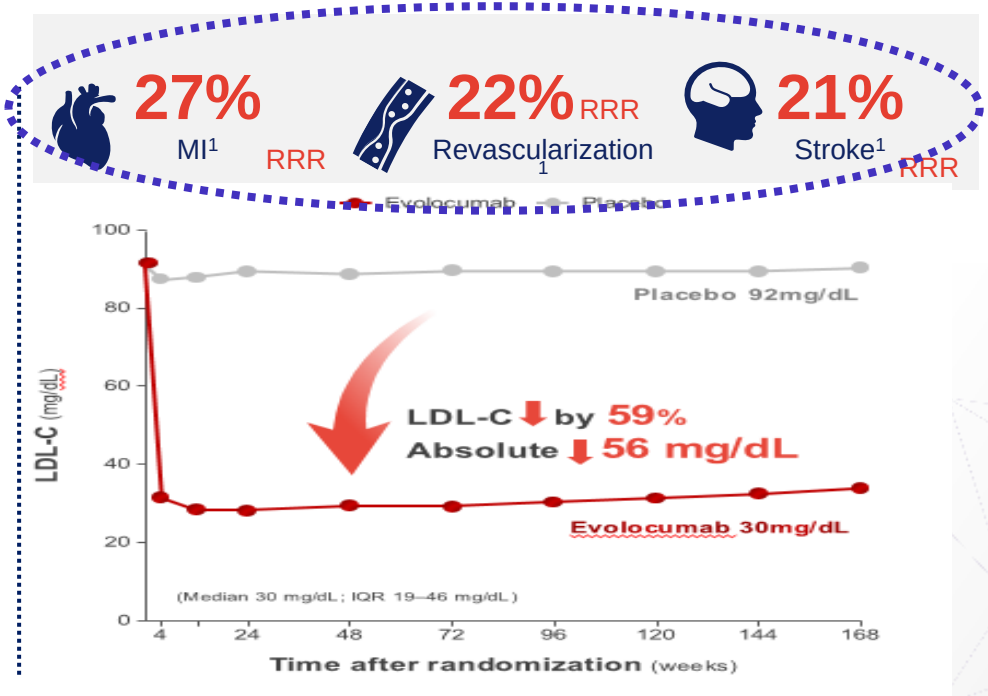
Study design This prespecified analysis compared outcomes in patients stratified by achieved LDL-C level at 1 month in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial and adjusted for baseline characteristics during 6 years' median follow-up. Patients were enrolled from October 26, 2005, to July 8, 2010, and the data analysis was conducted from December 2014 to February 2017. Safety end points included adverse events leading to drug discontinuation; adverse muscle, hepatobiliary, and neurocognitive events; and hemorrhagic stroke, heart failure, cancer, and noncardiovascular death. Efficacy events were as specified in the overall trial.[1]

1. Giugliano RP, *et al.* Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol*. 2017 May 1;2(5):547-555.

The FOURIER trial: For Patients With Established ASCVD, Evolocumab Added to a Statin Reduced the Risk of CV Events by 20% in a Median of 2.2 Years

Stain + PCSK9 inhibitor





- **Observed HR for CV death: 1.05 (95% CI, 0.88–1.25) and hospitalizations due to UA: 0.99 (95% CI, 0.82–1.18)**

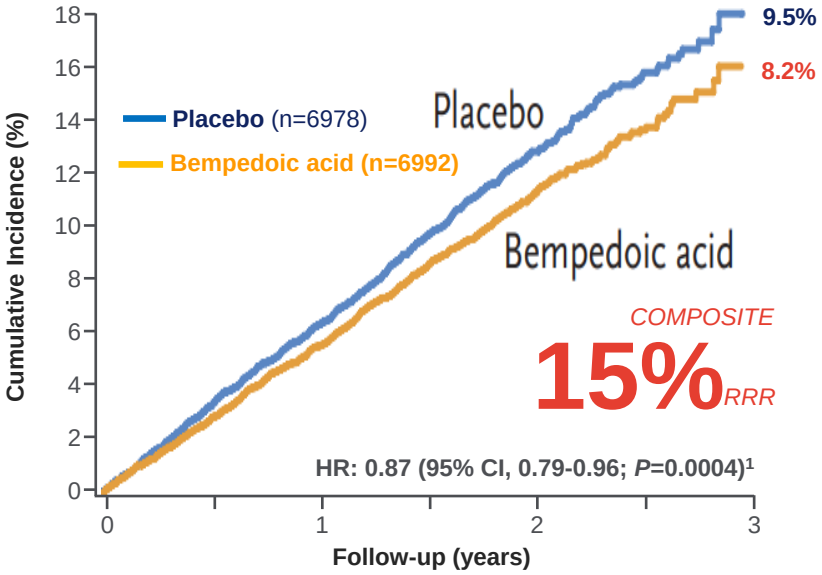
CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction.

1. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722.

Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid or Placebo (CLEAR Outcomes)

Stain→ Bempedoic Acid or Placebo

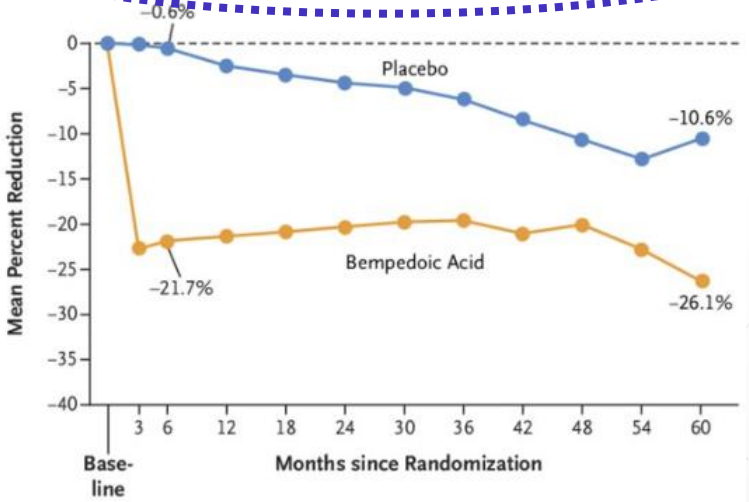
Key secondary endpoint : composite of CV death, MI, or stroke



23% MI[1] RRR

19% RRR Revascularization[1]

15% Stroke[1] RRR



1 Marc S. Sabatine, et al NEJM 2023

Changing the “concept” of lipid management

high-intensity statin

“ High-intensity ”

cholesterol-lowering therapy

Even with the highest doses of the most efficient statins, it is difficult to reduce LDL cholesterol beyond 50%.[1]

LDL-C : Low density lipoprotein cholesterol.

1. Luis Masana, *et al.* IMPROVE-IT clinical implications. Should the “high-intensity cholesterol-lowering therapy” strategy replace the “high-intensity statin therapy?”. *Atherosclerosis*. 2015;240:161-162.

Several questions and up-to-date evidence for ezetimibe combination therapy

1. Would adding ezetimibe to statin to lower LDL-C improve CV outcomes?

2. Is there any benefit of **moderate-intensity statin+ezetimibe therapy** compared to **high-dose statin therapy**?

- **Evidence:** moderate-intensity statin+ezetimibe compared with high-intensity statin **(RACING Trial)**
- **Evidence:** Comparative effectiveness of moderate-intensity statin+ezetimibe therapy VS high-intensity statin monotherapy in patients with ACS (a nationwide cohort study)

3. Which approach provides more benefit: high-intensity statin strategy or treat-to-target strategy?

RACING trial

Non-inferiority of moderate-intensity statin+ezetimibe compared with high-intensity statin in very high risk ASCVD patients

- **Objective** :

  1) To compare 3-year clinical efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients who are at very high risk for cardiovascular diseases

  2) To establish that adding ezetimibe to moderate-intensity statin could be an effective treatment for lowering cholesterol

- **Method** :

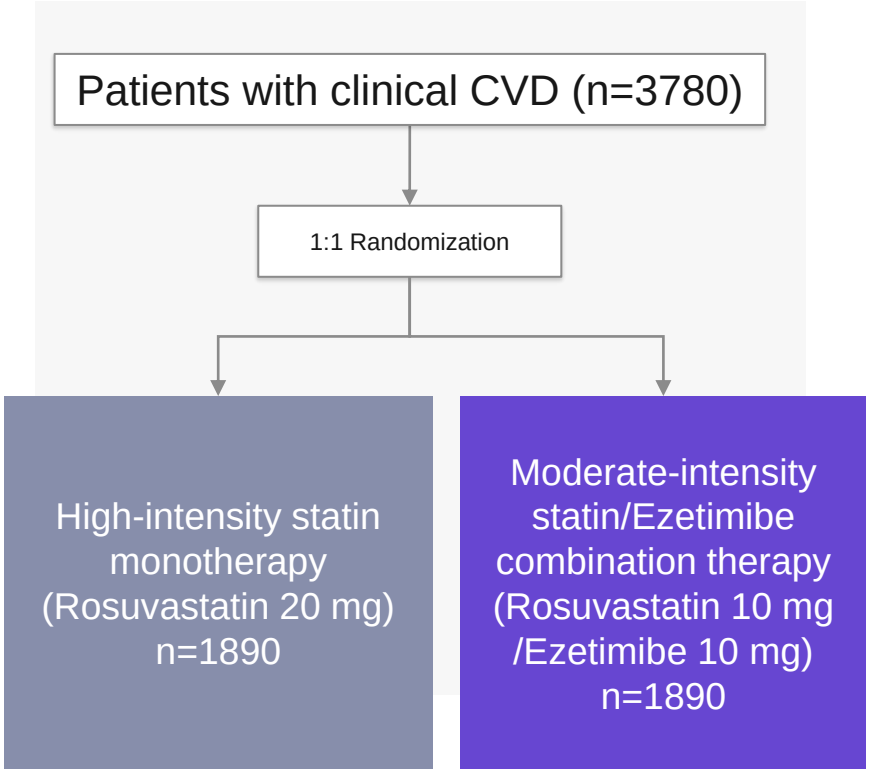
  Randomized, **open-label**, non-inferiority trial, 26 clinical centres in South Korea

- **Patients** :

  Documented ASCVD requiring high intensity statin therapy and achievement of LDL-C < 70 mg/dL*

- **Primary Endpoint** :

  The 3-year composite of **CVD**, major **CV events**, or **non-fatal stroke**, in the ITT population with a non-inferiority margin of 2.0%



* 양군의 LDL-C 평균은 80 mg/dL

RACING : Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease, **ASCVD :** Atherosclerotic cardiovascular disease, **LDL-C :** Low-density lipoprotein cholesterol, **CVD :** Cardiovascular disease, **CV :** Cardiovascular, **ITT :** Intention to treat

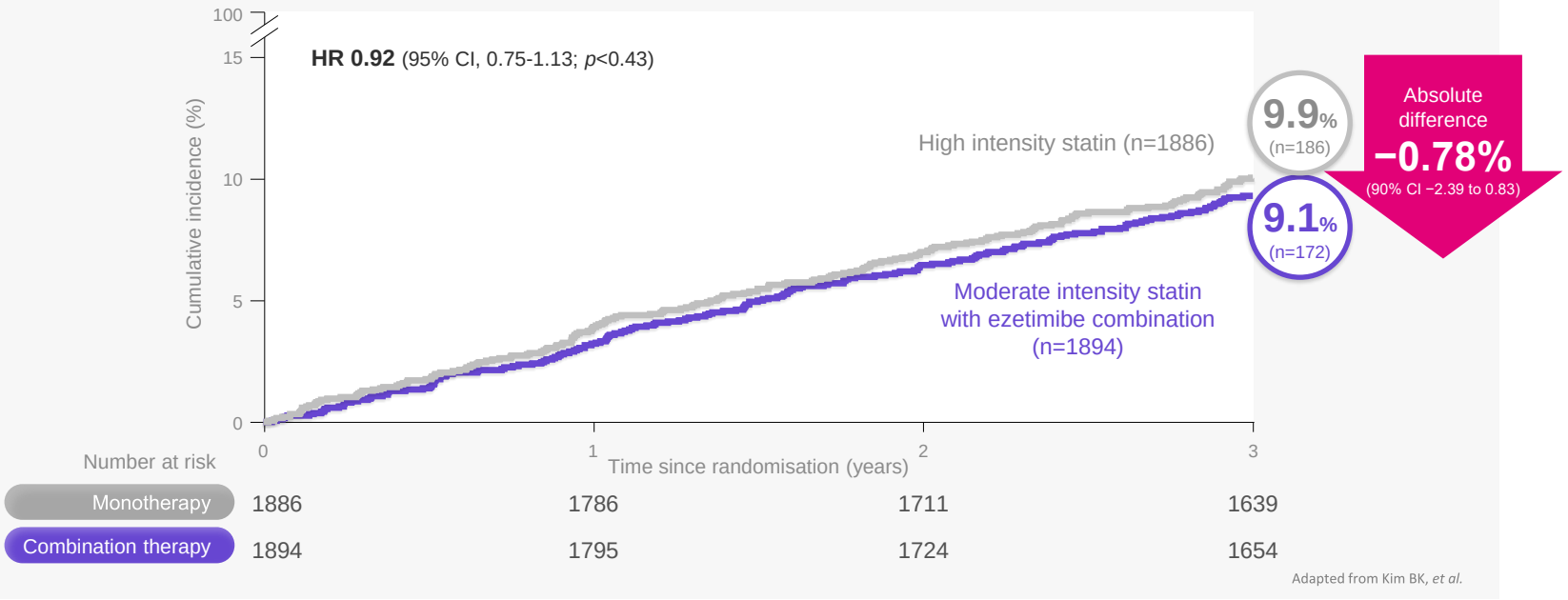
1. Kim BK, *et al*. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet*. 2022 Jul 30;400(10349):380-390.

RACING trial : ITT

Long-term efficacy of moderate-intensity statin with ezetimibe in patients with ASCVD

High intensity Stain vs Moderate intensity statin + ezetimibe

Kaplan-Meier curves of the primary endpoint* of the ITT population



Adapted from Kim BK, *et al.*

* Composite of cardiovascular death, major cardiovascular event, or non-fatal stroke

RACING : Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease, **ITT :** Intention to treat, **ASCVD :** Atherosclerotic cardiovascular disease, **HR :** Hazard ratio, **CI :** Confidence interval

Study design a. This RACING trial was a randomized, open-label, non-inferiority study was to to compare 3-year clinical efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients who are at very high risk for cardiovascular diseases. The trial was enrolled 3,780 patients from 26 clinical centres in South Korea who were randomly assigned (1:1) (each 1,890) to receive either moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg). The primary endpoint was the 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2.0%.

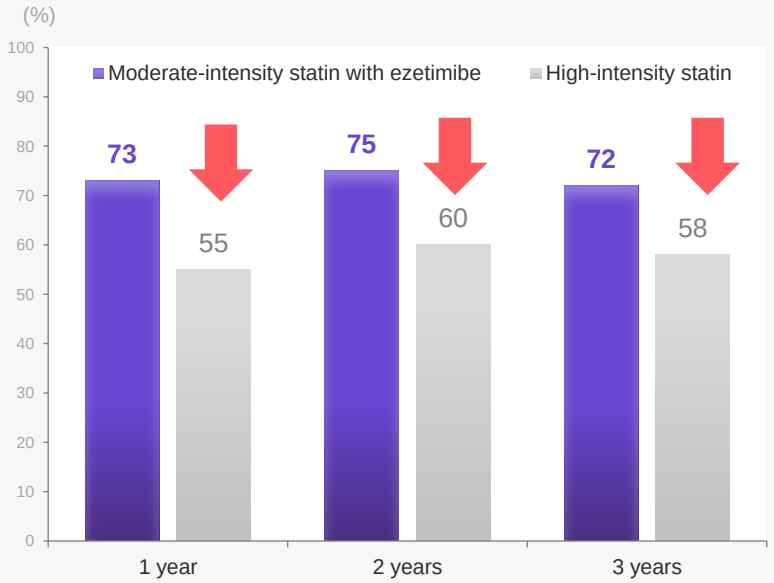
1. Kim BK, *et al.* Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet.* 2022 Jul 30;400(10349):380-390.

RACING trial : ITT

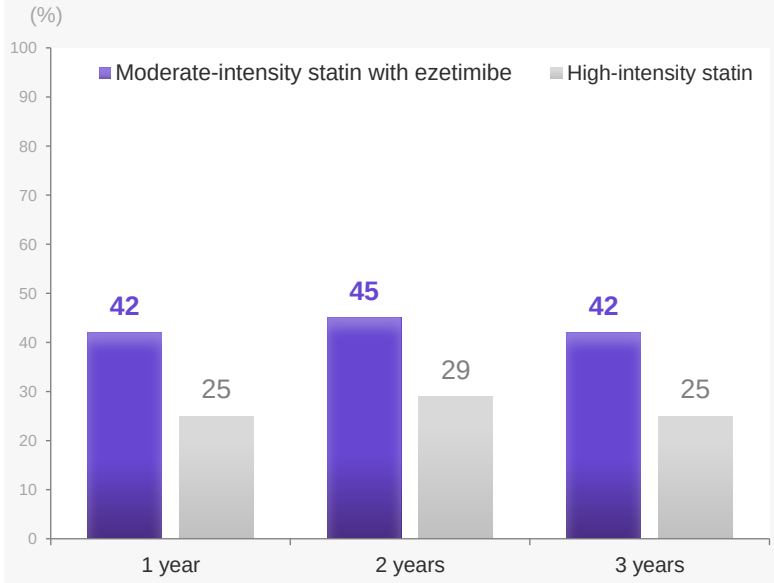
LDL-C goal achievement was higher in moderate-intensity statin with ezetimibe

High intensity Stain vs Moderate intensity statin + ezetimibe

LDL-C <70 mg/dL in the ITT population (%)



LDL-C <55 mg/dL in the ITT population (%)*



Adapted from Kim BK, *et al.*

* post-hoc analysis: LDL-C < 55 mg/dL at 1, 2, and 3 years were observed in 42%, 45%, and 42% of patients in the combination therapy group and 25%, 29%, and 25% of patients in the high-intensity statin monotherapy group, respectively(absolute difference 17.5% [95% CI 14.3–20.7] at 1 year; 14.9% [95% CI 11.7–18.2] at 2 years; 14.8% [95% CI 11.2–18.3] at 3 years).

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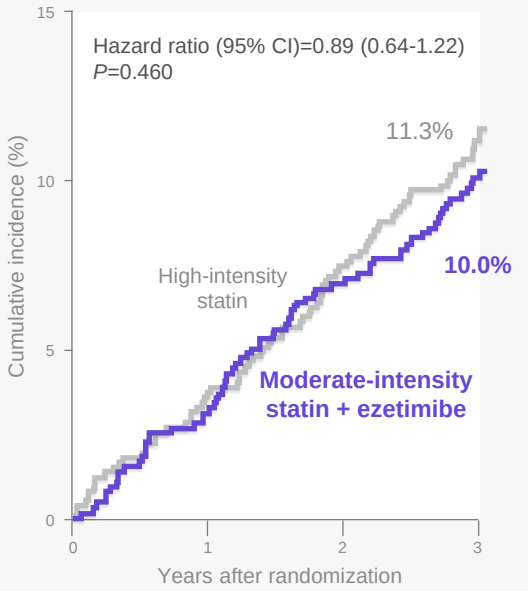
RACING trial DM cohort

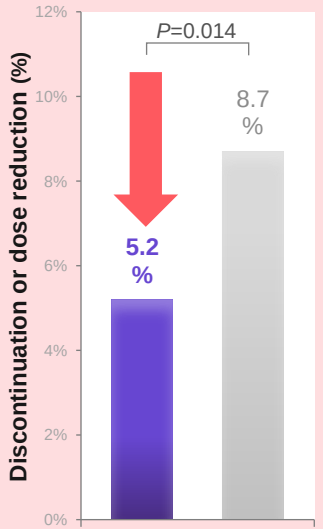
Non-inferiority of moderate-intensity statin + ezetimibe compared with high-intensity statin in patients with DM

High intensity Stain vs Moderate intensity statin + ezetimibe

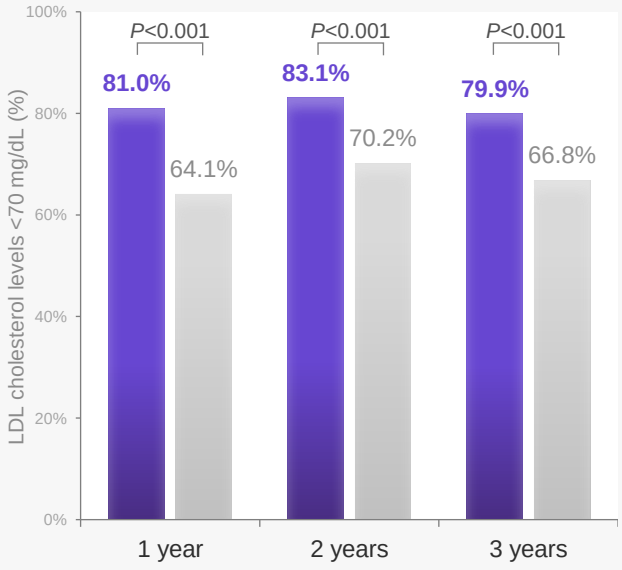
Composite cardiovascular outcomes



Intolerance



LDL cholesterol reduction



Adapted from Lee YJ, *et al.*

RACING : Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease, **DM :** Diabetes mellitus, **LDL :** Low-density lipoprotein, **CI :** Confidence interval

Study design a. This study was to evaluated the effect of moderate-intensity statin with ezetimibe combination therapy vs. high-intensity statin monotherapy among patients with diabetes mellitus (DM) and atherosclerotic cardiovascular disease (ASCVD) with a pre-specified stratified subgroup analysis of the DM cohort in the RACING trial. Among the total patients (N=3,780), 1,398 patients had at DM at baseline to receive moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg, n=701) or high-intensity statin monotherapy (rosuvastatin 20 mg, n=697). The primary outcome was a 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke.

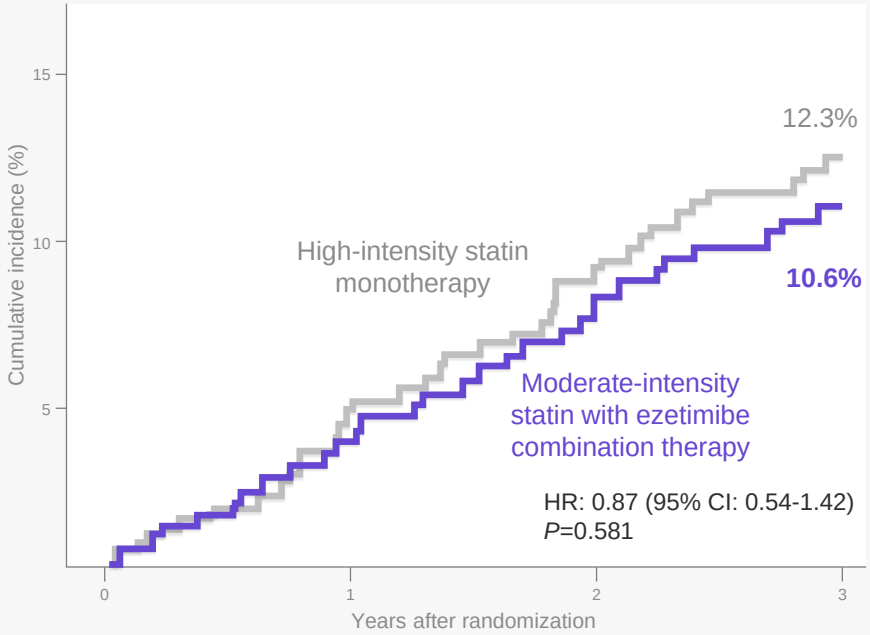
1. Lee YJ, *et al*. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. *Eur Heart J*. 2023 Mar 14;44(11):972-983.

RACING trial Elderly cohort

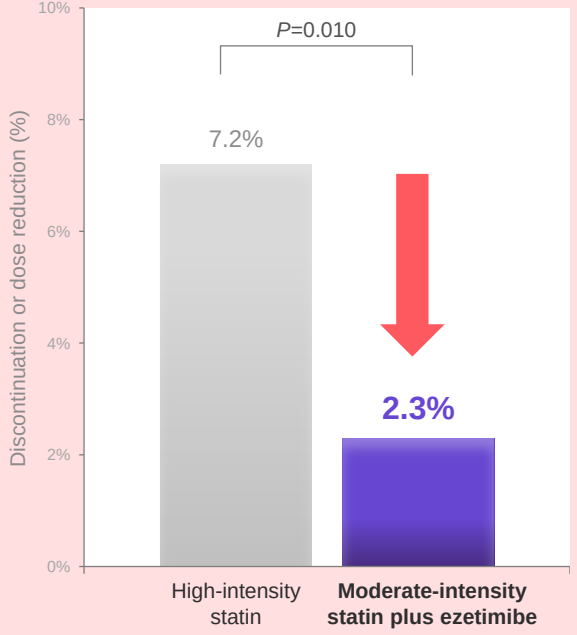
Non-inferiority of moderate-intensity statin + ezetimibe compared with high-intensity statin in elderly patients with ASCVD

High intensity Stain vs Moderate intensity statin + ezetimibe

3-Year composite CV events



Drug discontinuation or dose reduction



Adapted from Lee SH, *et al.*

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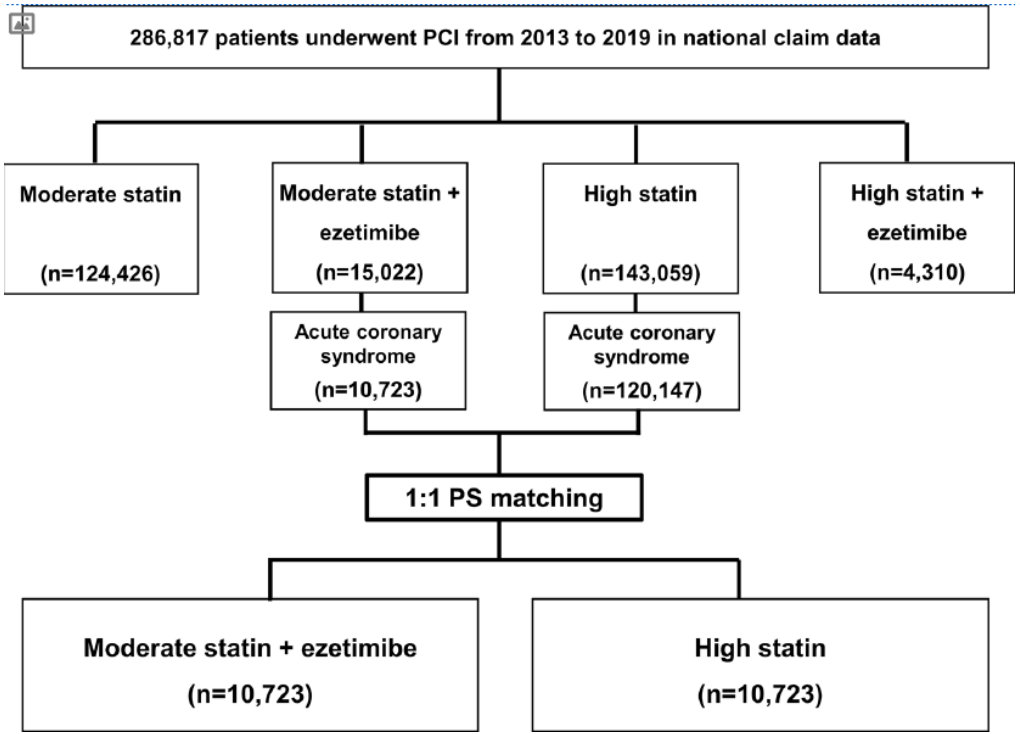
Study design a. This cohort RACING (Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease) study was to evaluate the impact of moderate-intensity statin with ezetimibe combination therapy compared with high-intensity statin monotherapy in elderly patients with atherosclerotic cardiovascular disease (ASCVD). 3,780 patients were enrolled, 574 patients were aged ≥75 years. The primary endpoint was a 3-year composite of cardiovascular death, major cardiovascular events, or nonfatal stroke.

1. Lee SH, *et al*. Combination Moderate-Intensity Statin and Ezetimibe Therapy for Elderly Patients With Atherosclerosis. *J Am Coll Cardiol*. 2023 Apr 11;81(14):1339-1349.

nationwide cohort study

Comparative effectiveness of moderate-intensity statin+ezetimibe therapy VS high-intensity statin monotherapy in patients with ACS

High intensity Stain vs Moderate intensity statin + ezetimibe

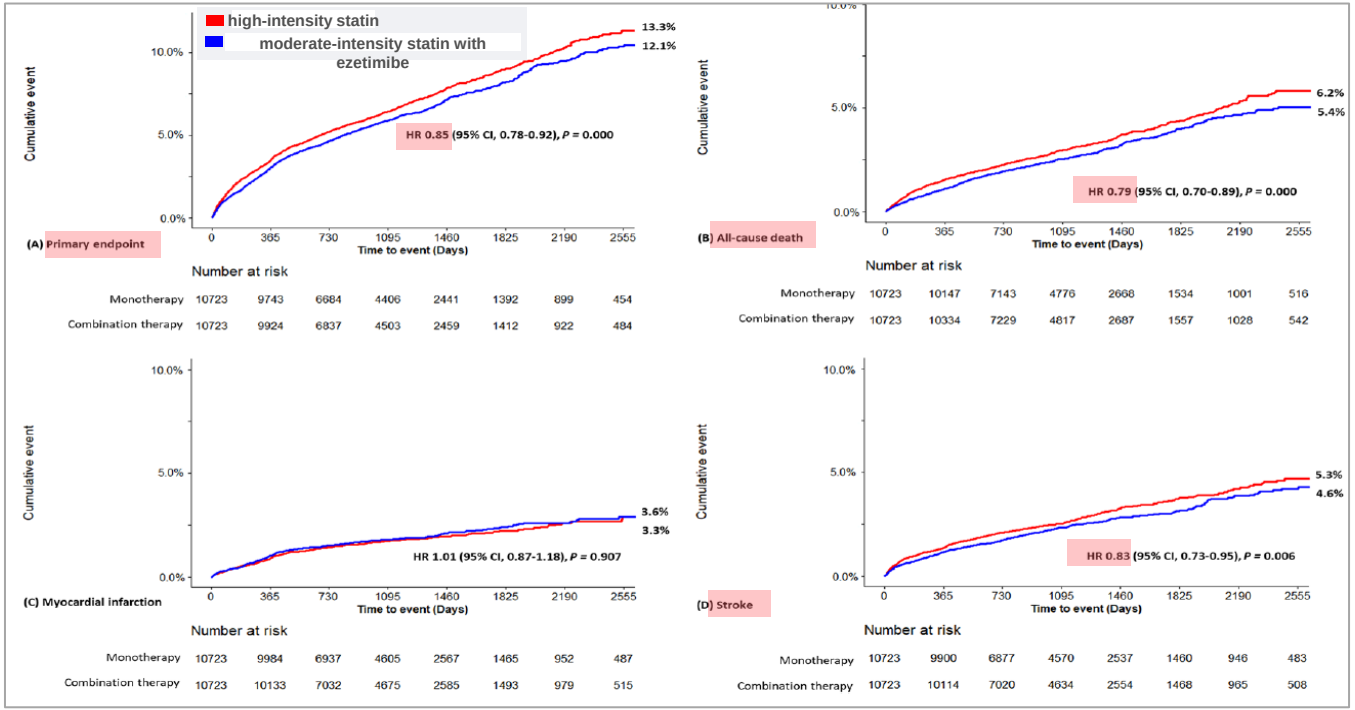


Comparative effectiveness of moderate.intensity statin with ezetimibe therapy versus high.intensity statin monotherapy in patients with acute coronary syndrome: a nationwide cohort study
Scientific Reports |(2024) 14:838 | https://doi.org/10.1038/s41598-024-51310-5

nationwide cohort study

The risk and incidence of the primary outcome were significantly lower in the moderate-intensity statin with ezetimibe combination group. (HR 0.85, 95% CI 0.78–0.92)

- **Kaplan–Meier curves of the primary endpoint (composite of all-cause death, myocardial infarction, and Stroke) in matched population.**



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1. Would adding ezetimibe to statin to lower LDL-C improve CV outcomes?

2. Is there any benefit of moderate-intensity statin+ezetimibe therapy compared to high-dose statin therapy?

3. Which approach provides more benefit: high-intensity statin strategy or treat-to-target strategy?

- **Evidence: Treat-to-target VS high-intensity statin in patients with CAD (LOADSTAR Trial)**

LODESTAR trial

Non-inferiority of treat-to-target of 50-70 mg/dL compared with high-intensity statins on 3 year MACE in patients with CAD

- **Objective** :

  1) Question is treatment to a goal low density lipoprotein (LDL-C) level between 50 ~ 70 mg/dL noninferior to a strategy using high intensity statin therapy among patients with coronary artery disease

- **Method** :

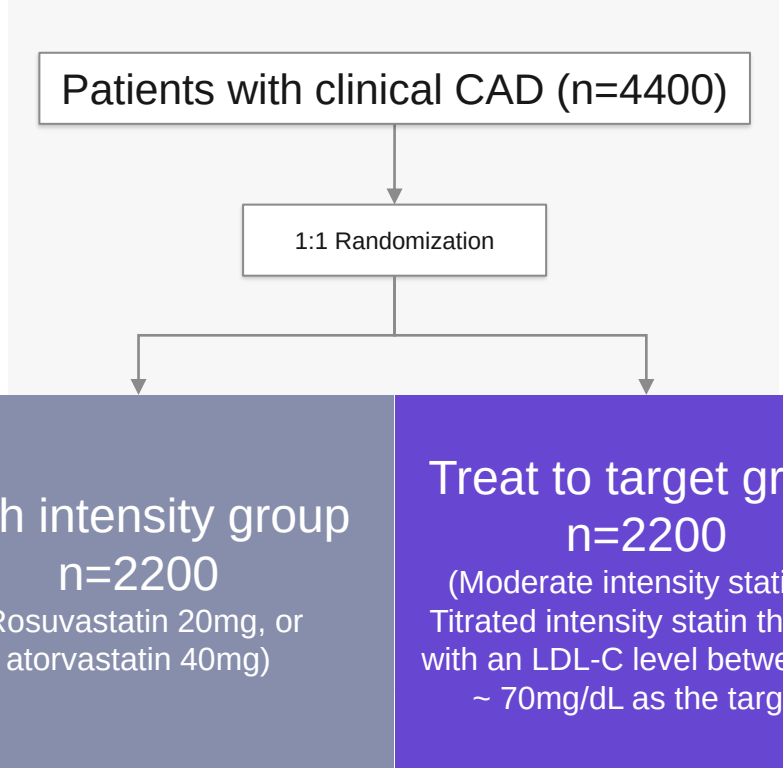
  Randomized, **open-label**, non-inferiority trial, 12 clinical centres in South Korea

- **Patients** :

  Documented coronary artery disease (mean age: 65.1 years)

- **Primary Endpoint** :

  The 3-year composite of **death**, myocardial infarction, stroke or coronary revascularization with a non-inferiority margin of 3.0%



* 양군의 LDL-C 평균은 80 mg/dL

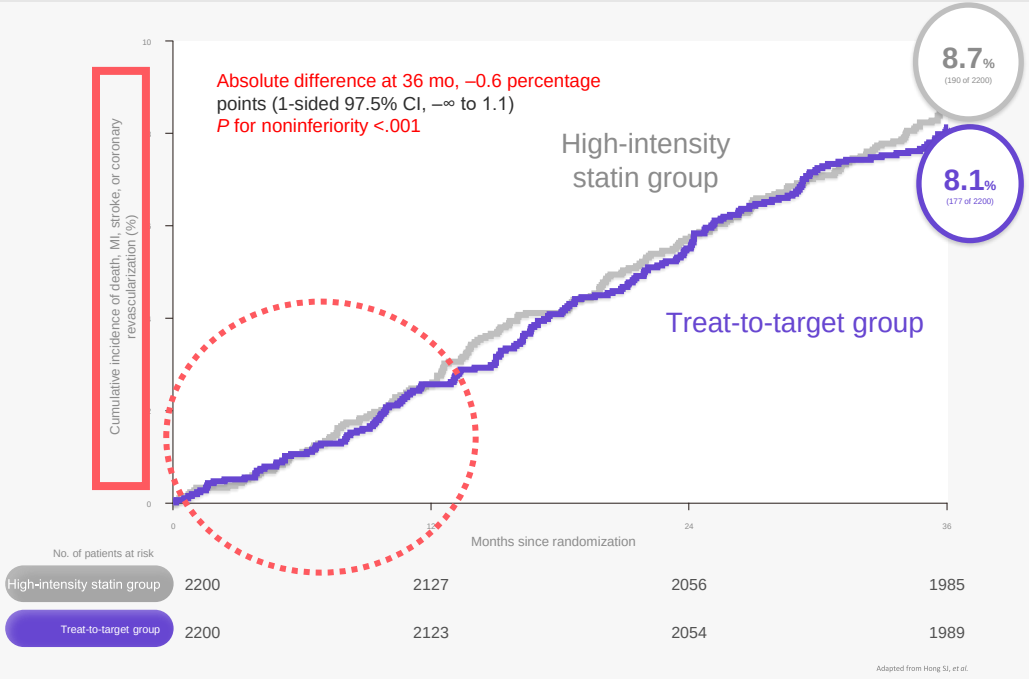
RACING : Randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease, **ASCVD :** Atherosclerotic cardiovascular disease, **LDL-C :** Low-density lipoprotein cholesterol, **CVD :** Cardiovascular disease, **CV :** Cardiovascular, **ITT :** Intention to treat

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

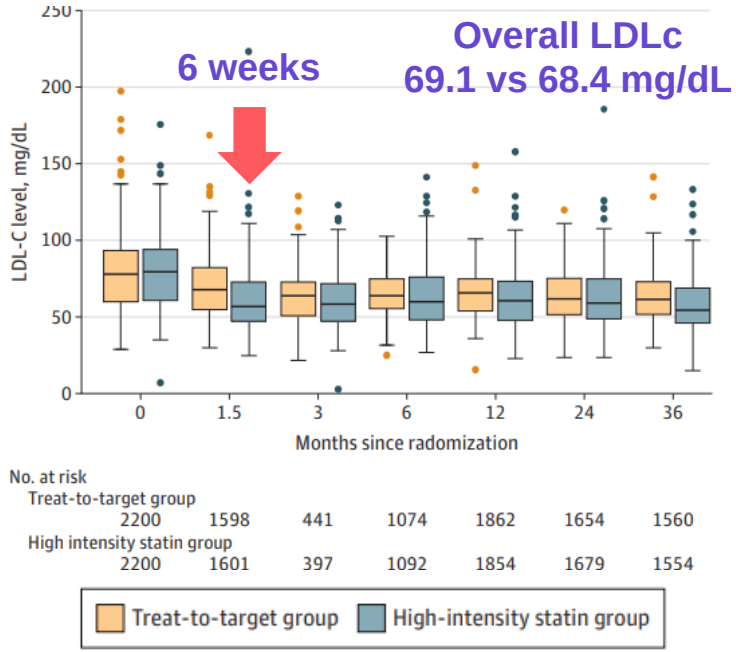
LODESTAR trial

Non-inferiority of treat-to-target of 50-70 mg/dL compared with high-intensity statins on 3 year MACE in patients with CAD

Cumulative incidence of the primary end point



Change in LDL-C levels



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

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

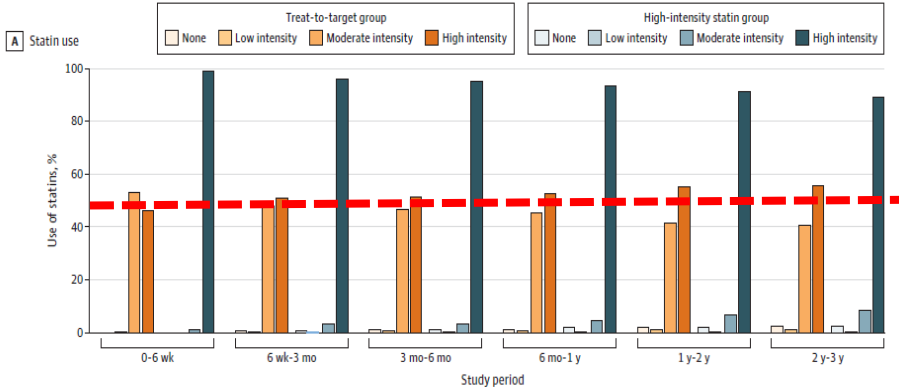
1. Hong SJ, *et al.* Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease: A Randomized Clinical Trial. *JAMA*. 2023 Apr 4;329(13):1078-1087.

Lipid-lowering treatment during study

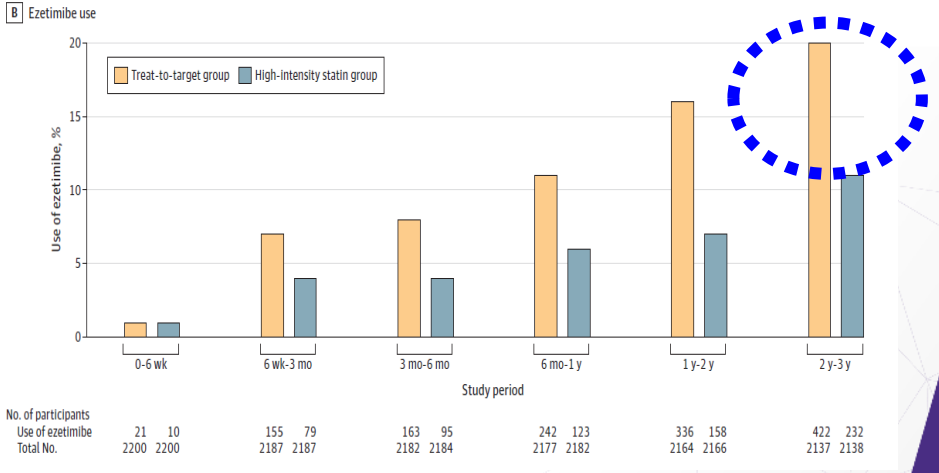
- In the **treat-to-target group**, **53%** were taking the high-intensity statin at 1 year, 55% at 2 years, and 56% at 3 years

- In the **high-intensity statin therapy group**, **93%** were taking the high-intensity statin at 1 year, 91% at 2 years, and 89% at 3 years

- **Ezetimibe** was **used more in the treat-to-target group** than in the high-intensity statin therapy group from 6 months, mostly as a combination therapy with high-intensity statin therapy.



No. of participants												
High intensity	1022	2176	1116	2099	1125	2080	1144	2036	1197	1975	1194	1903
Moderate intensity	1173	24	1047	70	1019	76	989	99	900	143	868	182
Low intensity	5	0	10	2	13	3	14	4	25	4	26	3
None	0	0	14	16	25	25	30	43	42	44	49	50
Total No.	2200	2200	2187	2187	2182	2184	2177	2182	2164	2166	2137	2138



No. of participants												
Use of ezetimibe	21	10	155	79	163	95	242	123	336	158	422	232
Total No.	2200	2200	2187	2187	2182	2184	2177	2182	2164	2166	2137	2138

LODESTAR trial

Lower rates of diabetes, kidney disease, lab abnormalities in the treat-to-target group compared with high-intensity statin group

Secondary end points at 3 years after randomization

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

25%

[Excerpt]

* The between-group difference was measured in the treat-to-target group compared with the high-intensity statin group. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. ** Aminotransferase elevation was defined as greater than baseline level and more than 3 times the upper limit of reference. Creatine kinase elevation was defined as greater than baseline level and more than 5 times the upper limit of reference. Creatinine level elevation was defined as greater than 50% increase from baseline and greater than the upper limit of reference. Reference values may vary based on laboratory and location.

LODESTAR : Low-Density Lipoprotein Cholesterol-Targeting Statin Therapy Versus Intensity-Based Statin Therapy in Patients With Coronary Artery Disease, **CI :** Confidence interval

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

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

LODESTAR trial

Treat-to-Target or high-intensity statin in patients with CAD

Benefit of Treat to target

Among patients with coronary artery disease, **the treat-to-target LDL-C strategy was noninferior to the high-intensity statin strategy** for major clinical outcomes and associated with a significantly lower rate of safety profile.

Need for aggressive Cholesterol-lowering

In the treat-to-target group, the proportion who met the target was 58% at 3 years. This number is attributed to the relatively **low use of nonstatin add-on therapy such as ezetimibe though recent guidelines strongly recommend its use.**
These findings highlight the **need for intensive efforts to attain the target LDL-C level.**

A tailored approach for individual

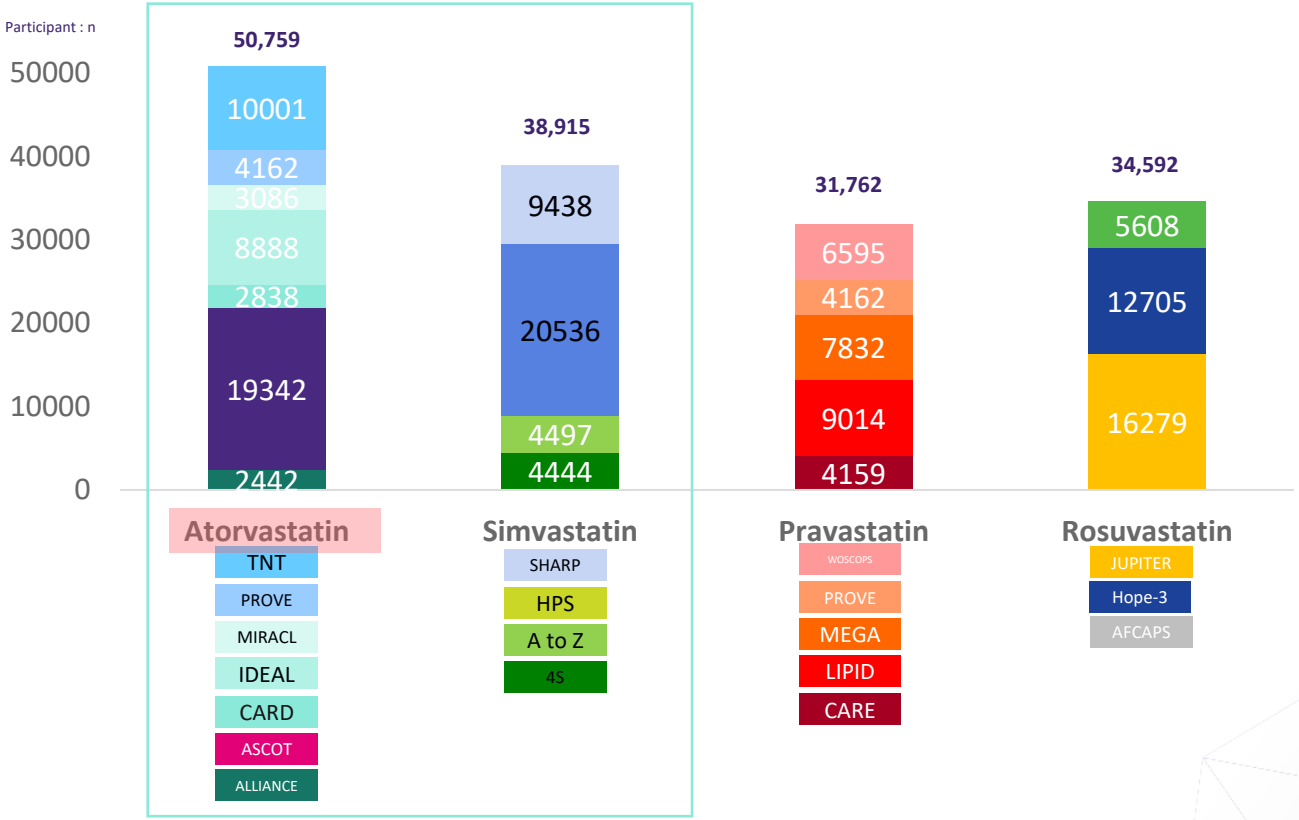
The suitability of a treat-to-target strategy may allow **a tailored approach with consideration for individual variability in drug response to statin therapy.**

LODESTAR : Low-Density Lipoprotein Cholesterol-Targeting Statin Therapy Versus Intensity-Based Statin Therapy in Patients With Coronary Artery Disease, **LDL-C :** Low-density lipoprotein cholesterol, **CAD :** Coronary artery disease

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

Contents

Tower of Evidence : RCT of statins based on Statins in Outcome trials



RCT : randomized controlled trials.

1. Raymond C, *et al.* New cholesterol guidelines: Worth the wait? *Cleve Clin J Med.* 2014;81(1):11-9.

Subgroup analysis studies are excluded due to participants # is duplicated

ESC/EAS Recommendations for lipid management in patients with moderate to severe CKD

2016 ESC/EAS Recommendations for lipid management [1]

Table 30 Recommendations for lipid management in patients with moderate to severe chronic kidney disease

Recommendations	Class[a]	Level[b]
Patients with stage 3-5 CKD have to be considered at high or very high CV risk.	I	A
The use of statins or statin/ ezetimibe combination is indicated in patients with non-dialysis dependent CKD.	I	A
In patients with dialysis-dependent CKD and free of atherosclerotic CVD, statins should not be initiated.	III	A
In patients already on statins, ezetimibe or a statin/lezetimibe combination at the time of dialysis initiation, these drugs should be continued, particularly in patients with CVD.	IIa	C
In adult kidney transplant recipients treatment with statins may be considered.	IIb	C

Adapted from 2016 ESC/EAS *et al.*[2]

CKD : Chronic kidney disease, CV : Cardiovascular.
[a]Class of recommendation
[b]Level of evidence

Safety of lipid management in patients with Chronic Kidney Disease[1]

Statins that are eliminated mainly by the **hepatic route** may be **preferred**

(fluvastatin, atorvastatin, pitavastatin)

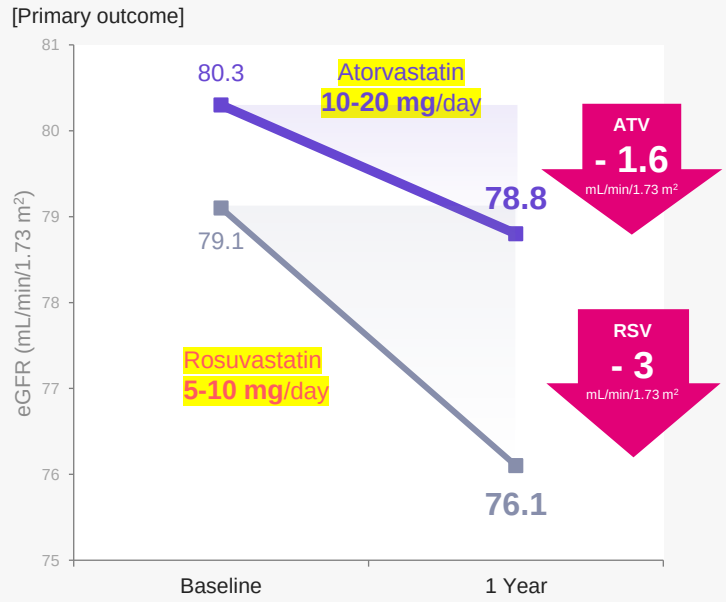
ESC : European society of cardiology, EAS : European atherosclerosis society, LDC-C : Low-density lipoprotein-cholesterol, PCSK9 : Proprotein convertase subtilisin/kexin type 9

1. 2016 ESC/EAS Guidelines for the Management of Dyslipidemias. *European Heart Journal.* 2016 Aug 27. [Epub ahead of print]. doi:10.1093/eurheartj/ehw272.

Retrospective study in Korea

Atorvastatin in diabetic patients is more beneficial in preserving the eGFR than rosuvastatin

eGFR reduction eGFR after statin use



Odds ratio and 95% CI of rapid renal function decline (>3% per Year) according to statin types

Variable	Atorvastatin 10-20 mg/day	Rosuvastatin 5-10 mg/day	*P* value
Crude	1 (reference)	1.51 (1.04-2.18)	0.030
Model 1‡	1 (reference)	1.48 (1.01-2.15)	0.042
Model 2§	1 (reference)	1.48 (1.00-2.20)	0.052
Model 3¶	1 (reference)	1.60 (1.06-2.42)	0.026

60%

‡ Model 1: adjusted for age and sex § Model 2: adjusted for age, sex, diabetes duration, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, systolic blood pressure, and hypertension ¶ Model 3: adjusted for age, sex, diabetes duration, ACE inhibitor/ARB use, systolic blood pressure, hypertension, baseline glomerular filtration rate, Low-density lipoprotein cholesterol change, triglyceride change, and glycated hemoglobin change

eGFR : Estimated glomerular filtration rate, **ATV :** Atorvastatin, **RSV :** Rosuvastatin, **CI :** Confidence interval

Study design a. This retrospective study aimed to investigate whether, and which, statins affected renal function in Asian patients with diabetes notes using the electronic medical records at Severance Hospital, a tertiary university hospital in Korea. This study enrolled 484 patients with diabetes who received moderate-intensity dose statin treatment (atorvastatin 10 to 20 mg/day [n=295] or rosuvastatin 5 to 10 mg/day [n=189) for more than 12 months. The primary outcome was a change in estimated glomerular filtration rate (eGFR) during the 12-month statin treatment, and rapid renal decline was defined as a >3% reduction in eGFR in a 1-year period.

1. Han E, *et al*. Comparison between Atorvastatin and Rosuvastatin in Renal Function Decline among Patients with Diabetes. *Endocrinol Metab*. 2017;32(2):274-280.

Real-world data links rosuvastatin with signs of kidney damage

- Despite reports of hematuria and proteinuria with rosuvastatin use at the time of its approval by the FDA, little postmarketing surveillance exists to assess real-world risk.
- This study is **one of the first and largest real-world studies** examining **rosuvastatin vs. atorvastatin on the risk of kidney damage** in a heterogeneous population.

Method

Target trial emulation with inverse probability of treatment weighting (IPTW) using data from optumlabs data warehouse

152,101 rosuvastatin new users

vs.

795,799 atorvastatin new users

Safety

- Hematuria
- Proteinuria
- Kidney failure

Benefit

- ASCVD

HR for Renal and ASCVD outcome of Rosuvastatin (vs. Atorvastatin)

Outcome	HR (95% CI)
Hematuria	**1.08 (1.04-1.11)**
Proteinuria	**1.17 (1.10-1.25)**
Kidney failure	**1.15 (1.02-1.30)**
ASCVD	1.02 (0.96-1.08)

※ Labeling suggests dose reduction (maximum daily dose of 10 mg) for patients with severe CKD.

FDA : Food and Drug Administration, **ASCVD :** Atherosclerotic cardiovascular disease, **HR :** Hazard ratio, **CI :** Confidence interval

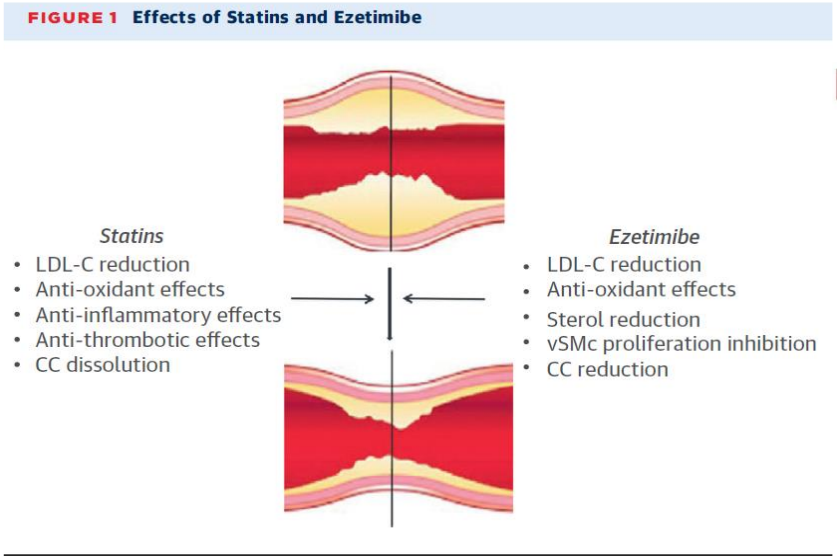
Study design a. This multicenter observational cohort study aimed to assess the associations of rosuvastatin use versus atorvastatin use with the risk of hematuria and proteinuria across the range of kidney function, and rosuvastatin-dosing practice patterns in relation to kidney function. This study analyzed deidentified electronic health record data with 152,101 and 795,799 new users of rosuvastatin and atorvastatin, respectively, from 2011 to 2019. The main outcome was the initial rosuvastatin dose across eGFR categories and evaluated for a dose effect on hematuria and proteinuria.

1. Shin JI, *et al*. Association of Rosuvastatin Use with Risk of Hematuria and Proteinuria. *J Am Soc Nephrol.* 2022 Sep;33(9):1767-1777.

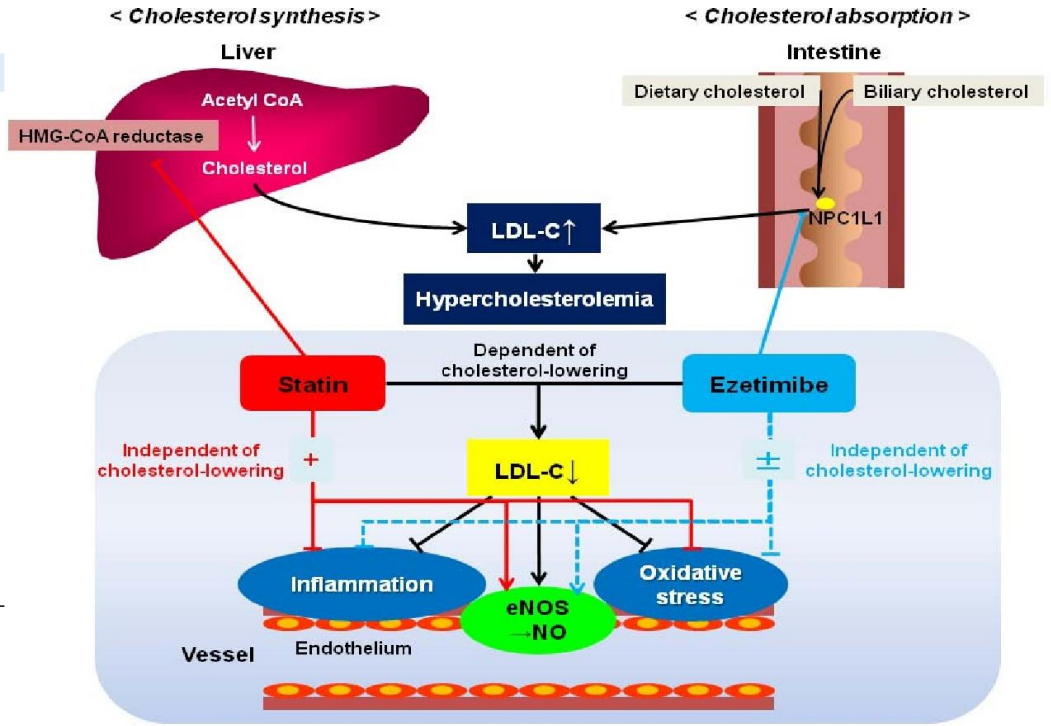
Contents

Complementary Effect of statin and ezetimibe combination therapy

FIGURE 1 Effects of Statins and Ezetimibe



Various mechanisms mediate the beneficial effects of statins and ezetimibe on plaque growth. CC = cholesterol crystals; LDL-C = low-density lipoprotein cholesterol; vSMC = vascular smooth muscle cells.

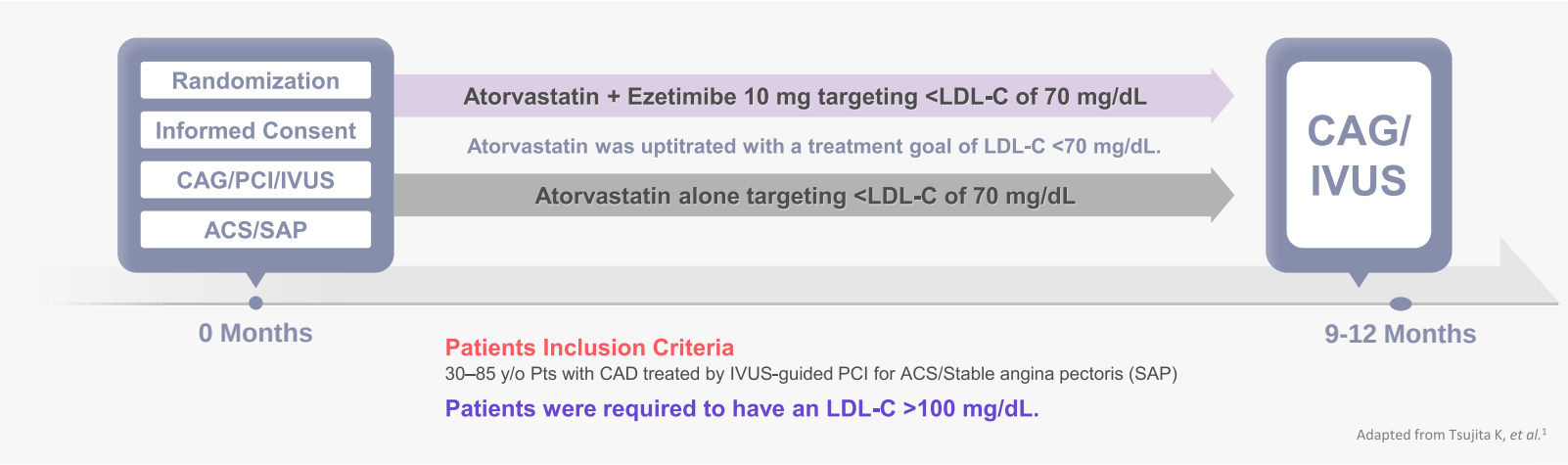


Crea and Niccoli, *JACC 2015;66 (5):508-10.*

PRECISE-IVUS Trial

Atozet on Coronary Plaque Regression in Patients With PCI

- The aim of this study was to evaluate the effects of ezetimibe plus atorvastatin versus atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent PCI.[1]



Adapted from Tsujita K, *et al.*[1]

- **Eligible 246 pts who underwent PCI were randomly assigned to atorvastatin alone (n=124) or atorvastatin + ezetimibe (n=122) daily.[1]**

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

PCI : Percutaneous coronary intervention, **ACS** : Acute coronary syndrome, **IVUS** : Intravascular ultrasound, **CAD** : Coronary artery disease, **PAD** : Peripheral artery disease, **SAP** : Stable angina pectoris, **CAG** : Coronary angiography, **LDL-C** : Low-density lipoprotein cholesterol, **HDL-C** : High-density lipoprotein cholesterol, **DM** : Diabetes mellitus, **HTN** : Hypertension, **TG** : Triglyceride, **PRECISE-IVUS Trial** : Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound, **y/o :** Year-olds

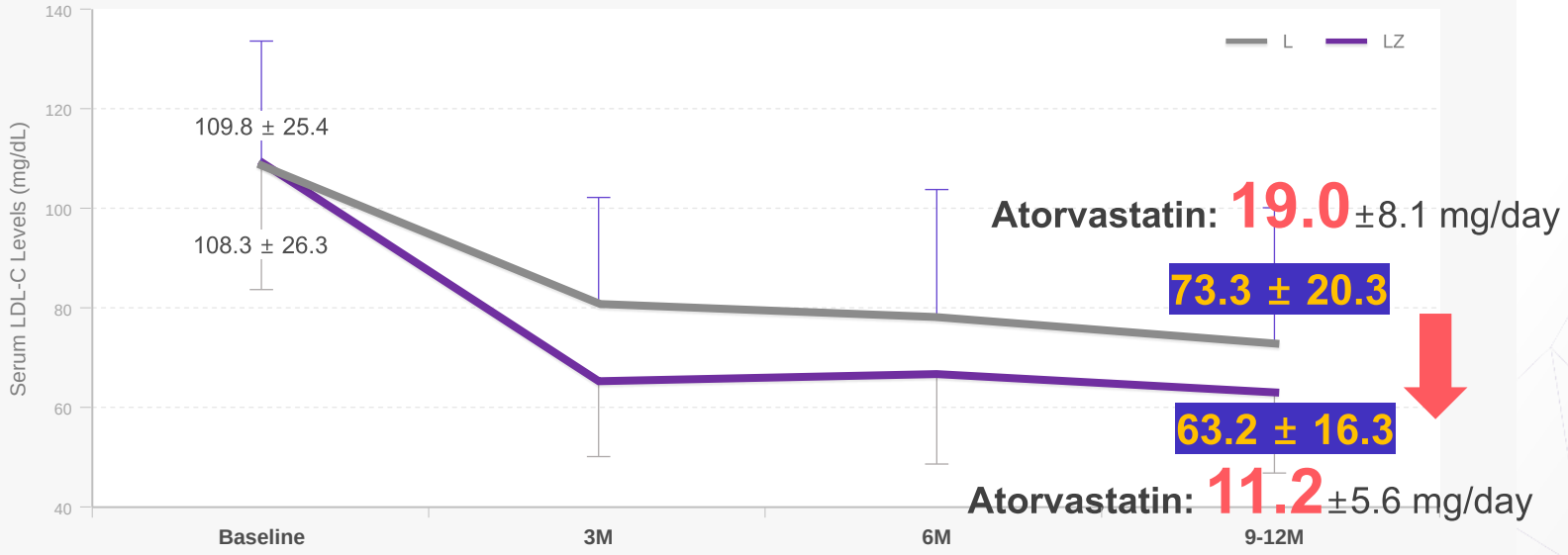
1. Tsujita K, *et al.* Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. *J Am Coll Cardiol* 2015;66:495–507

PRECISE-IVUS Trial

Atozet on Coronary Plaque Regression in Patients With PCI

- The **f/u LDL-C level** at 9-12 months(63.2±16.3 vs. 73.3±20.3 mg/dL) and the **final dosage of atorvastatin were significantly lower** in the **ezetimibe/atorvastatin (LZ)** group than in the atorvastatin (L) group. The goal achievement rate of LDL-C <70 mg/dL was significantly higher in the LZ group(72% vs. 47%).[1]

Baseline and Follow up LDL-C data



Adapted from Tsujita K, *et al.*[1]

PRECISE-IVUS Trial : Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound, **PCI** : Percutaneous coronary intervention, **LDL-C** : Low-density lipoprotein cholesterol

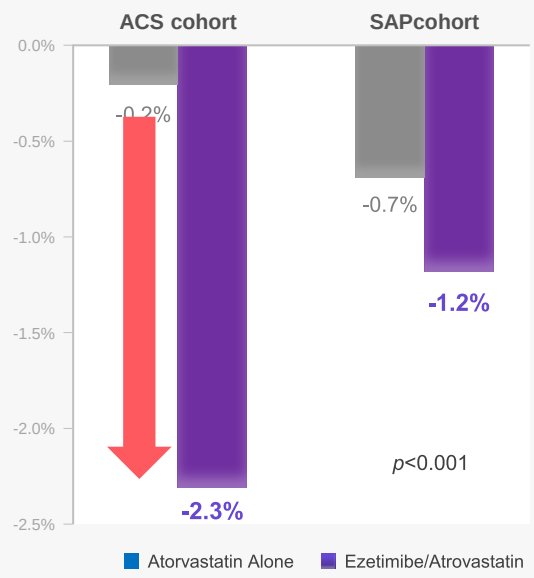
1. Tsujita K, *et al.* Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. *J Am Coll Cardiol* 2015;66:495–507

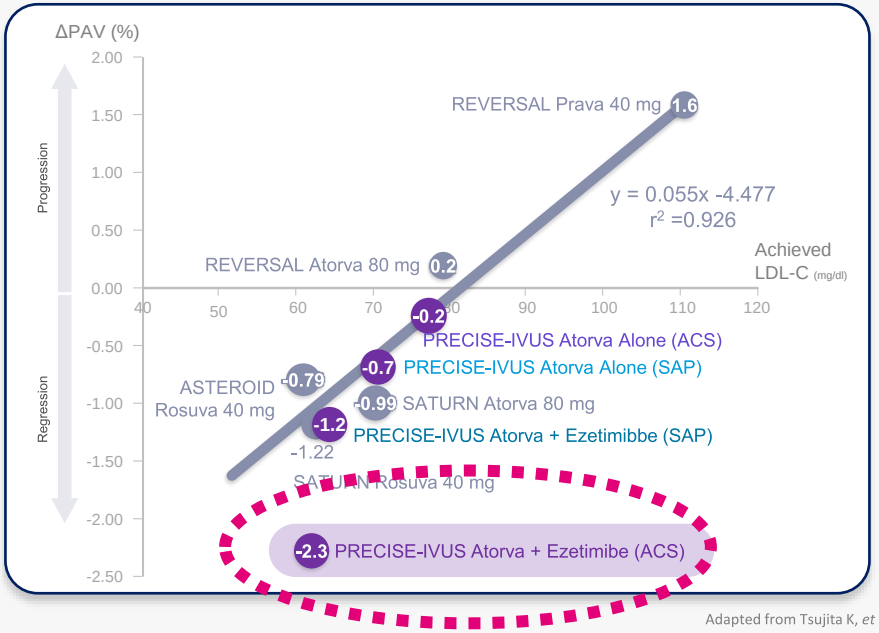
PRECISE-IVUS Trial

Atozet on Coronary Plaque Regression in Patients With PCI

- **Aggressive dual lipid-lowering with atorvastatin/ezetimibe** might **reverse the coronary plaque development process** in patients with ACS rather than with SAP.[1]

% Change in Atheroma Volume





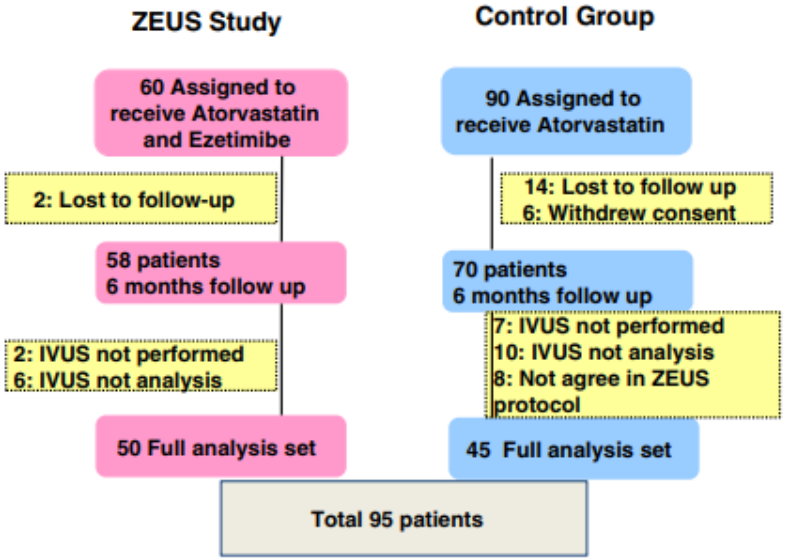
Adapted from Tsujita K, *et al.*[1]

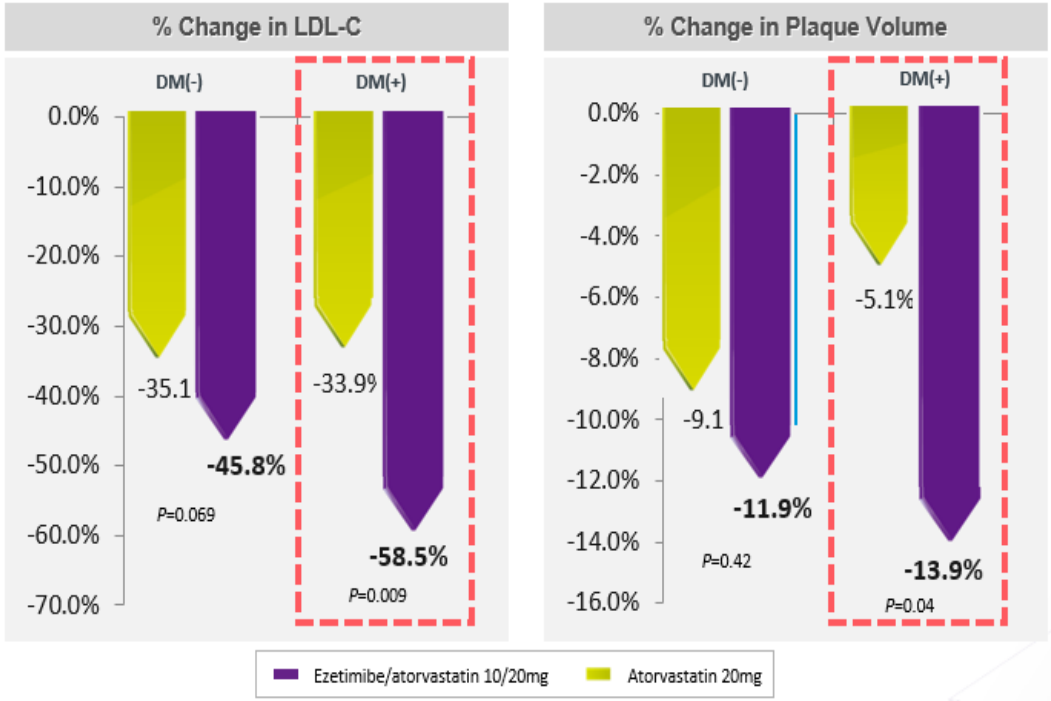
PRECISE-IVUS Trial : Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound, **PCI** : Percutaneous coronary intervention, **ACS** : Acute coronary syndrome, **ASTEROID** : A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound–Derived Coronary Atheroma Burden, **Atorva** : Atorvastatin, **ΔPAV :** Absolute change in percent atheroma volume, **Prava** : Pravastatin, **REVERSAL** : Reversal of Atherosclerosis With Aggressive Lipid-Lowering, **SAP** : Stable angina pectori, **SATURN** : Study of Coronary Atheroma by Intravascular Ultrasound, **Rosuva :** Rosuvastatin, **LDL-C** : Low-density lipoprotein cholesterol

1. Tsujita K, *et al.* Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. *J Am Coll Cardiol* 2015;66:495–507

ZEUS Trial

ATOZET demonstrated a stronger reduction in LDL-C levels and Plaque Regression in 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.

1. *N. Nakajima et al. IJC Metabolic & Endocrine* 3 (2014) 8–13

Summary

❶ Ezetimibe Combination Therapy: Clinical Evidence and Benefits

- **Evidence for Changing Lipid Management Strategy to Focus on Ezetimibe Combination Therapy.**

1) IMPROVE-IT Trial: This trial demonstrated that adding Ezetimibe to statin therapy reduces LDL-C levels and the risk of cardiovascular events. Additionally, it confirms the long-term safety profile of Ezetimibe.

2) RACING Trial: moderate-intensity statin + ezetimibe therapy was inferior to high-dose statin therapy regarding CV outcomes. However, it showed an improved safety profile and compliance.

3) LOADSTAR Trial: This trial compared the treat-to-target strategy with high-intensity statin therapy and found the former to be inferior in CV outcomes. Nevertheless, it showed an improved safety profile and compliance.
It suggests that a tailored approach is needed for individuals, considering their cardiovascular risk and medication compliance, rather than relying solely on statin therapy

❷ A Comparison of Statin Molecules for Dyslipidemia Management

- Atorvastatin has extensive scientific evidence from primary to secondary prevention and from moderate to high-intensity doses.
- Atorvastatin has been shown to provide renal protection in various clinical trials and real-world studies.

❸ The Role of Atorvastatin/Ezetimibe Combination Therapy in ASCVD High-risk Patients

- The statin/ezetimibe combination exhibited a more plaque regression compared to stain alone in high-risk ASCVD patients.
- The significant favorable effect of the dual lipid-lowering strategy on the coronary atherosclerotic development was pronounced, especially in the ACS cohort