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# Recent Trends and Clinical Evidence for Optimizing Lipid Management

## : A Focus on the strategies of LDL management

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※ This material contains disease information relating to LDL-C level and CVD. Not all Organon LDL-C lowering products have indications on CVD treatment. Please refer to the SSI inserted. Only Zocor (simvastatin) has indications of CVD risk reduction.

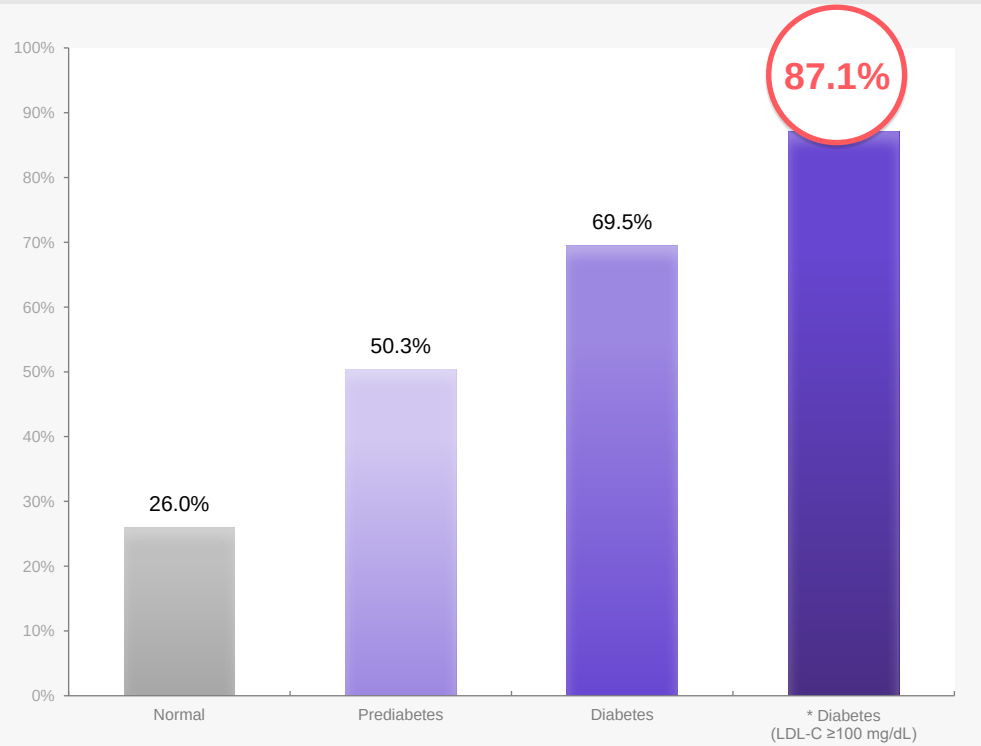
**LDL-C** : Low-density lipoprotein cholesterol

ORGANON

# Dyslipidemia according to comorbidity status in Korea

- Almost 90% of people with diabetes have dyslipidemia.

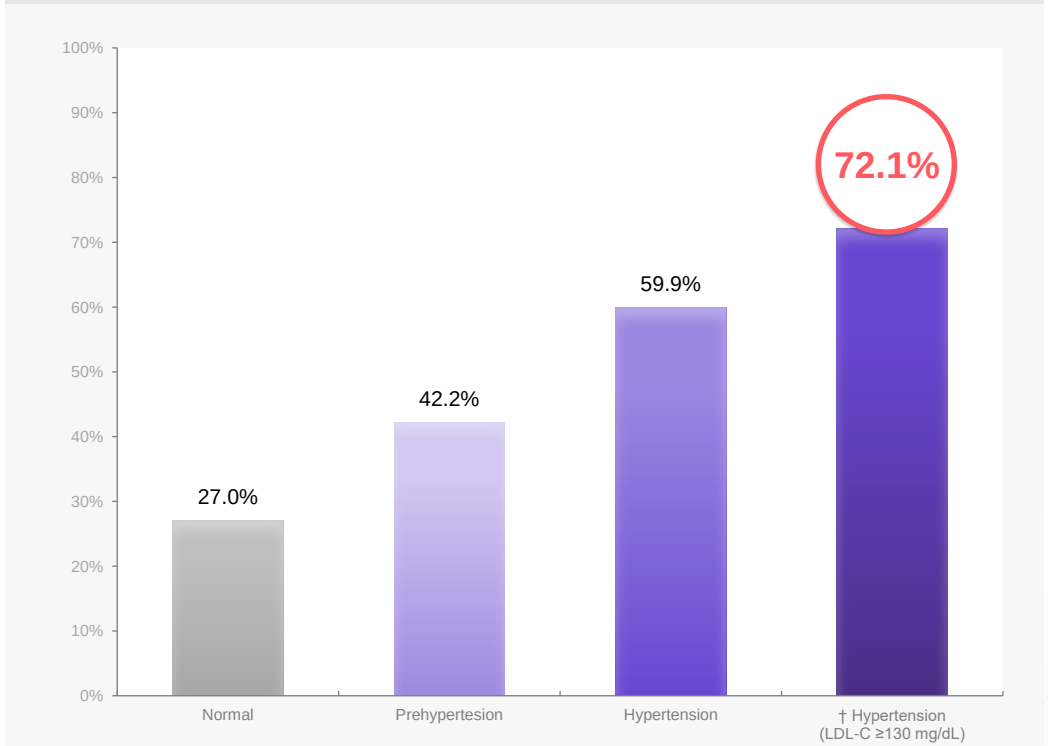
## Dyslipidemia in adults with diabetes




Data: 2016-2020 KNHANES; adults aged 20+ years
Prediabetes: fasting glucose 100-125 mg/dL or HbA1c 5.7-6.4%
Diabetes: fasting glucose ≥126 mg/dL, HbA1c ≥6.5%, previously diagnosed, or taking glucose-lowering drugs or insulin
Dyslipidemia: LDL-cholesterol ≥160 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug
* Dyslipidemia: LDL-cholesterol ≥100 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug

- Almost 70% of people with hypertension have dyslipidemia.

## Dyslipidemia in adults with hypertension

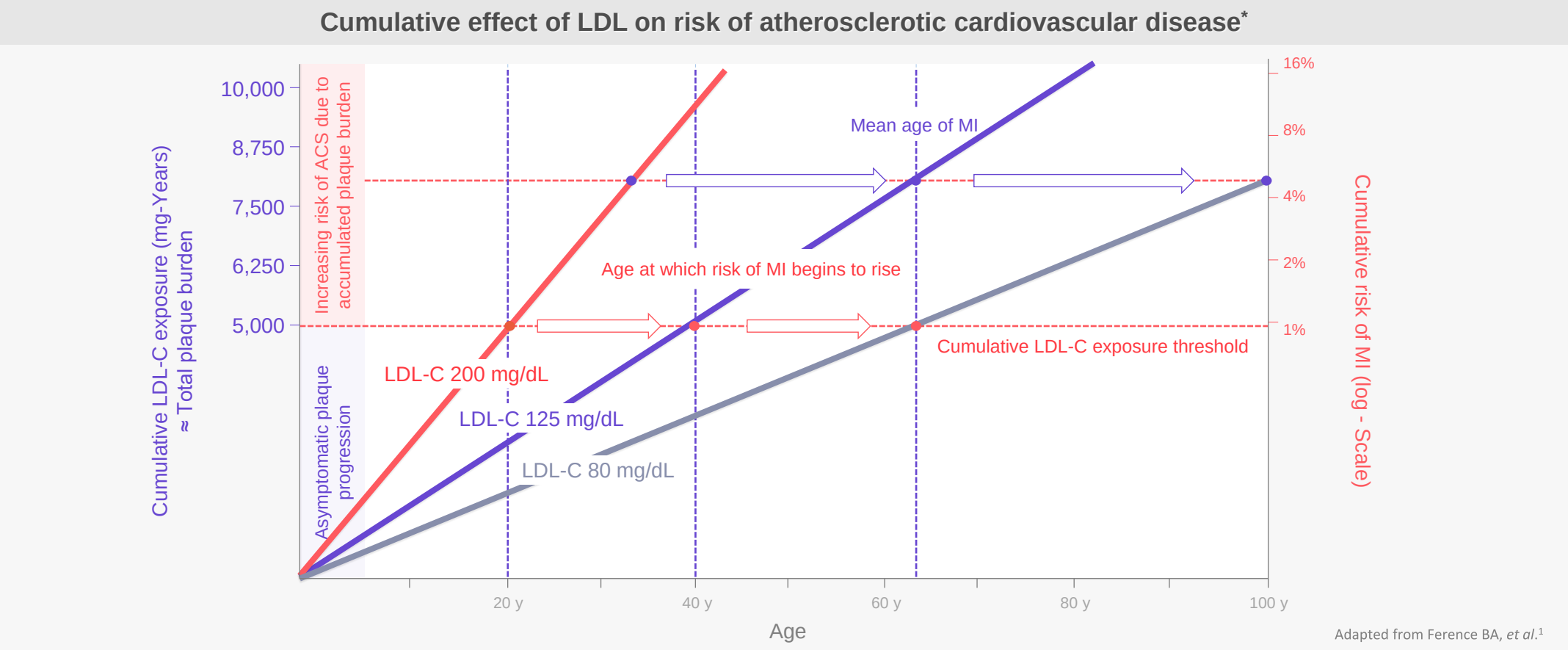



Data: 2016-2020 KNHANES; adults aged 20+ years
Prehypertension: SBP 120-139 mmHg or DBP 80-89 mmHg
Hypertension: SBP ≥140 mmHg, DBP ≥90 mmHg, or taking a BP-lowering drug
Dyslipidemia: LDL-cholesterol ≥160 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug
† Dyslipidemia: LDL-cholesterol ≥130 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug

**Reference 1.** The Korean Society of Lipid and Atherosclerosis (KSoLA). *Dyslipidemia fact sheet in Korea*. 2022.

# Legacy effect (early and intensive control)

- Total atherosclerotic plaque burden is proportional to person's cumulative exposure to LDL and other apo B.

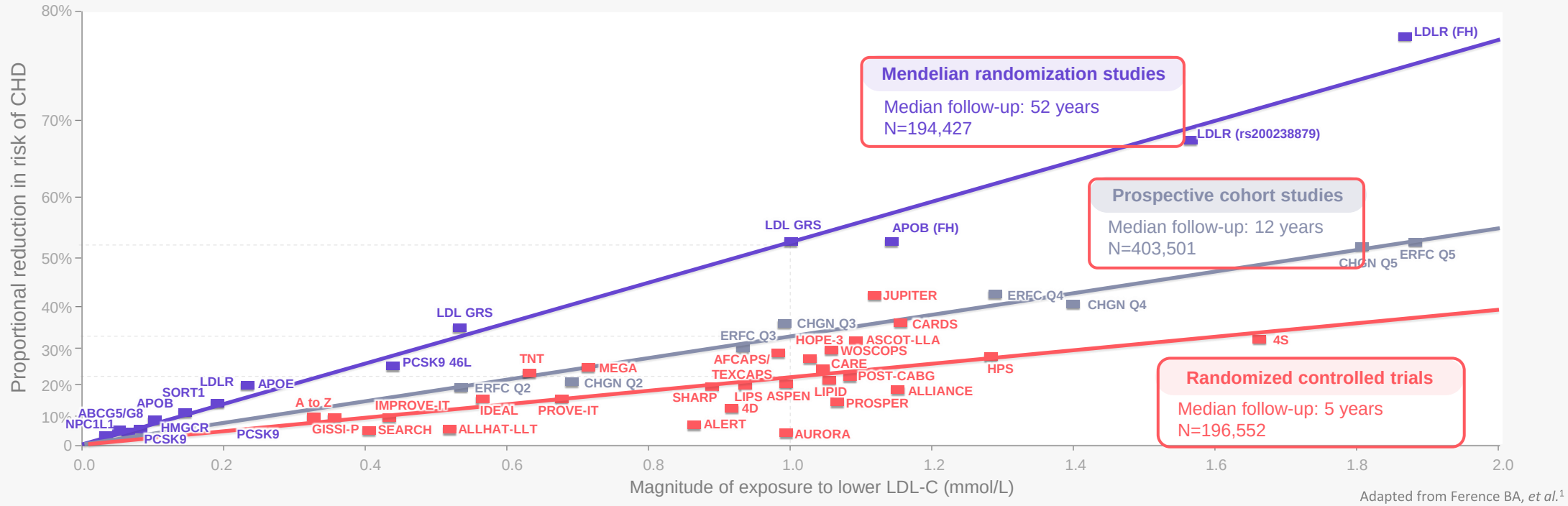



**Reference 1.** Ference BA, *et al.* Impact of Lipids on Cardiovascular Health: *JACC* Health Promotion Series. *J Am Coll Cardiol.* 2018 Sep 4;72(10):1141-1156.

# Lower is Better ➔ *Early & Lower for Longer*

- The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and a cumulative effect on the risk of cardiovascular disease.

## Change in LDL-C and the risk of cardiovascular disease

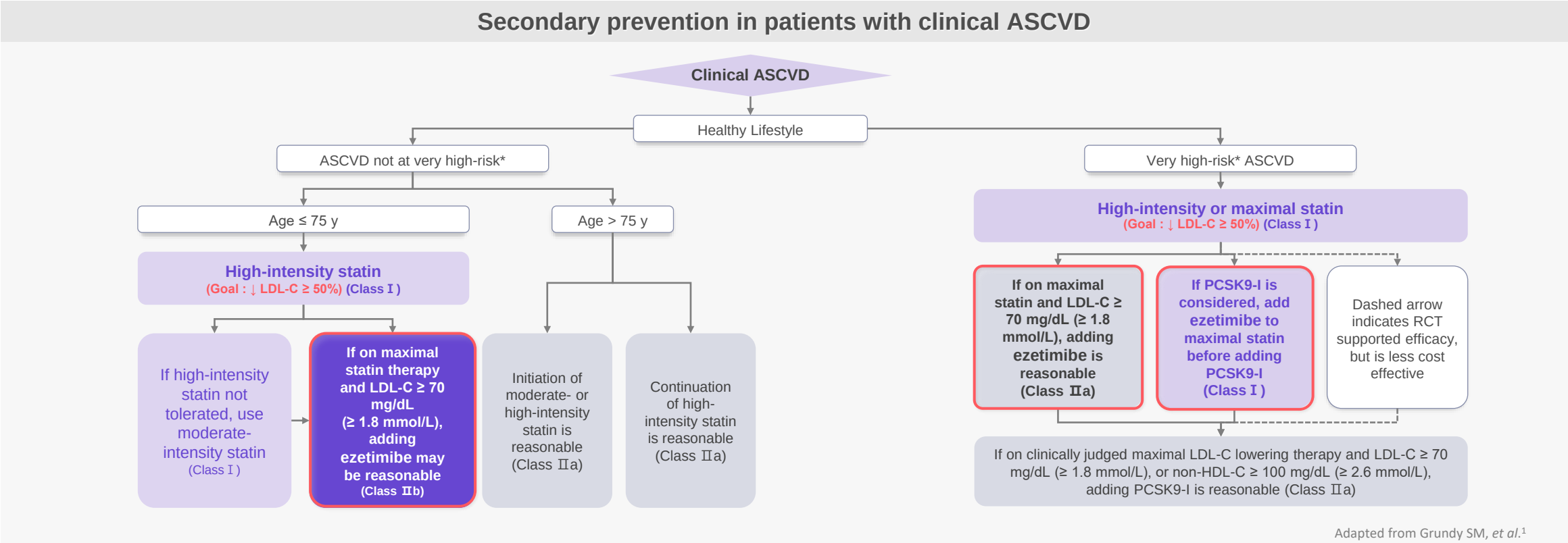



Adapted from Ference BA, *et al.*[1]

**Reference 1.** Ference BA, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017 Aug 21;38(32):2459-2472.

# Secondary prevention in patients with clinical ASCVD

- 2018 ACC/AHA guideline recommend that ASCVD high risk patient is considered add ezetimibe or PCSK9-I to statin therapy.




Adapted from Grundy SM, *et al*.[1]

**Reference 1.** Grundy SM, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019 Jun 18;139(25):e1082-e1143.

# 2023 ESC guidelines

## Are you sure that you are reducing LDL-C by ≥ 50% from baseline ?

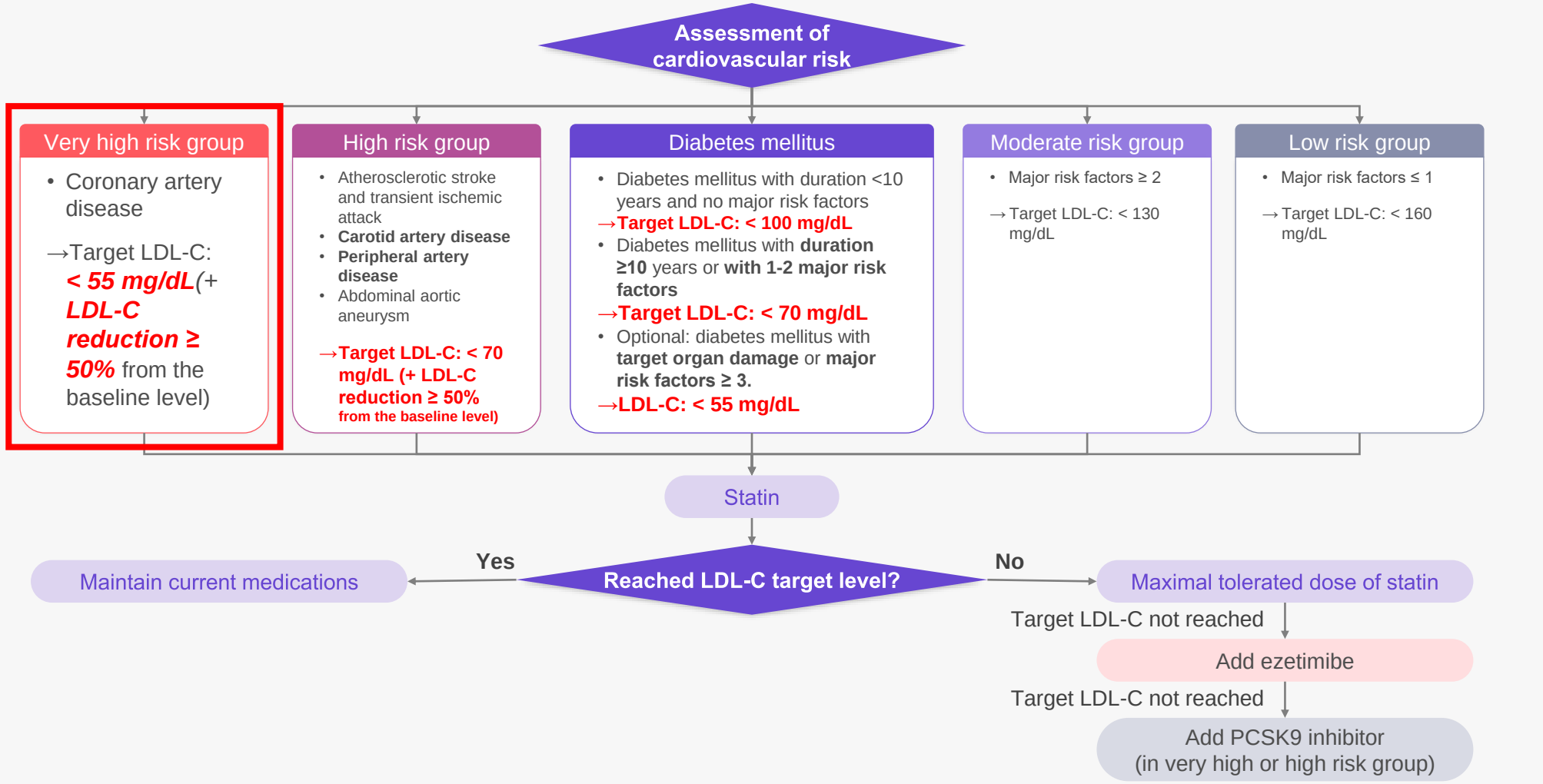
| Recommendations | COR | LOE |
|---|---|---|
| It is recommended that **high-dose statin therapy is initiated or continued as early as possible**, regardless of initial LDL-C values. | I | A |
| It is recommended to aim **to achieve an LDL-C level of < 55 mg/dL and to reduce LDL-C by ≥50% from baseline.** | I | A |
| If the LDL-C goal is not achieved despite maximally tolerated statin therapy after 4–6 weeks, the addition of ezetimibe is recommended. | I | B |
| If the LDL-C goal is not achieved despite maximally tolerated statin therapy and ezetimibe after 4–6 weeks, the addition of a PCSK9 inhibitor is recommended. | I | A |
| new It is recommended to intensify lipid-lowering therapy* during the index ACS hospitalization for patients who were on lipid-lowering therapy before admission. | I | C |
| For patients with a recurrent atherothrombotic event (recurrence within 2 years of first ACS episode) while taking maximally tolerated statin-based therapy, an LDL-C goal of <40 mg/dL may be considered. | IIb | B |
| new Combination therapy with high-dose statin plus ezetimibe may be considered during index hospitalization | IIb | B |

*Increase statin potency/dose if the patient was on low-potency/low-dose statin, add ezetimibe if the patient was only on statins at highest tolerated dose, or add PCSK9 inhibitor if the patient was on statins plus ezetimibe.

**Ref.** Byrne RA, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023 Aug 25:ehad191.

2022 KSoLA Guideline

# Guidelines for dyslipidemia in KOREA

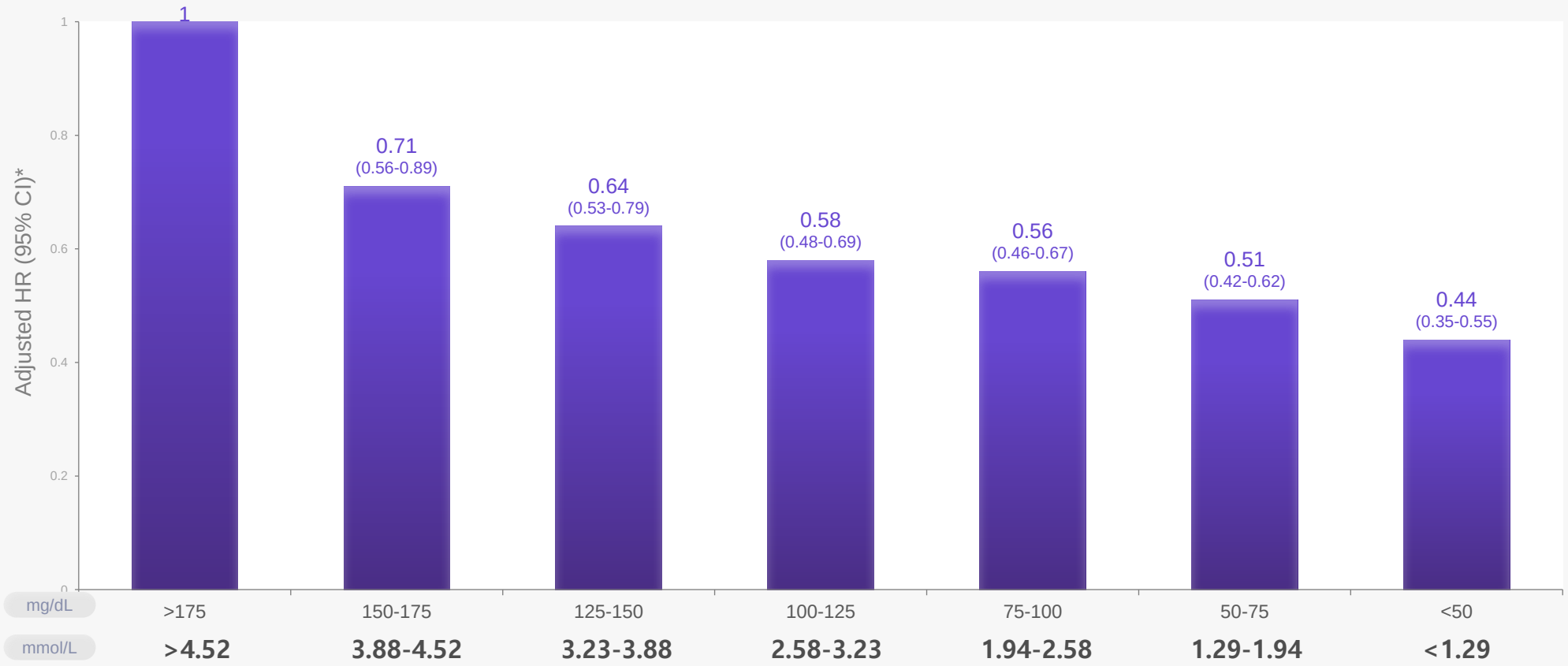



Adapted from KSoLA.[1]

**Reference 1.** The Korean Society of Lipid and Atherosclerosis (KSoLA). *Guidelines for management of dyslipidemia 5th edition*. 2022.

# Even below LDL-C target further LDL-C reduction gives additional CV benefit

## Risk for major CV events by achieved on-trial LDL-C levels




**Reference 1.** Boekholdt SM, *et al*. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol.* 2014;64:485-494.

# In the SWEDEHEART Registry, Greater LDL-C Reduction 6 to 10 Weeks Post-MI Is Associated With Lower Risk of CV Events

Kaplan–Meier curves of the cumulative incidence rates by quartile LDL-C change from index event to the cardiac rehabilitation visit. Outcomes are assessed after the cardiac rehabilitation visit.

Observational study using the SWEDEHEART registry, a nationwide MI quality registry

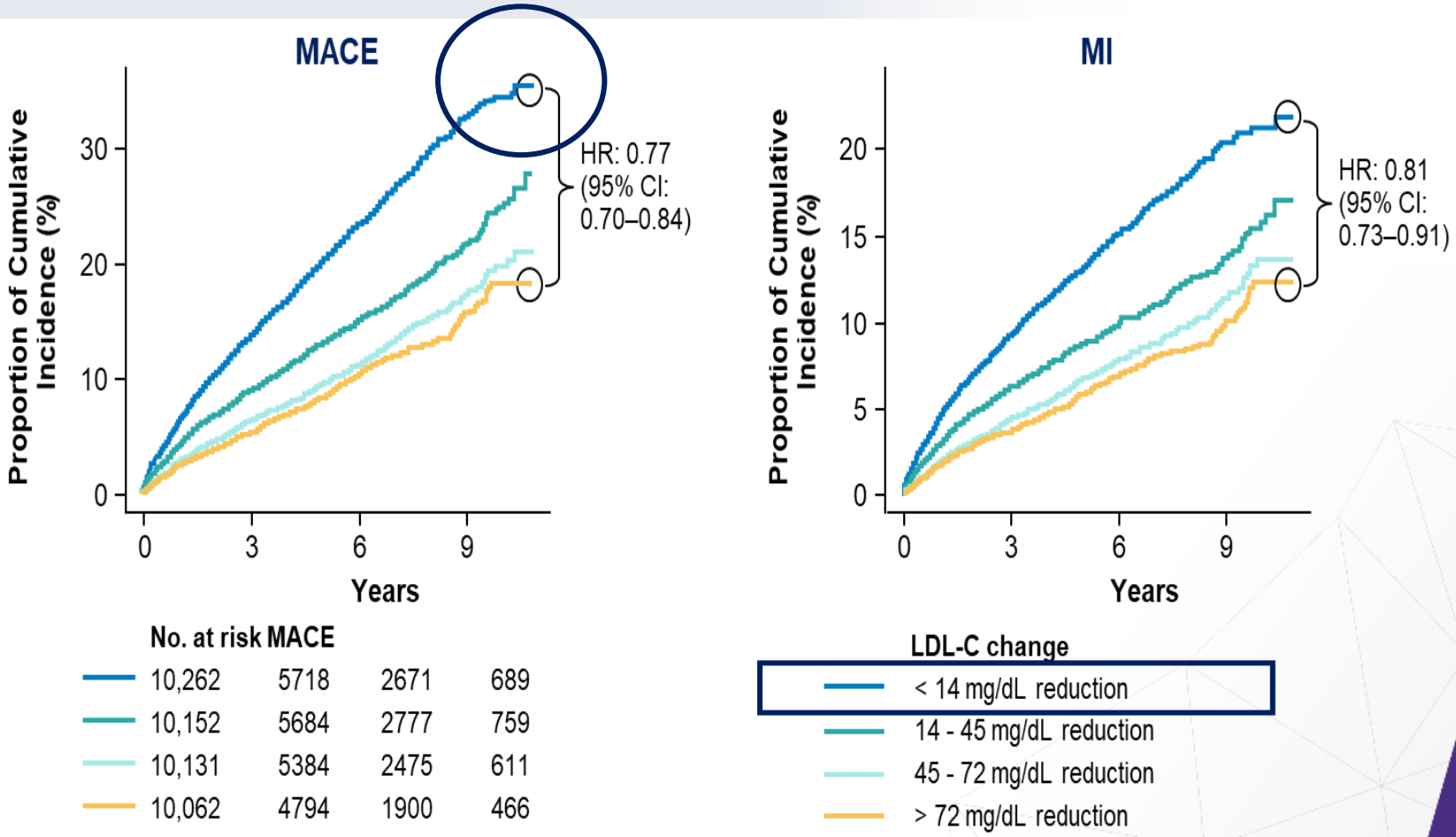
N = 40,607

Population: 30–74 years of age admitted for MI in Sweden 2006–2016, alive at follow-up in cardiac rehab 6–10 weeks post-discharge

Follow-up: Maximum 11 years, median: 3.8 years

**LDL-C measured within 24 hours of admission and 6–10 weeks post-discharge**

Prior to hospitalization: 77% were not on statin, mean LDL-C: 120 mg/dL




European Heart Journal (2021) 42, 243–252

# The Lowest Quartile Group is a Statin Neglecting Group ?

**Most lowest quartile group of LDL-C change has on-going statin group, not statin naive**

| | | LDL-C reduction from index event to cardiac rehabilitation visit (mmol/L) | | | |
|---|---|---|---|---|---|
| **Variable** | **Overall** | **<0.36** | **0.36 - 1.17** | **1.17 - 1.85** | **>1.85** |
| Number of patients | 40 607 | 10 262 | 10 152 | 10 131 | 10 062 |
| LDL at admission | 3.1 (2.4 - 3.9) | 2.1 (1.7 - 2.7) | 2.8 (2.3 - 3.2) | 3.4 (3 - 3.8) | 4.3 (3.8 - 4.8) |
| LDL at follow-up | 2.0 (1.6 - 2.4) | 2.3 (1.8 - 2.9) | 1.9 (1.5 - 2.4) | 1.9 (1.5 - 2.2) | 1.8 (1.5 - 2.2) |

| **Variable** | **All patients** | **Statin naive** | **Ongoing statin** |
|---|---|---|---|
| Number of patients | 40 607 | 31 263 | 9344 |
| LDL at admission | 3.1 (2.4 - 3.9) | 3.4 (2.8 - 4.1) | 2.2 (1.8 - 2.8) |
| LDL at follow-up | 2.0 (1.6 - 2.4) | 1.9 (1.5 - 2.4) | 2.1 (1.6 - 2.5) |

Low-density lipoprotein cholesterol (LDL-C) levels at admission and at follow-up, presented overall, by low-density lipoprotein cholesterol reduction quartile, and by statin treatment at admission. Values are medians (interquartile ranges).

**>72mg/dL : >1.85**

**45-72mg/dL : 1.17-1.85**

**14-44mg/dL : 0.36-1.17**

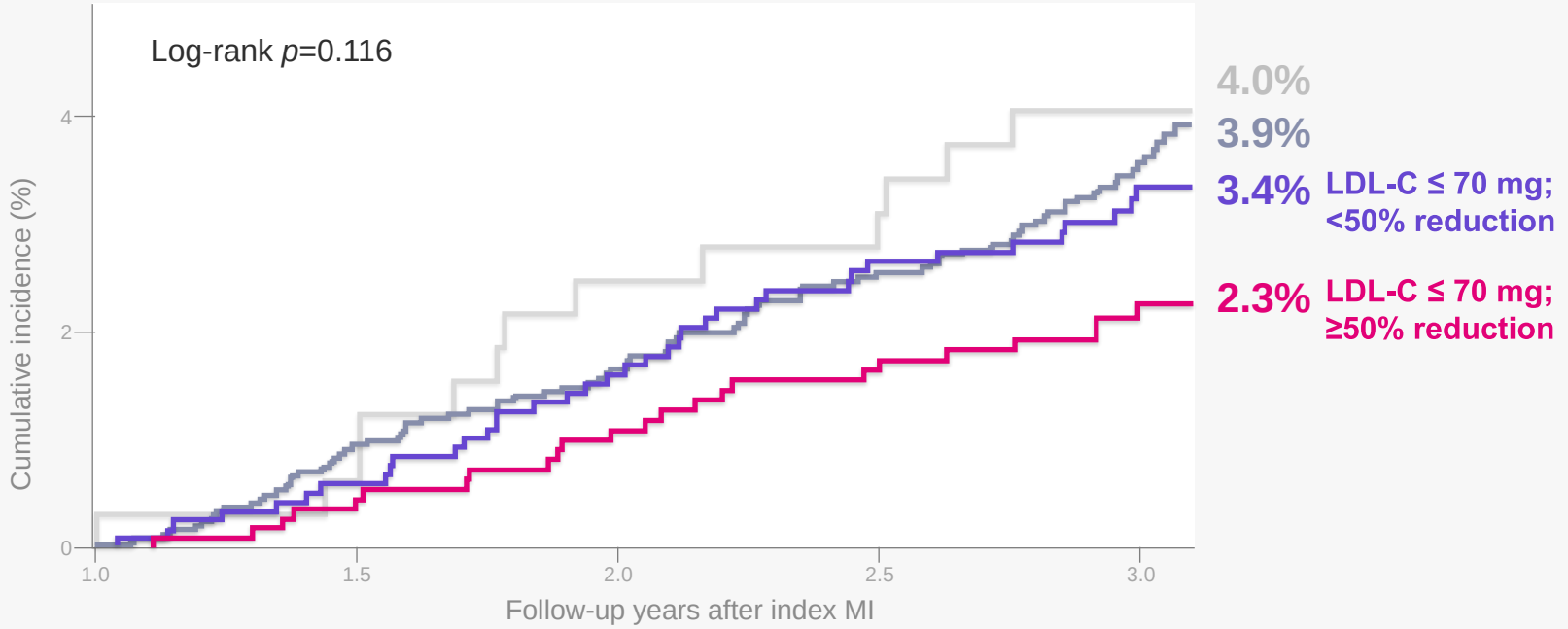
**<14mg/dL : <0.36**

European Heart Journal (2021) 42, 243–252

A Korean Nationwide Cohort Study

# Achieving both a ≥50% reduction and an LDL-C level ≤ 70 mg/dL for secondary prevention is crucial for improving clinical outcomes in post-MI patients.

## Major adverse cardiac and cerebrovascular events




| Number at risk | | | | | | HR [95% CI] | *p*-value |
|---|---|---|---|---|---|---|---|
| LDL-C ≤ 70 mg/dL; ≥ 50% reduction | 1114 | 1106 | 1080 | 1045 | 762 | **Reference** | |
| LDL-C ≤ 70 mg/dL; < 50% reduction | 1189 | 1180 | 1153 | 1102 | 805 | **1.49 [0.90-2.49]** | **0.123** |
| LDL-C > 70 mg/dL; ≥ 50% reduction | 324 | 322 | 316 | 307 | 220 | 1.86 [0.95-3.65] | 0.071 |
| LDL-C > 70 mg/dL; < 50% reduction | 2422 | 2396 | 2346 | 2265 | 1616 | **1.70 [1.08-2.66]** | **0.022** |

Adapted from Kim JH, *et al.*

**LDL-C :** Low-density lipoprotein cholesterol, **MI :** Myocardial infarction, **HR :** Hazard ratio, **CI :** Confidence interval

**Study design a.** A Korean Nationwide Cohort Study was to investigate recurrent ASCVD events in post-MI patients who did or did not achieve LDL-C target goals and evaluate the relationship between LDL-C changes and clinical outcomes. From the Korea Acute Myocardial Infarction-National Institutes of Health registry, a total of 5,049 patients with both measurements of plasma LDL-C levels at index admission and at the one-year follow-up visit were identified from November 2011 to December 2015. Patients who achieved an LDL-C reduction ≥ 50% from the index MI and an LDL-C level ≤ 70 mg/dL at follow-up were classified as target LDL-C achievers. The primary endpoint was a two-year major adverse cardiac and cerebrovascular event (MACCE), including cardiovascular mortality, recurrent MI, and ischemic stroke.

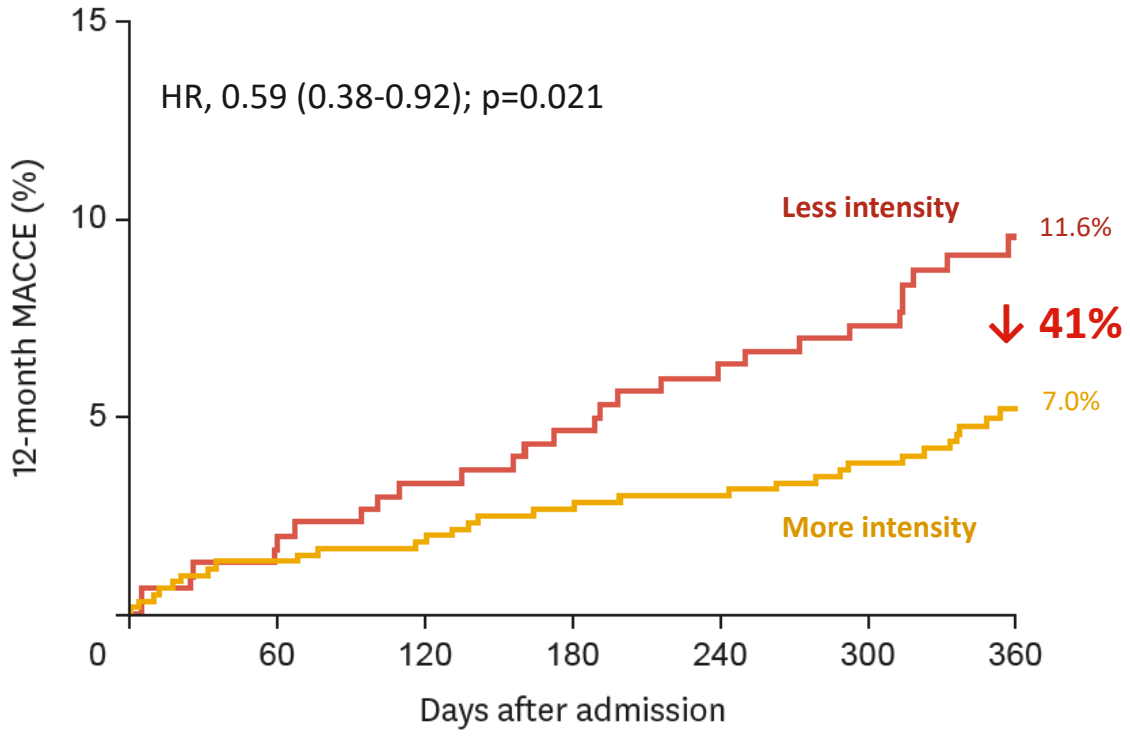
**1.** Kim JH, *et al.* Target Low-Density Lipoprotein-Cholesterol and Secondary Prevention for Patients with Acute Myocardial Infarction: A Korean Nationwide Cohort Study. *J Clin Med.* 2022 May 8;11(9):2650.

# Group with LDL-C <70 mg/dL, However <50% LDL reduction

## *They need more intensive strategies …even with no-statin*

### Cumulative MACCE at 12 months with adjustment using propensity score matching

Cardiac death, nonfatal MI, coronary revascularization by PCI or CABG occurring at least 30 days after admission, and stroke




### Cumulative secondary endpoints at 12 months

| Clinical outcomes | Propensity-matched patients | |
|---|---|---|
| | Adjusted HR (95% CI) | *p*-value |
| Cardiac death | 1.01 (0.08–12.3) | 0.994 |
| MI | 0.51 (0.24–1.10) | 0.086 |
| PCI | 0.60 (0.34–1.06) | 0.081 |
| TLR | 0.35 (0.13–0.91) | 0.032 |
| TVR | 0.41 (0.19–0.90) | 0.027 |
| Non-TVR | 0.93 (0.40–2.20) | 0.876 |
| CABG | - | 0.333 |
| Stroke | 0.59 (0.24–1.42) | 0.240 |
| Ischemic stroke | 0.53 (0.22–1.32) | 0.173 |
| Hemorrhagic stroke | 1.50 (0.16–14.4) | 0.727 |
| Cardiac death or MI | 0.55 (0.27–1.15) | 0.114 |
| Cardiac death, MI, PCI, or CABG | 0.61 (0.37–1.03) | 0.065 |
| Cardiac death, MI, or stroke | 0.55 (0.32–0.97) | 0.039 |
| Cardiac death, MI, PCI, CABG, or stroke | 0.59 (0.38–0.92) | 0.021 |
| Stent thrombosis | 1.00 (0.09–11.0) | 0.999 |
| TIMI major bleeding | 2.68 (0.78–9.19) | 0.118 |

**MACCE,** major adverse cardiac and cerebrovascular event; **CABG**, coronary artery bypass graft; **TIMI**, Thrombolysis in Myocardial Infarction; **TLR**, target-lesion revascularization; **TVR**, target-vessel revascularization

**Ref.** Sim DS, et al. Intensity of Statin Treatment in Korean Patients with Acute Myocardial Infarction and Very Low LDL Cholesterol. J Lipid Atheroscler. 2019 Sep;8(2):208-220.

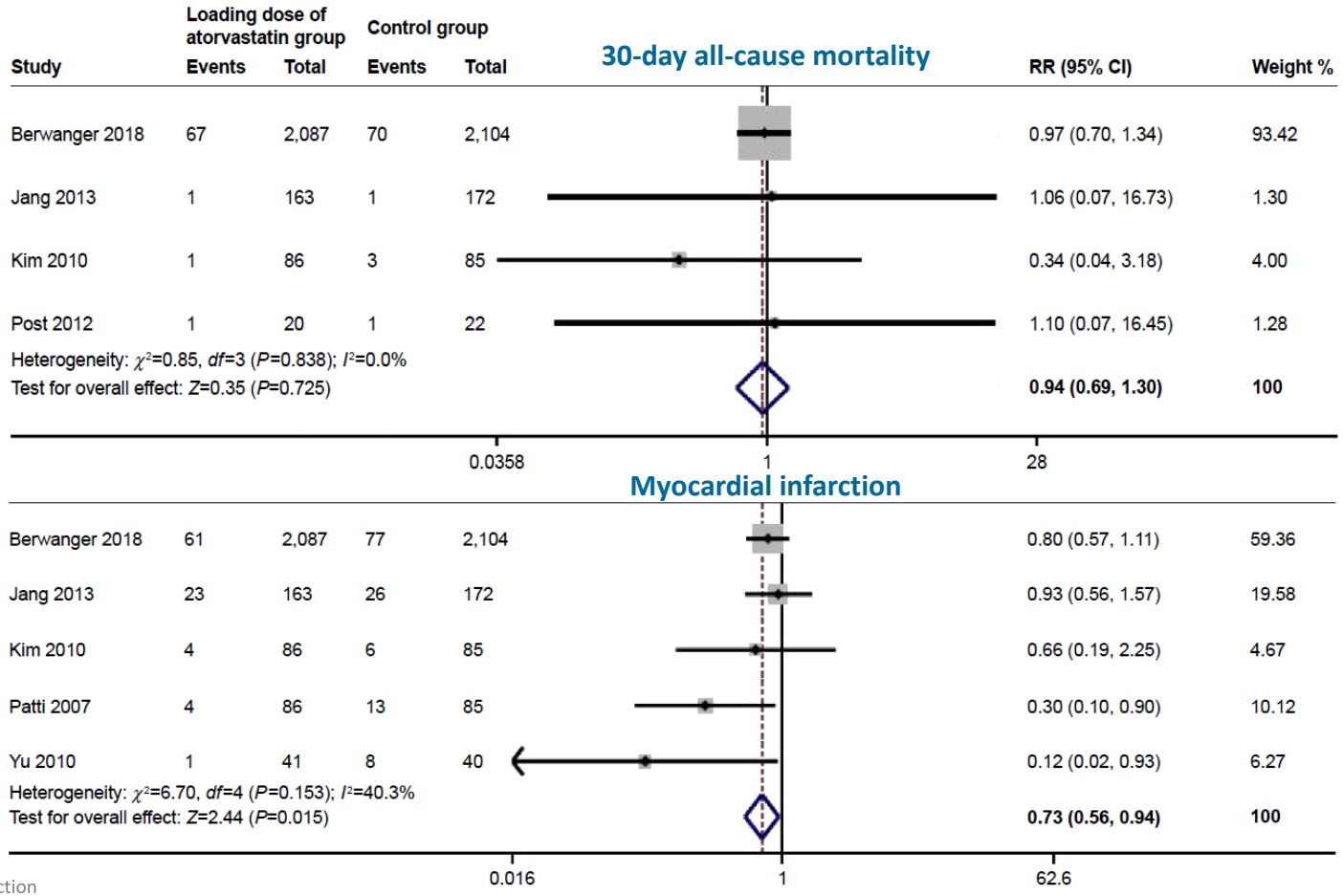
# In ACS patient

# Effect of High dose Atorvastatin 80 mg Loading regardless of baseline LDL-C

**A meta-analysis of 6 RCTs published up to July 2018**

Atorvastatin 80 mg before PCI (n=2,483) vs. placebo, no statin or atorvastatin 10-20 mg (n=2,508)

**Pooled RR of loading dose of atorvastatin pretreatment vs control for 30-day all-cause mortality and MI after PCI**




**30-day all-cause mortality**

RR, 0.94 (1.69-1.30); P=0.725

**Myocardial infarction**

RR, 0.73 (0.56-0.94); P=0.015

**↓ 27%**

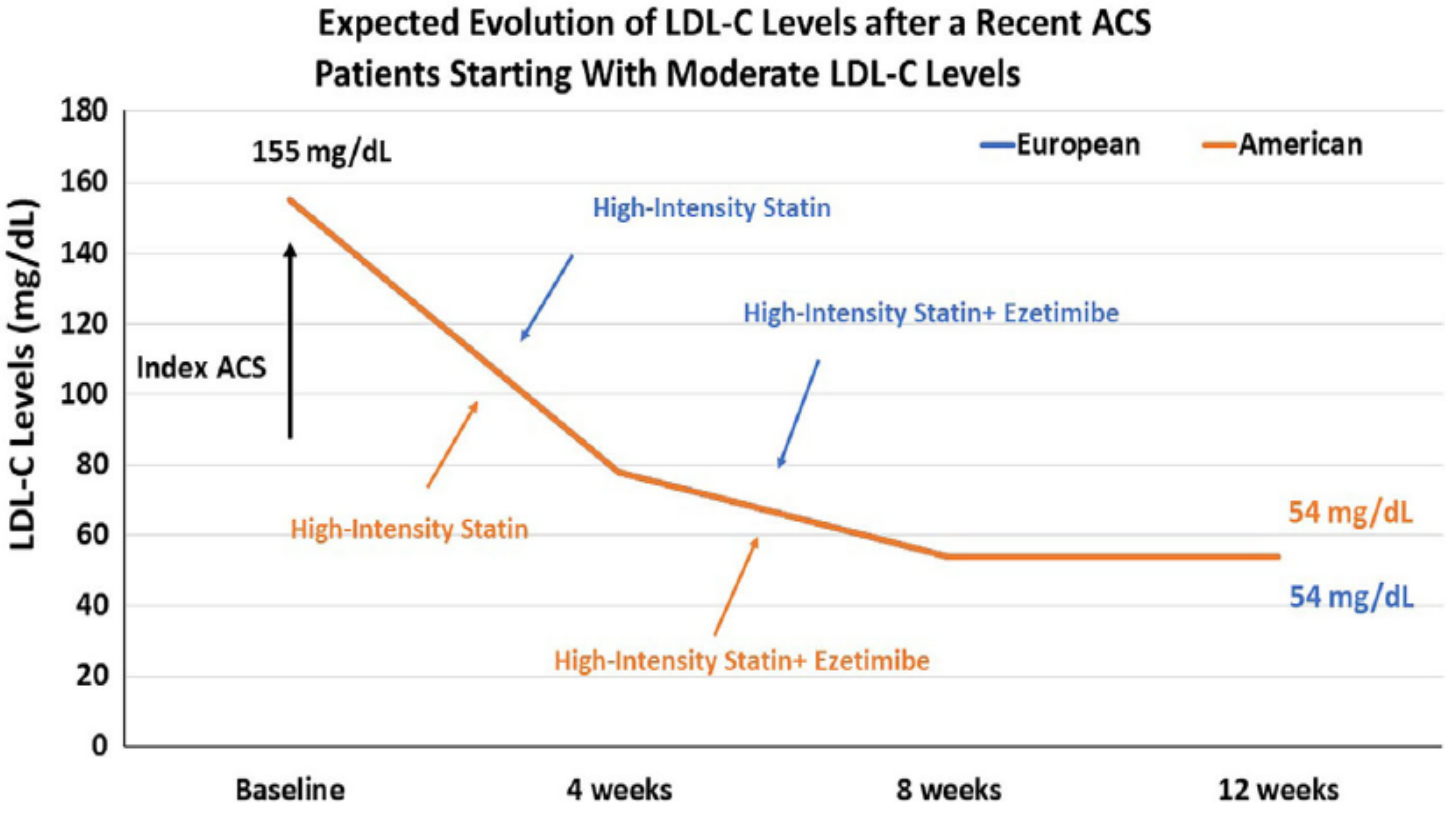
**RR,** risk ratio; **MI,** myocardial infarction

**Ref.** Ma M, et al. Effect of loading dose of atorvastatin therapy prior to percutaneous coronary intervention in patients with acute coronary syndrome: a meta-analysis of six randomized controlled trials. Drug Design, Development and Therapy 2019:13 1233–1240.

# How to reduce LDL-C and Residual CV risk early and potently?

## -CLINICAL SCENARIO & IMPLICATIONS

**Step by step therapy strategy vs. Planning therapy strategy according to baseline LDL-C & goal**




### Intensity of lipid lowering treatment

| Treatment | Average LDL-C reduction |
|---|---|
| Moderate intensity statin | ≈ 30% |
| High intensity statin | ≈ 50% |
| **High intensity statin plus ezetimibe** | **≈ 65%** |
| PCSK9 inhibitor | ≈ 60% |
| PCSK9 inhibitor plus high intensity statin | ≈ 75% |
| PCSK9 inhibitor plus high intensity statin plus ezetimibe | ≈ 85% |

2020 Jul;43(7):684-690. doi: 10.1002/clc.23410. Epub 2020 Jun 29.
Reference 1. Mach F, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188.

# What is your favorite strategy in real practice?

**Reduction of a large amount of LDL for high or very high risk group**
(reduction of LDL-C by ≥50% from baseline & LDL target up to 55mg/dL )

**High potency Statin**

**High intensity Statin**

*Regardless of baseline LDL*

**Upfront combination Tx**
moderate or high intensity statin
with ezetimibe ?

**High potency**

**Moderate intensity statin**

*(Target to treat strategy)*

Titration of statin

Based on Target LDL

Statin tolerability

PCSK9i

inclisiran

Add on therapy

# IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

## Compared to Simvastatin alone, **Ezetimibe** add-on therapy reduced LDL-C in **24%** with **NNT of 50**

This study was conducted with ezetimibe and simvastatin.

**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)

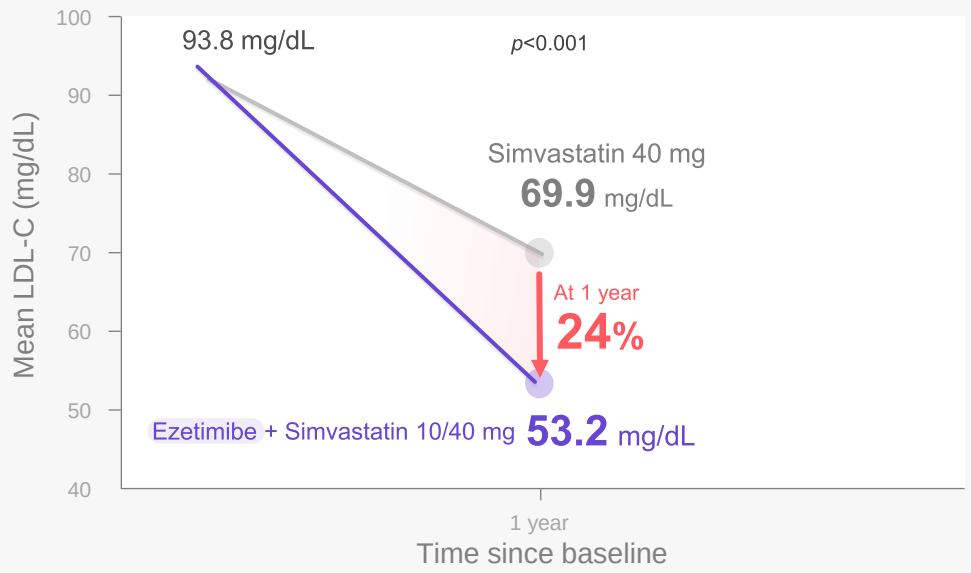
- **Simvastatin 40 mg** (n=9,077)
- **Ezetimibe/simvastatin 10/40 mg** (n=9,067)

### Primary endpoint:

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

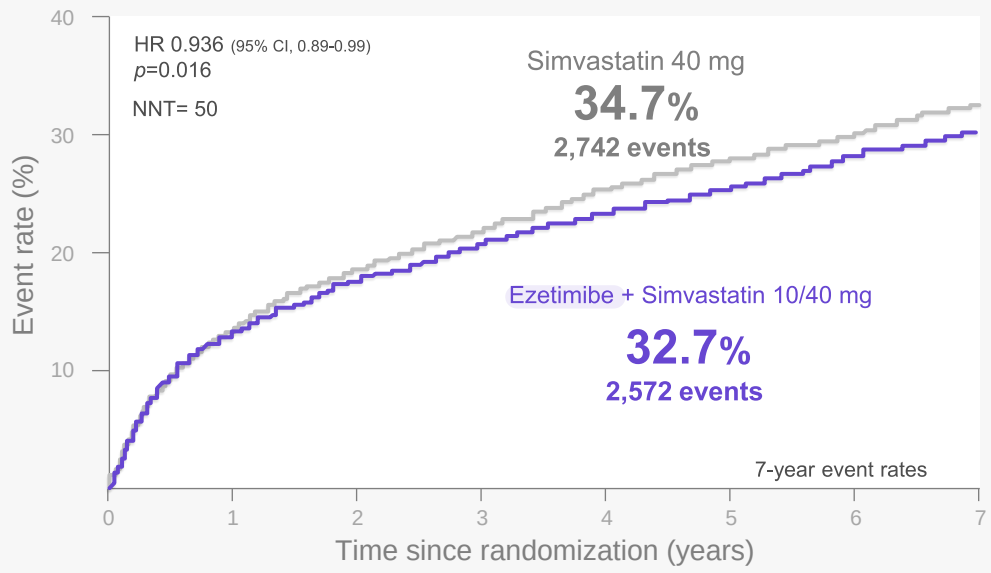
Duration: Minimum 2½-year follow-up (at least 5,250 events)
The median follow-up was 6 years.

### Change of LDL-C




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

### Primary endpoint



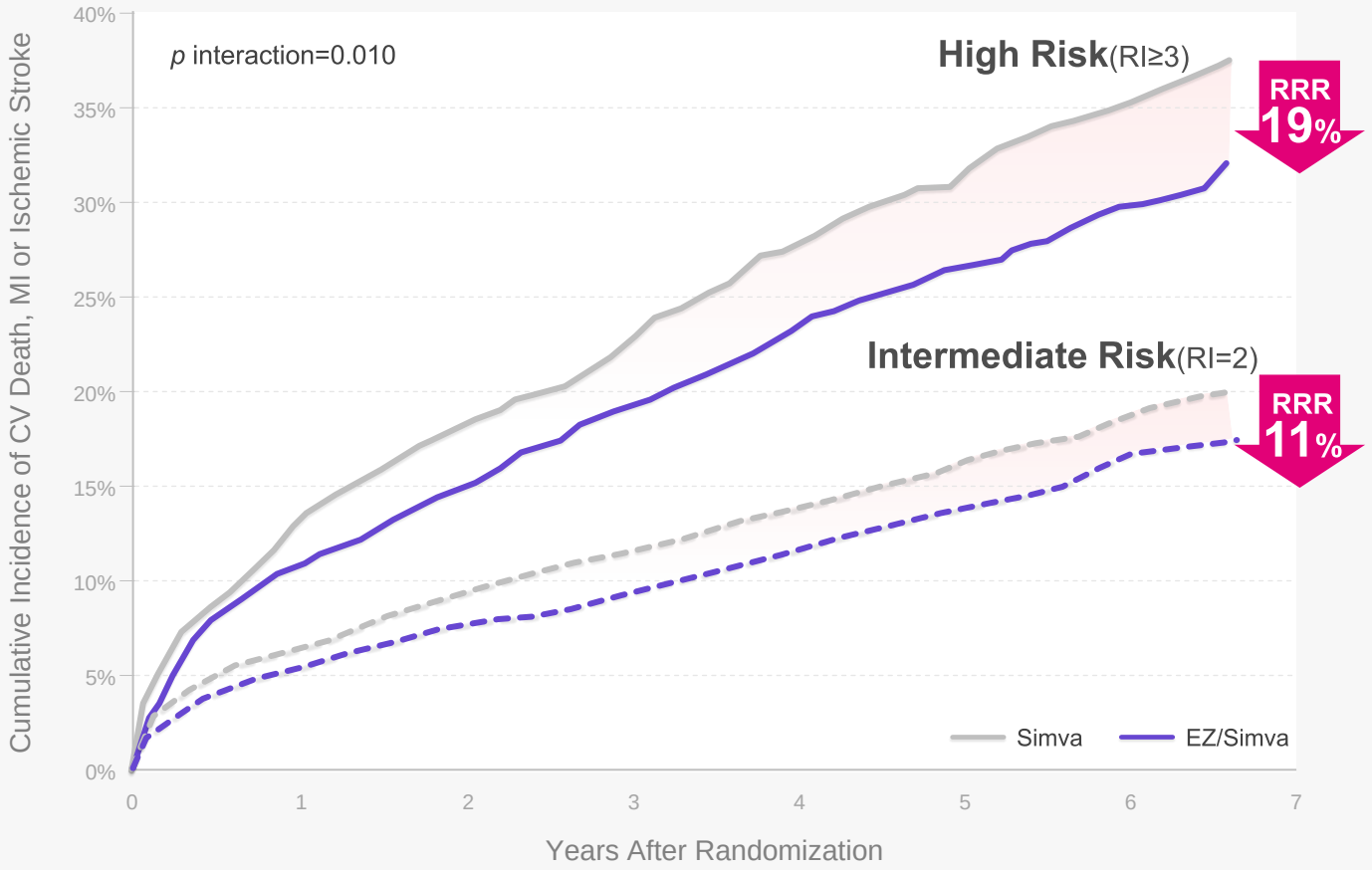

Adapted from Cannon CP, *et al.*[1]

**Reference 1.** Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397.

IMPROVE-IT: TRS 2°P sub-analysis

# Addition of Ezetimibe to Simvastatin demonstrated a significant 19% relative risk reduction with a NNT of 16 in high risk patients.[1]

## Outcomes by risk category and randomized treatment : CV death, MI or ischemic stroke[1]




**NNT=16**

| 7yr KM | ARR | HR |
|---|---|---|
| Simva 40.2% | 6.3% (2.9, 9.7) | 0.81 (0.73, 0.90) |
| EZE/Simva 33.9% | | |

**NNT=44**

| 7yr KM | ARR | HR |
|---|---|---|
| Simva 21.5% | 2.2% (-0.3, 4.6) | 0.89 (0.78, 1.01) |
| EZE/Simva 19.3% | | |

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

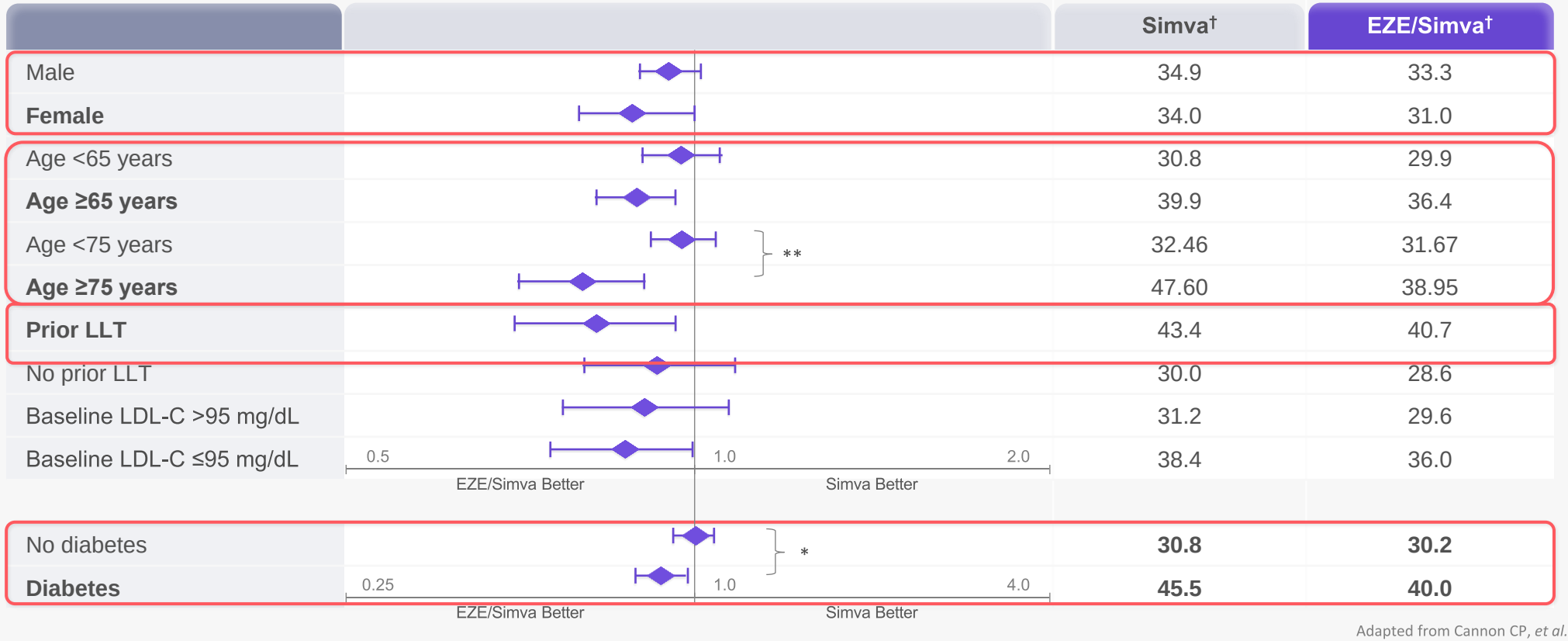
**IMPROVE-IT :** Improved Reduction of Outcomes: Vytorin Efficacy International Trial, **NNT :** Number needed to be treated, **CV :** Cardiovascular, **MI :** Myocardial infarction, **RI :** Risk indicators, **RRR :** Relative risk reduction, **KM :** Kaplan-Meier, **ARR :** Absolute risk reduction,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

**1**. Bohula EA, *et al*. Atherothrombotic risk stratification and Ezetimibe for secondary prevention. *Journal of the American college of cardiology.* 2017;69(8):911-921.

IMPROVE-IT sub-analysis

# Group with prior Lipid lowering therapy was a good candidate of add-on Tx

## Major prespecified subgroups[2]




| | Simva† | EZE/Simva† |
|---|---|---|
| Male | 34.9 | 33.3 |
| **Female** | 34.0 | 31.0 |
| Age <65 years | 30.8 | 29.9 |
| **Age ≥65 years** | 39.9 | 36.4 |
| Age <75 years | 32.46 | 31.67 |
| **Age ≥75 years** | 47.60 | 38.95 |
| **Prior LLT** | 43.4 | 40.7 |
| No prior LLT | 30.0 | 28.6 |
| Baseline LDL-C >95 mg/dL | 31.2 | 29.6 |
| Baseline LDL-C ≤95 mg/dL | 38.4 | 36.0 |
| No diabetes | **30.8** | **30.2** |
| **Diabetes** | **45.5** | **40.0** |

Adapted from Cannon CP, *et al.*[2]

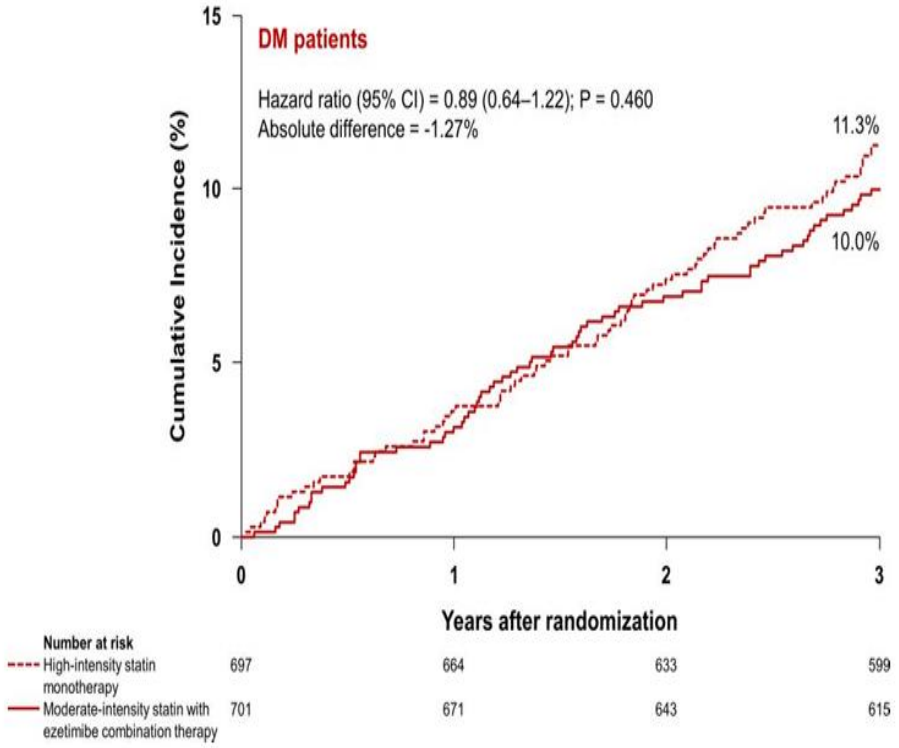
† 7-year event rates * *p*-interaction =0.023, otherwise >0.05 ** *p*-interaction =0.005, otherwise >0.05

**References 1.** Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372(25):2387-2397. **2.** Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. Supplementary Appendix. *N Engl J Med.* 2015;372(25):2387-2397.

# Moderate Intensity statin with Ezetimbe (RACING trial)

Ezetimibe combination with moderate-intensity statin therapy was comparable with high-intensity statin monotherapy in terms of a 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke.

Kaplan–Meier survival curves for the primary outcome




Baseline characteristics of statin medication and baseline LDL

| | Total population (n=3780) | DM patients (n=1398) | Non-DM patients (n=2382) | P-value |
|---|---|---|---|---|
| Medication for dyslipidaemia before randomization[b] | | | | 0.002 |
| High-intensity statin | 1440 (38.1) | 564 (40.3) | 876 (36.8) | |
| High-intensity statin with ezetimibe | 148 (3.9) | 55 (3.9) | 93 (3.9) | |
| Moderate-intensity statin | 1366 (36.1) | 524 (37.5) | 842 (35.3) | |
| Moderate-intensity statin with ezetimibe | 499 (13.2) | 163 (11.7) | 336 (14.1) | |
| Low-intensity statin | 11 (0.3) | 4 (0.3) | 7 (0.3) | |
| None | 316 (8.4) | 88 (6.3) | 228 (9.6) | |
| Serum LDL cholesterol level, mg/dL | 80 (64–100) | 74 (59–93) | 83 (68–104) | <0.001 |
| Patients with LDL cholesterol levels <70 mg/dL (%) | 1259 (33.3) | 595 (42.6) | 664 (27.9) | <0.001 |

Yong-Joon Lee et al. European Heart Journal (2023) 44, 972–983

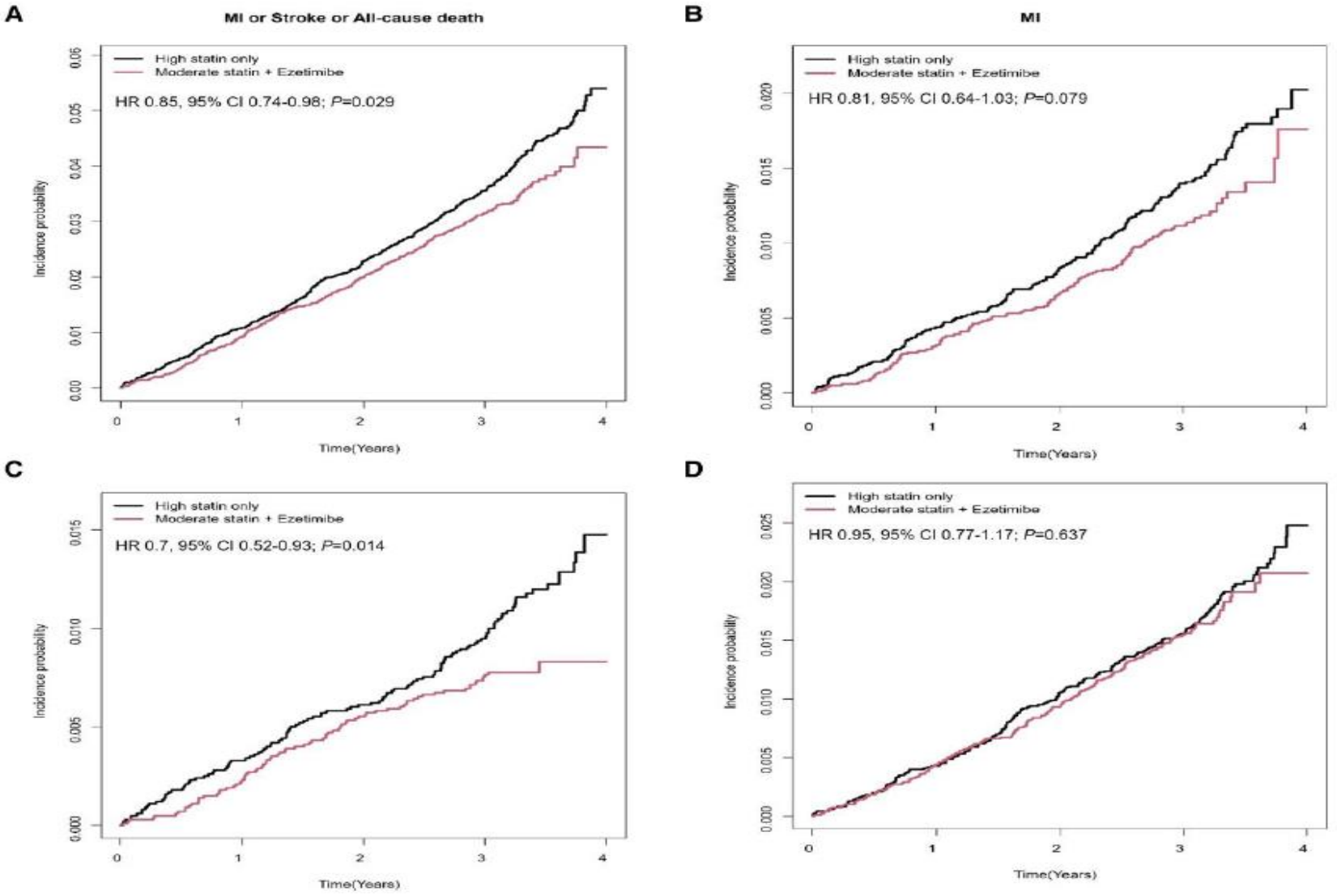
# Moderate Intensity statin with Ezetimbe and even better LDL Achievement

Ezetimibe combination with moderate-intensity statin therapy was comparable with high-intensity statin monotherapy in terms of a 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke.

| | DM patients (n=1398) | | | Non-DM patients (n=2382) | | | |
|---|---|---|---|---|---|---|---|
| | Moderate-intensity statin with ezetimibe combination therapy | High-intensity statin monotherapy | P-value | Moderate-intensity statin with ezetimibe combination therapy | High-intensity statin monotherapy | P-value | P-value for interaction[a] |
| **Baseline** | | | | | | | |
| Number of patients | 701 | 697 | | 1193 | 1189 | | |
| Patients with LDL cholesterol levels <55 mg/dL (%) | 137 (19.5) | 123 (17.6) | 0.400 | 118 (9.9) | 123 (10.3) | 0.765 | - |
| **3 years** | | | | | | | |
| Number of patients | 497 | 476 | | 852 | 839 | | |
| Patients with LDL cholesterol levels <55 mg/dL (%) | 261 (52.5) | 166 (34.9) | P<0.001 | 302 (35.4) | 164 (19.5) | P<0.001 | 0.603 |

Yong-Joon Lee et al. European Heart Journal (2023) 44, 972–983

# moderate-intensity statin with ezetimibe combination therapy and high-intensity statin monotherapy group



# What about the Efficacy of Ezetimibe Monotherapy (EWTOPIA 75) ?

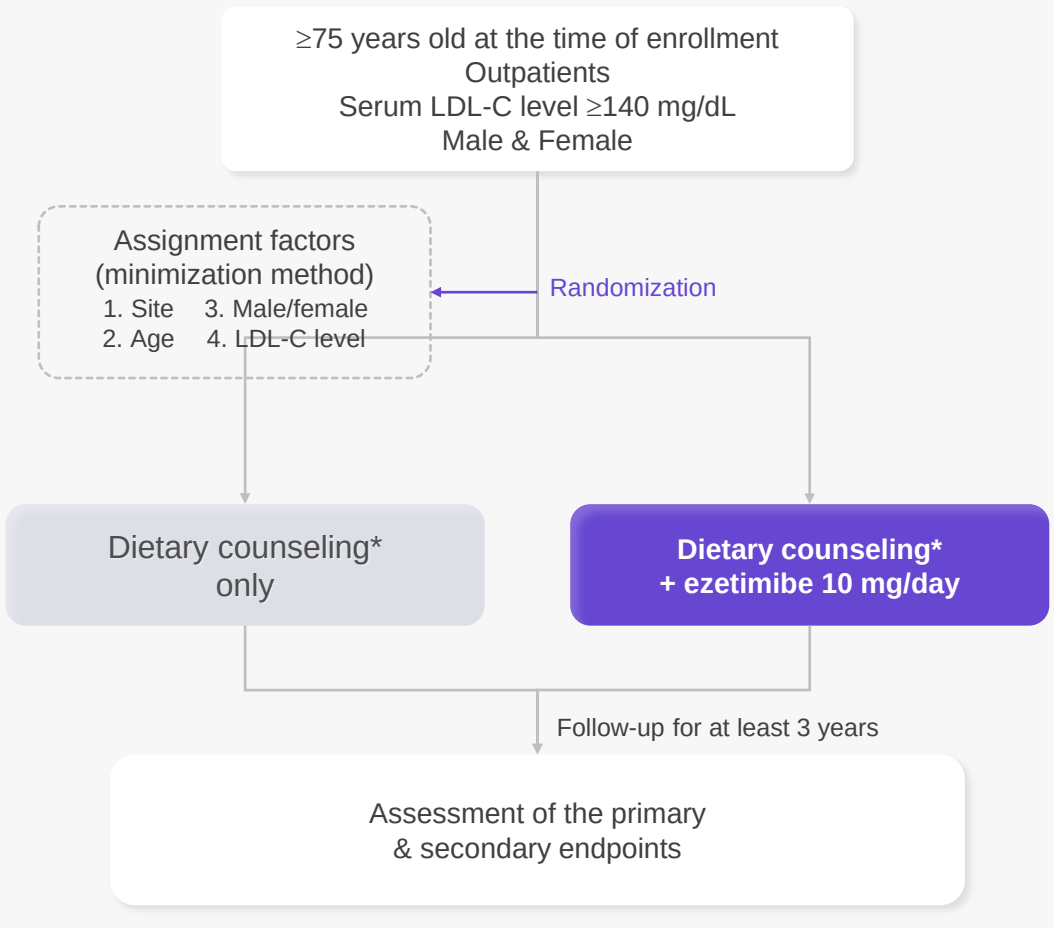
## PROBE design

**P**rospective **R**andomized **O**pen-label **B**linded-**E**ndpoint

### Inclusion criteria

Patients with at least 1 of 7 conditions

| | |
|---|---|
| 1 | Diabetes mellitus |
| 2 | Hypertension |
| 3 | Low HDL-cholesterolemia |
| 4 | Hypertriglyceridemia |
| 5 | Smoking |
| 6 | Previous history of cerebral infarction documented by apparent clinical symptoms and CT/MRI scanning |
| 7 | Peripheral artery disease |




Enrollment period: February 2009 to December 2014 (363 institutions participated.)
Follow-up period: February 2009 to March 2016

* Dietary counseling should be conducted based on 2007 Guideline for Prevention of ASCVD by Japan Atherosclerosis Society.

**LDL-C :** Low-density lipoprotein cholesterol, **HDL :** High-density lipoprotein, **CT :** Computed tomography, **MRI :** Magnetic resonance imaging

**1.** Ouchi Y, *et al*. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial. *Circulation.* 2019 Sep 17;140(12):992-1003.

# Primary Endpoint[1]

EWTOPIA75 ユートピア75

## A composite of the following atherosclerotic cardiovascular events

- **Sudden cardiac death**
- **Fatal & nonfatal Myocardial infarction**
- **Coronary Revascularization** (PCI or CABG)
- **Fatal & nonfatal stroke**

## Major secondary endpoints

- **All types of cardiac events** including sudden cardiac death, fatal & nonfatal myocardial infarction, and coronary revascularization (PCI or CABG)
- **All types of stroke** including fatal & nonfatal cerebral infarction, TIA, fatal & nonfatal cerebral hemorrhage
- **Revascularization** of carotid artery (CAS or CEA) or peripheral arteries (PPI or bypass surgery)
- **Aortic diseases** including aortic dissection, rupture of aortic aneurysm, surgical intervention of aortic aneurysm
- **All-cause mortality**
- **New onset of malignant tumors etc.**

**PCI :** Percutaneous coronary intervention, **CABG :** Coronary artery bypass grafting, **TIA :** Transient ischemic attack, **CAS :** Carotid Artery Stenting, **CEA :** Carotid Endoarterectomy, **PPI :** Proton pump inhibitors

**1.** Ouchi Y, *et al*. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial. *Circulation.* 2019 Sep 17;140(12):992-1003.

# The reduction rates of serum LDL-C, non-HDL-C, and TG levels during 5 years of follow-up were significantly greater in the ezetimibe group than in the control group (*P*<0.001, *P*<0.001, and *P*=0.003, respectively).[1]

EWTOPIA75 ユートピア75

## Time-course changes in the serum levels of LDL-C, HDL-C, non-HDL-C, and TG for 5 years after randomization in the ezetimibe group and the control group[1]

### LDL-C


| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1,700 | 1,489 | 1,245 | 1,009 | 685 | 311 |
| Not treated by ezetimibe | 1,685 | 1,464 | 1,227 | 1,023 | 706 | 314 |

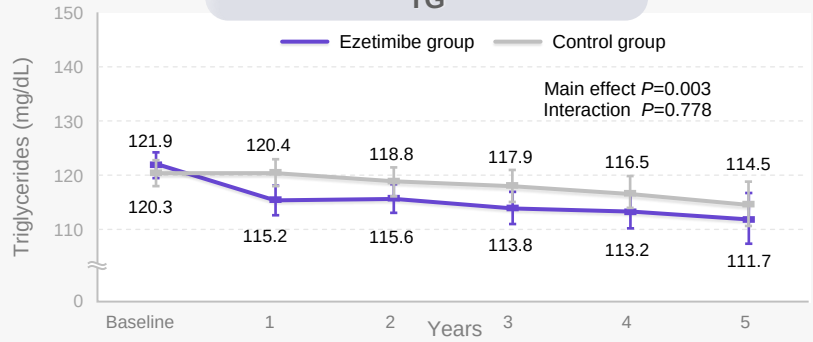
### HDL-C


| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1,700 | 1,508 | 1,259 | 1,018 | 701 | 318 |
| Not treated by ezetimibe | 1,685 | 1,484 | 1,244 | 1,028 | 718 | 319 |

### Non-HDL-C


| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1,700 | 1,490 | 1,247 | 1,009 | 687 | 311 |
| Not treated by ezetimibe | 1,685 | 1,466 | 1,230 | 1,024 | 707 | 314 |

### TG




| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1,700 | 1,507 | 1,258 | 1,019 | 699 | 317 |
| Not treated by ezetimibe | 1,685 | 1,484 | 1,242 | 1,029 | 717 | 321 |

Adapted from Ouchi Y, *et al.*[1]

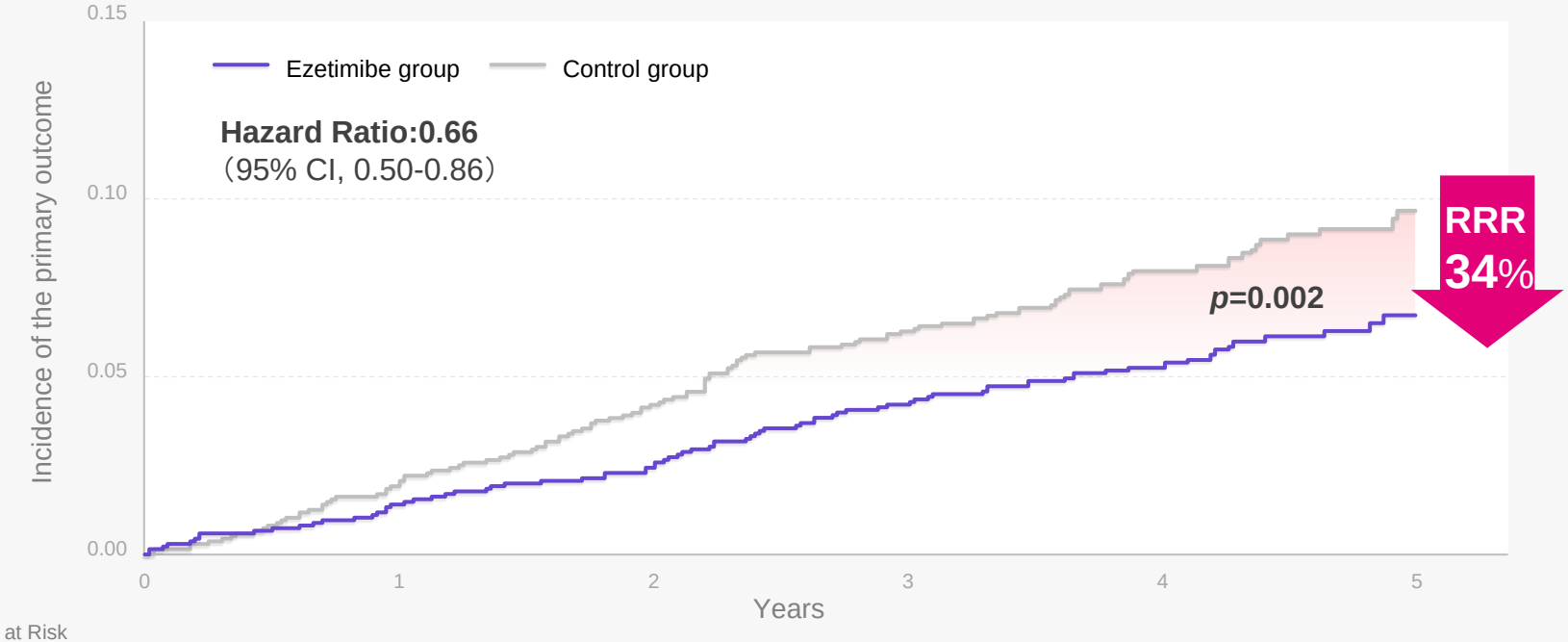
**LDL-C :** Low-density lipoprotein cholesterol, **HDL-C :** High-density lipoprotein cholesterol, **TG :** Triglycerides

**1.** Ouchi Y, *et al*. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial. *Circulation.* 2019 Sep 17;140(12):992-1003.

# Ezetimibe reduced the risks of primary outcome by 34%.[1]

EWTOPIA75 ユートピア75

## A composite of the atherosclerotic cardiovascular events
(Sudden cardiac death, myocardial infarction, PCI or CABG, and/or stroke)[1]




No. at Risk

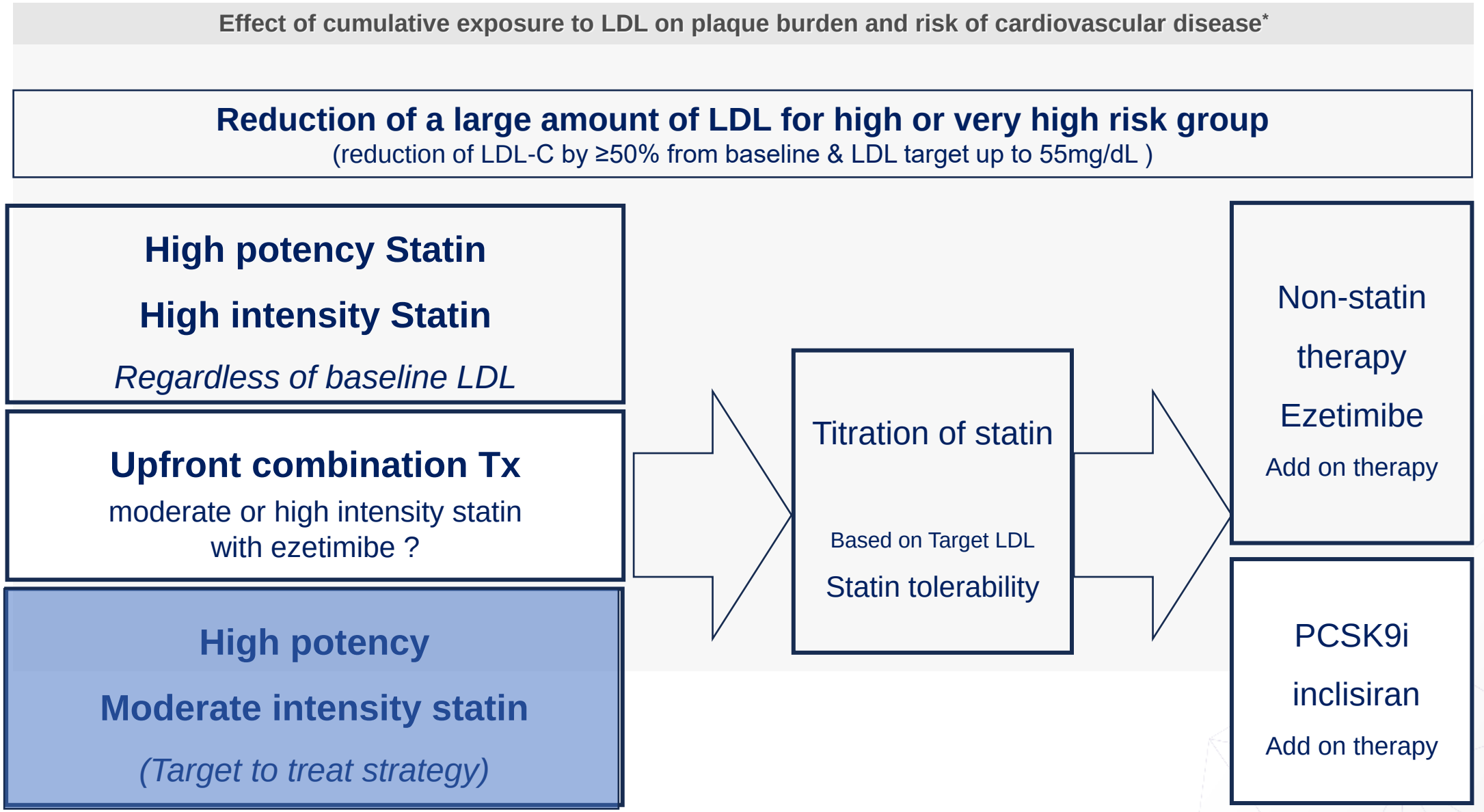
| | | | | | | |
|---|---|---|---|---|---|---|
| Control | 1,695 | 1,582 | 1,418 | 1,217 | 887 | 383 |
| Ezetimibe | 1,716 | 1,617 | 1,445 | 1,219 | 897 | 387 |

Adapted from Ouchi Y, *et al.*[1]

**PCI :** Percutaneous coronary intervention, **CABG :** Coronary artery bypass grafting, **CI :** Confidence interval, **RRR :** Relative risk reduction

**1.** Ouchi Y, *et al*. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial. *Circulation.* 2019 Sep 17;140(12):992-1003.

# What is your favorite strategy in real practice?

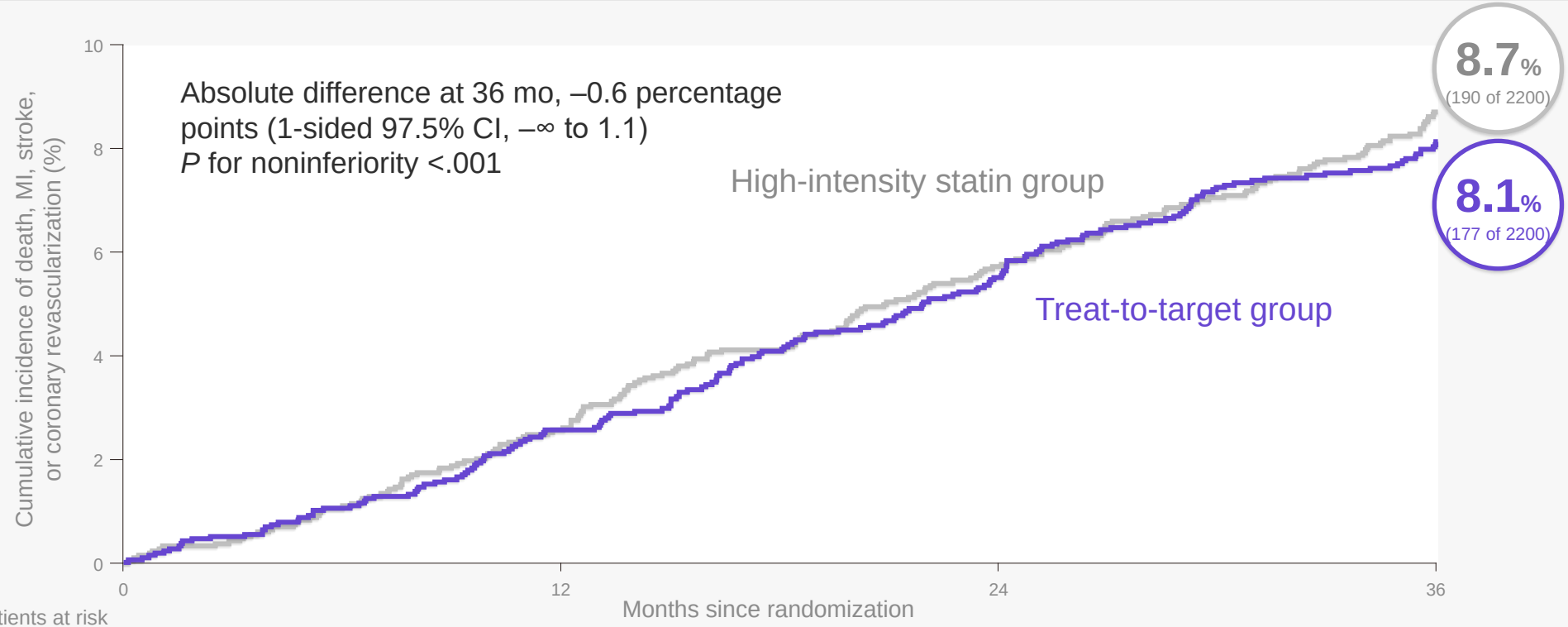


LODESTAR trial

# Treat-to-target starting with moderate statin and uptitration

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




No. of patients at risk

| | | | | |
|---|---|---|---|---|
| High-intensity statin group | 2200 | 2127 | 2056 | 1985 |
| Treat-to-target group | 2200 | 2123 | 2054 | 1989 |

Adapted from Hong SJ, *et al.*

**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.

# Changes in statin intensity in the treat-to-target group

Treat to target group : 17% uptitration to high dose statin, even 9% down titration

| | Overall study period | Initial – 3 months | 3 months – 6 months | 6 months – 1 year | 1 year – 2 years | 2 years – 3 years |
|---|---|---|---|---|---|---|
| **Total number of patients** | **2200** | **2200** | **2182** | **2177** | **2164** | **2137** |
| **Up-titration** | **378 (17)** | | | | | |
| Low-intensity to moderate-intensity | 3 (<1) | 2 (<1) | 3 (<1) | 3 (<1) | 4 (<1) | 0 |
| Moderate-intensity to high-intensity | 375 (17) | 219 (10) | 67 (3) | 109 (5) | 72 (33) | 16 (1) |
| **Without intensity changes** | **1614 (73)** | | | | | |
| Low-intensity statin maintenance | 2 (<1) | 3 (<1) | 10 (1) | 11 (<1) | 21 (1) | 26 (1) |
| Moderate-intensity statin maintenance | 765 (35) | 947 (43) | 950 (44) | 869 (40) | 828 (38) | 894 (42) |
| High-intensity statin maintenance | 847 (39) | 927 (42) | 1083 (50) | 1107 (51) | 1149 (53) | 1151 (54) |
| **Down-titration** | **208 (9)** | | | | | |
| High-intensity to moderate-intensity | 179 (8) | 92 (4) | 46 (2) | 14 (1) | 53 (2) | 1 (<1) |
| High-intensity to low-intensity | 3 (<1) | 3 (<1) | 0 | 0 | 1 (<1) | 0 |
| Moderate-intensity to low-intensity | 26 (1) | 7 (<1) | 5 (<1) | 41 (2) | 4 (<1) | 0 |
| **No maintenance of statin therapy** | – | – | 18 (1) | 23 (1) | 32 (2) | 49 (2) |

Data are numbers (percentages). When patients underwent ≥2 intensity changes for a given period, the initial and final intensity were considered as the overall change in statin intensity.

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

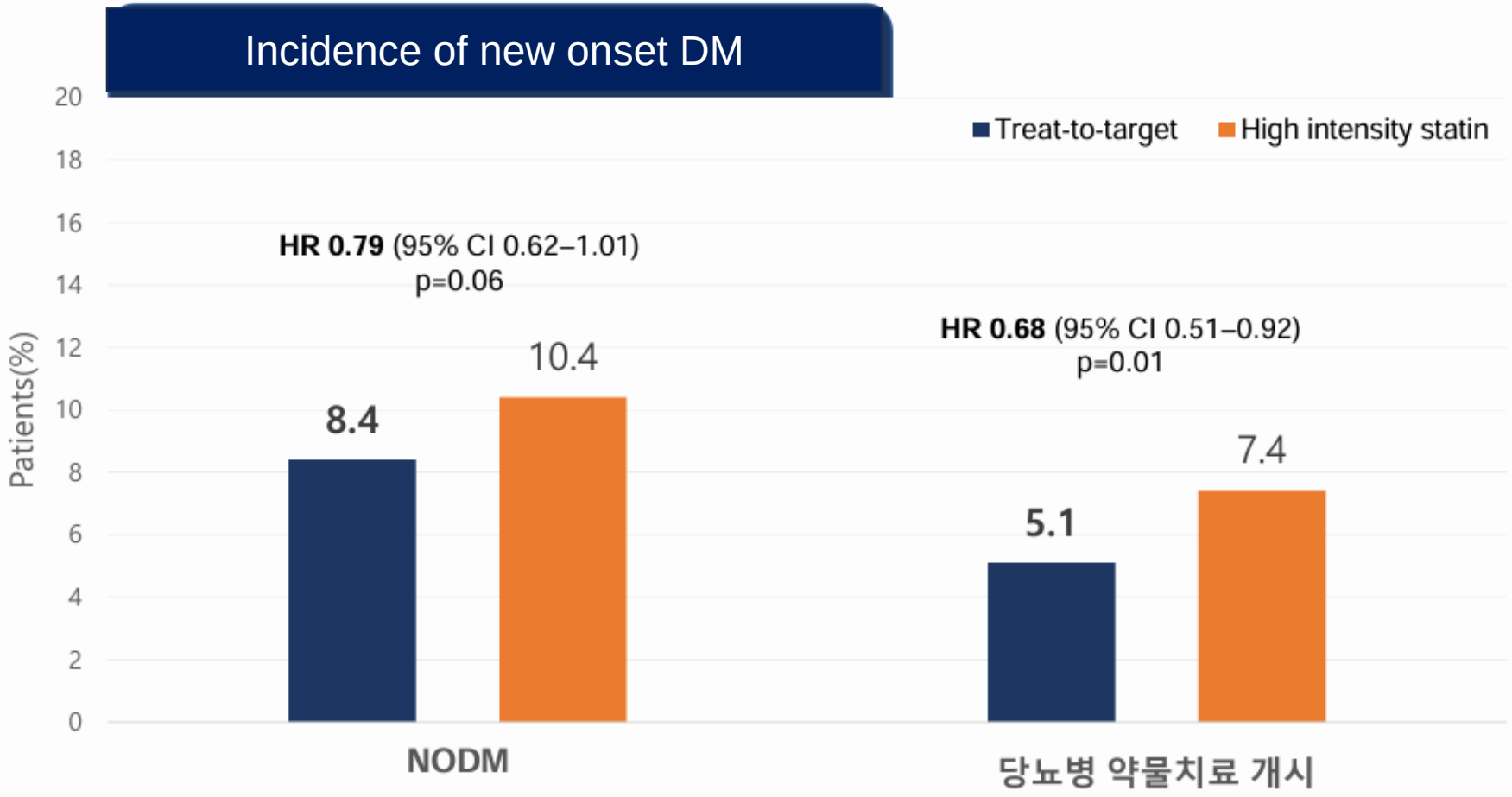
**Study design a.** This randomized, multi center, noninferiority study was to assess whether a treat-to-target strategy is noninferior to a strategy of high-intensity statins for long-term clinical outcomes in patients with coronary artery disease. Eligible patients (N=4,400) were randomized in a 1:1 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.

# Secondary outcomes - NODM

- **In patients without DM**

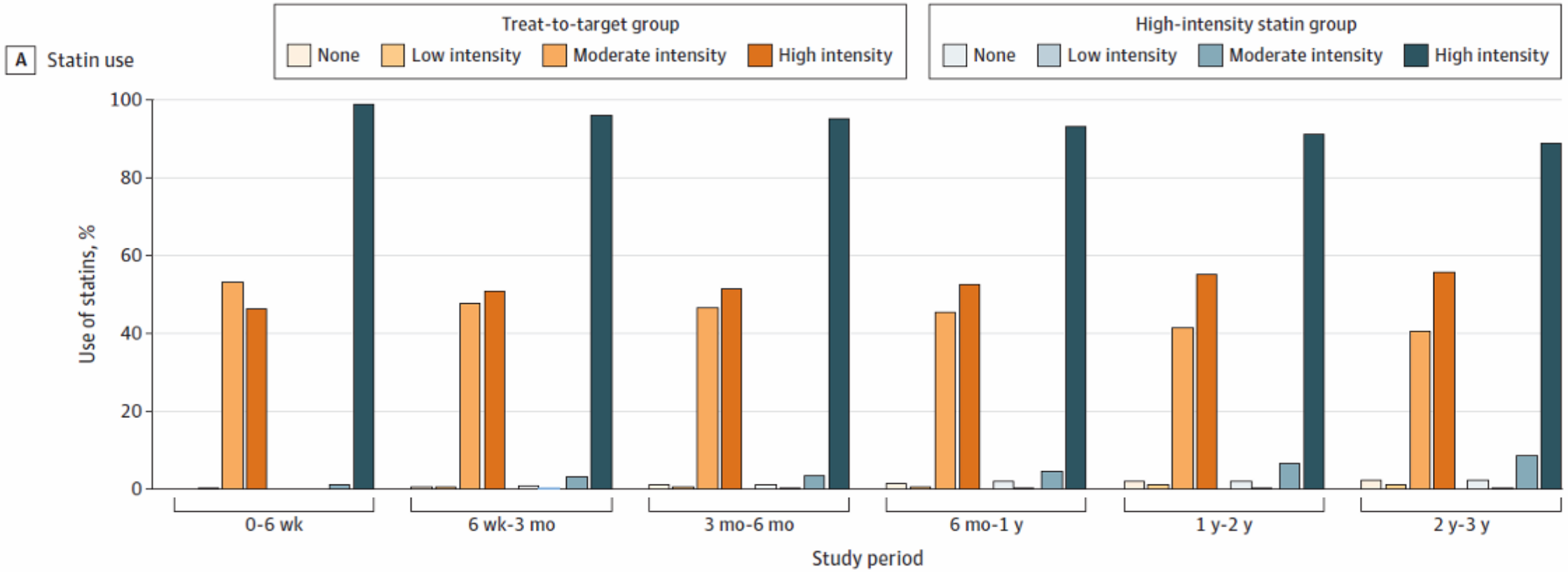
Treat to target group showed a lower rate of initiating anti-diabetic agents than that of high intensity statin group



# Lipid-lowering treatment during study

- **High intensity statin received**

Treat to target group : 53% at 1 year, 55% at 2 year and 56% at 3 year
High intensity group : 93% at 1 year, 91% at 2 years, and 89% at 3 year

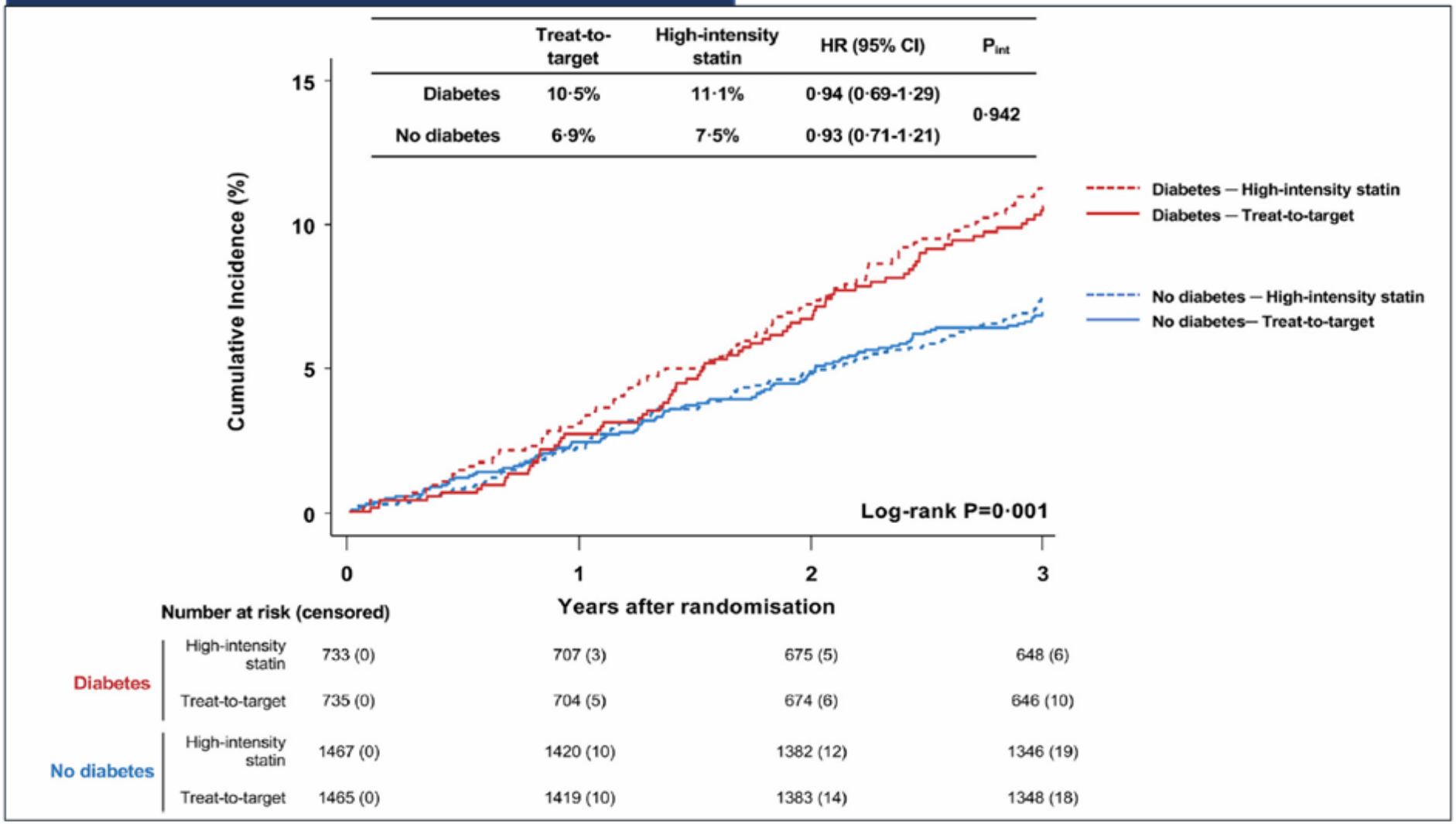



| No. of participants | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High intensity | 1022 | 2176 | 1116 | 2099 | 1125 | 2080 | 1144 | 2036 | 1197 | 1975 | 1194 | 1903 |
| Moderate intensity | 1173 | 24 | 1047 | 70 | 1019 | 76 | 989 | 99 | 900 | 143 | 868 | 182 |
| 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 |

# Primary outcome

## Regardless of diabetes, treat-to target strategy was comparable to the high intensity statin group

### 주요 심뇌혈관 사건 3년 누적 발생률
(모든 원인에 의한 사망, 심근경색, 뇌졸중, 모든 관상동맥재개통술)



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 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.

# Summary

## 1 Early & Lower for Longer

A strategy is required to maintain the LDL-C target low from the early stage for long periods of time in patients with high risk of ASCVD, including secondary prevention.

## 2 Remember the high risk group of <50% reduction of baseline LDL and more aggressive treatment required

Prior Lipid lowering therapy,  low level of baseline LDL, Diabetes could be groups of poor LDL reduction %

## 3 Upfront combination with ezetimibe is a good alternative option for more LDL reduction than high intensity Tx.

A few data demonstrated it’s clinical outcomes could be not inferior to the high intensity statin  but better LDL reduction and lower adverse events.

## 4 Moderate intensity statin with treat to target should be stringent  and individualized of LDL management

Moderate intensity statin responsive to the LDL target goal can be differentiate and then further up-titration for the rest