THE 14th INTERNATIONAL CONGRESS OF
ENDOCRINE DISORDERS

Lipid Management in Patients with Type 2 Diabetes:

Treat-to-Target vs High-Intensity Statin

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Tehran, Iran

Disclosures

- I have no relevant conflicts of interest.

Outline

- Overview of recent guidelines on cholesterol management
- Lipid-lowering therapy use in the real world
- LODESTAR trial
- LODESTAR-DM
- RACING trial
- RACING-DM
- Concluding remark

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Circulation
Volume 129, Issue 25_suppl_2, 24 June 2014; Pages S1-S45
https://doi.org/10.1161/01.cir.0000437738.63853.7a

ACC/AHA PREVENTION GUIDELINE

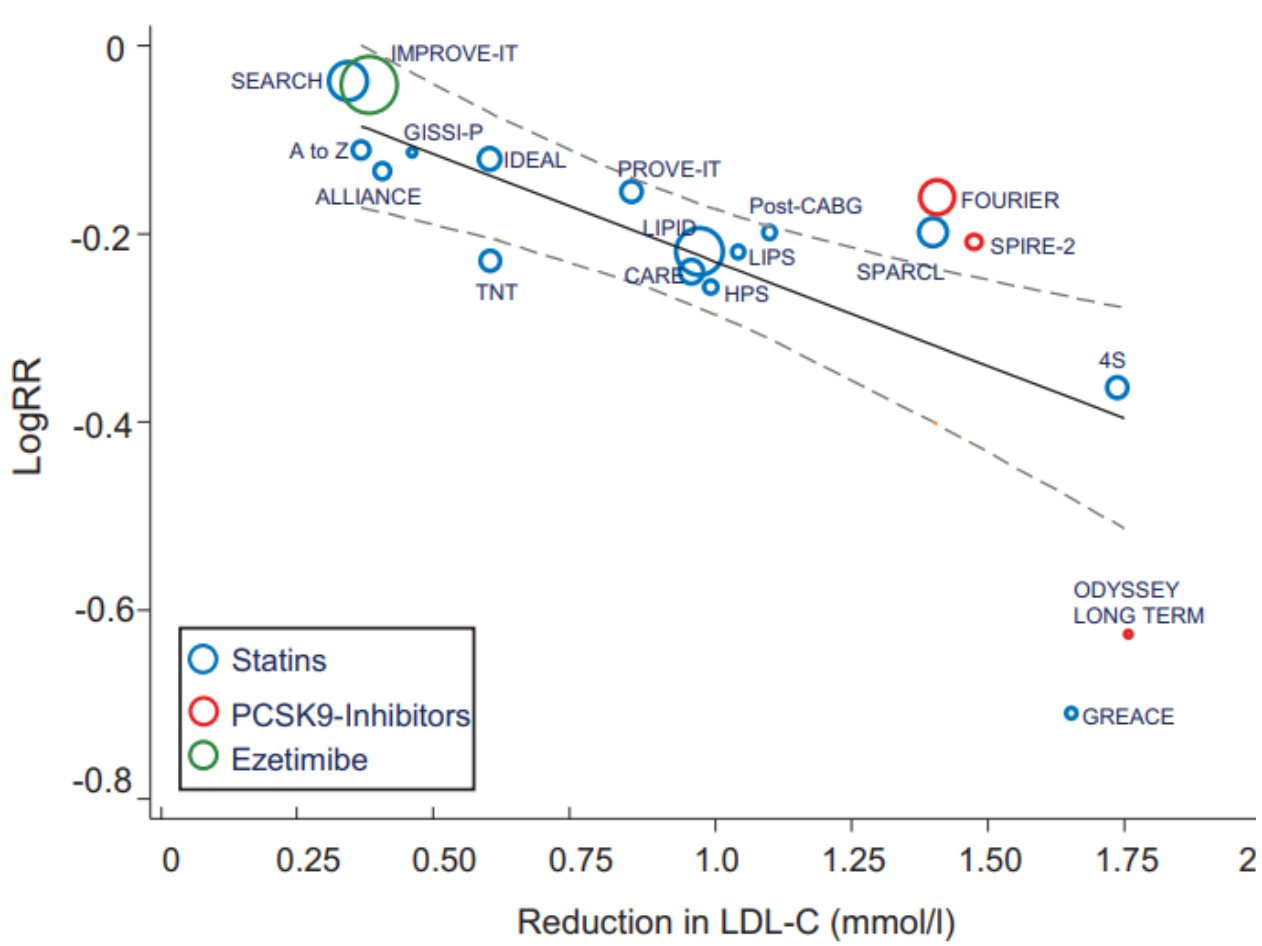
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

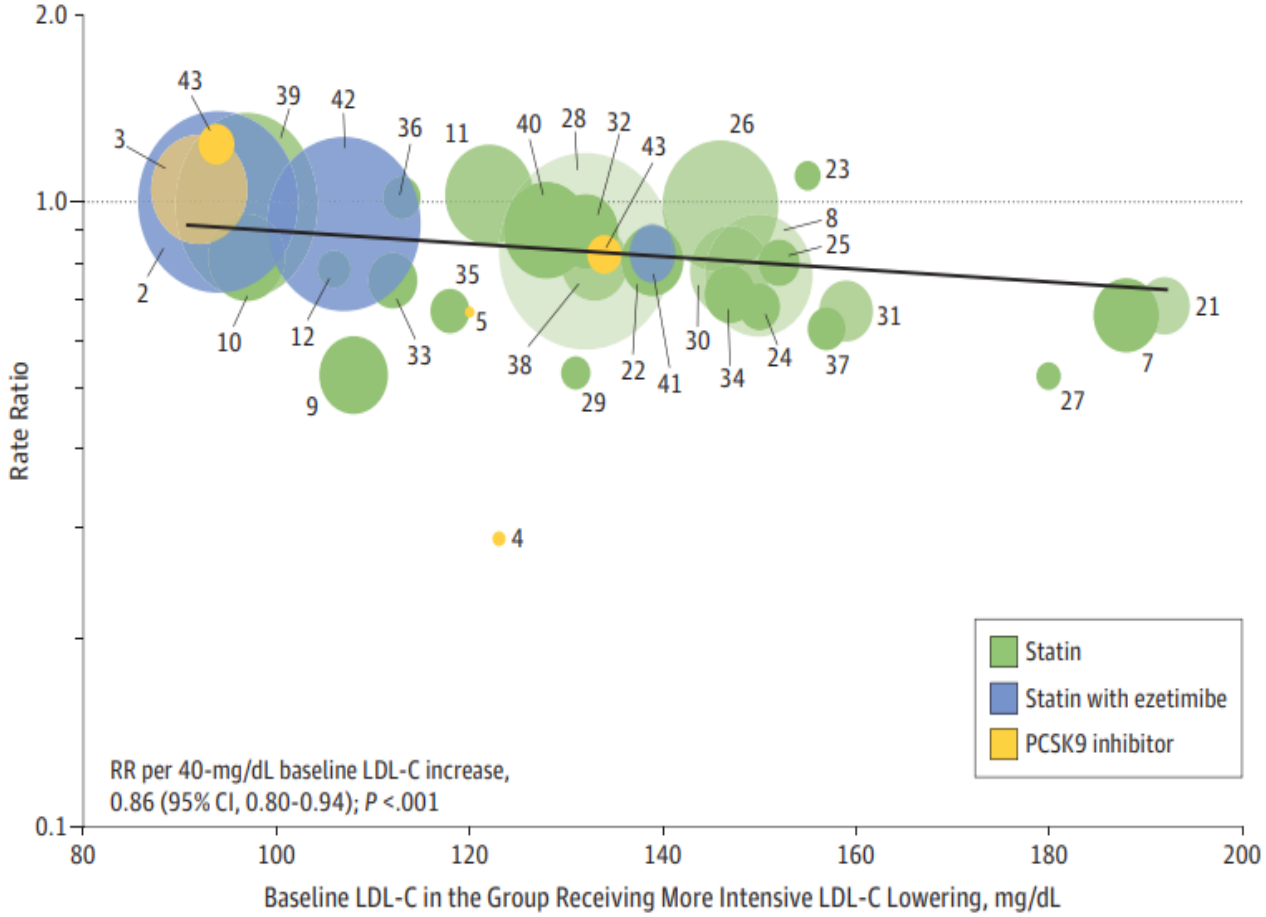
A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

- **Treatment targets:**

- The panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD.
- LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.

Two meta-analyses of randomized clinical trials





Koskinas KC, et al. Eur Heart J 2018 Apr 7;39(14):1172-1180.

Navarese EP, et al. JAMA 2018;319(15):1566-1579.

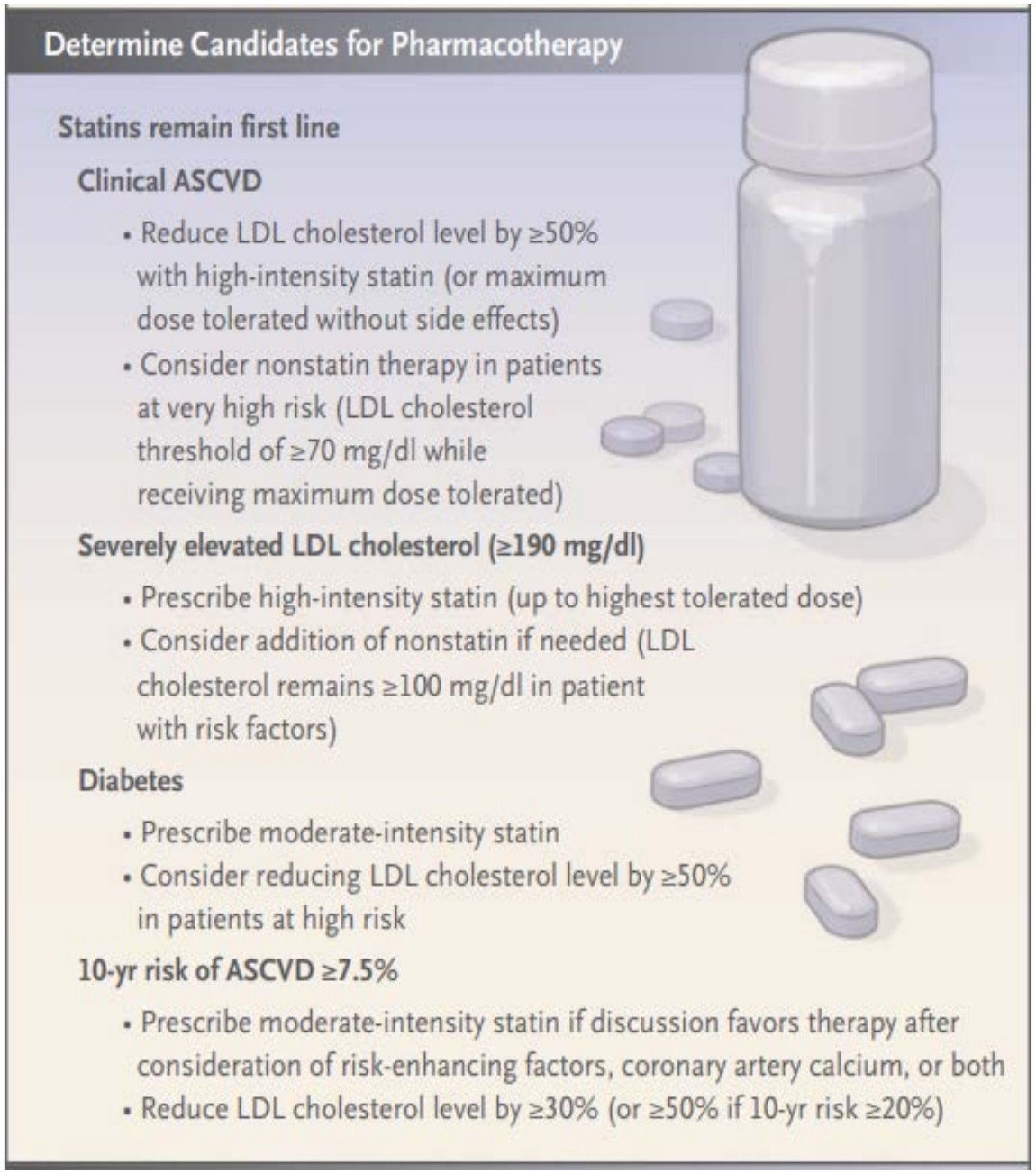
Circulation
Volume 139, Issue 25, 18 June 2019; Pages e1082-e1143
https://doi.org/10.1161/CIR.0000000000000625

American Heart Association.

CHOLESTEROL CLINICAL PRACTICE GUIDELINES

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Grundy SM, et al. Circulation 2019;139:e1082-e1143.
Michos ED, et al. N Engl J Med 2019;381:1557-67.

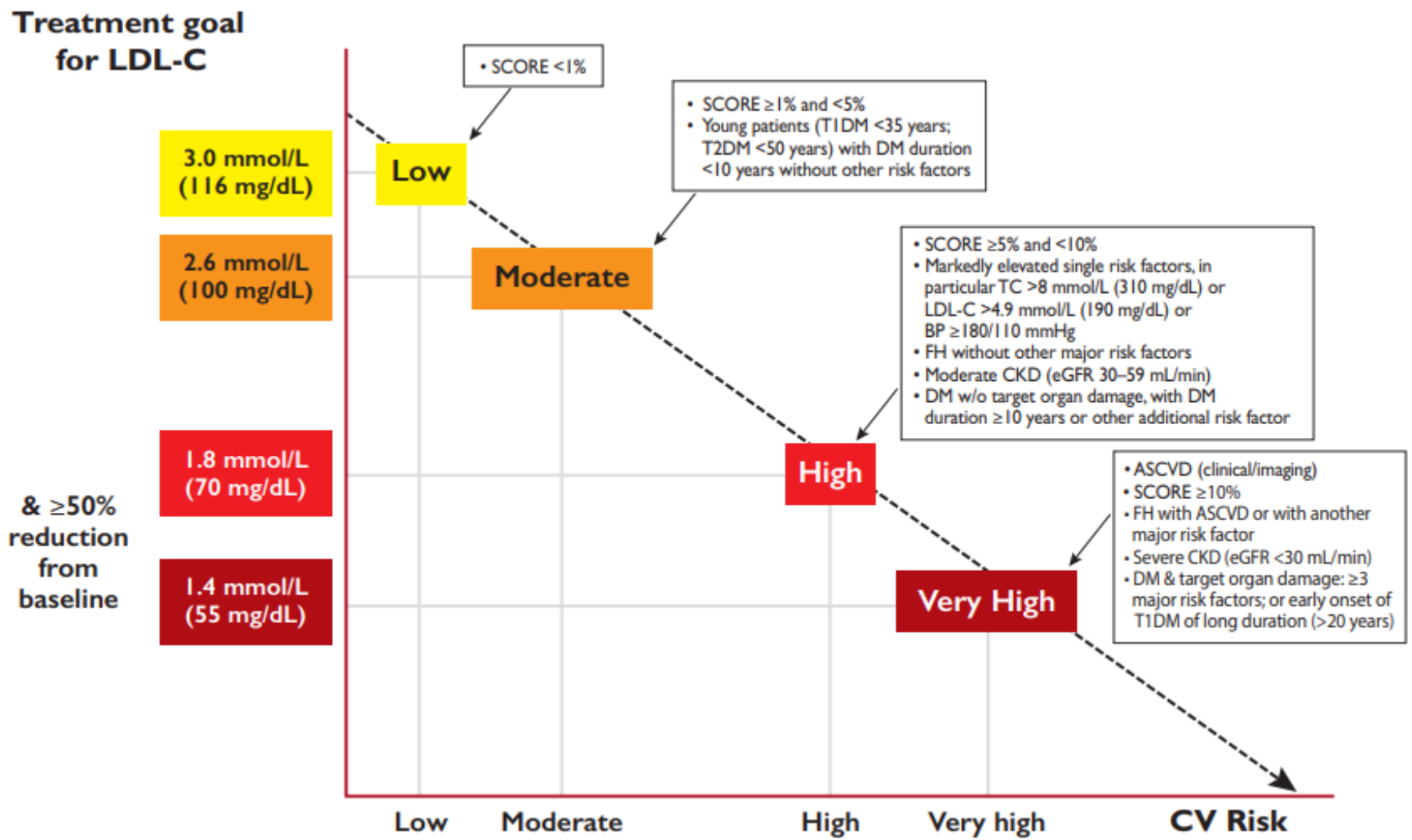


ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

**The Task Force for the management of dys
European Society of Cardiology (ESC) and
Atherosclerosis Society (EAS)**



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ESC European Society of Cardiology
European Journal of Preventive Cardiology (2021) **28**, 1279–1289
doi:10.1093/eurjpc/zwaa047

FULL RESEARCH PAPER

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study

Objective: To provide contemporary data on the implementation of European guideline recommendations for lipid-lowering therapies across different settings and populations and how this impacts LDL-C goal achievement.

Setting: Primary and secondary care clinics across 18 European countries.

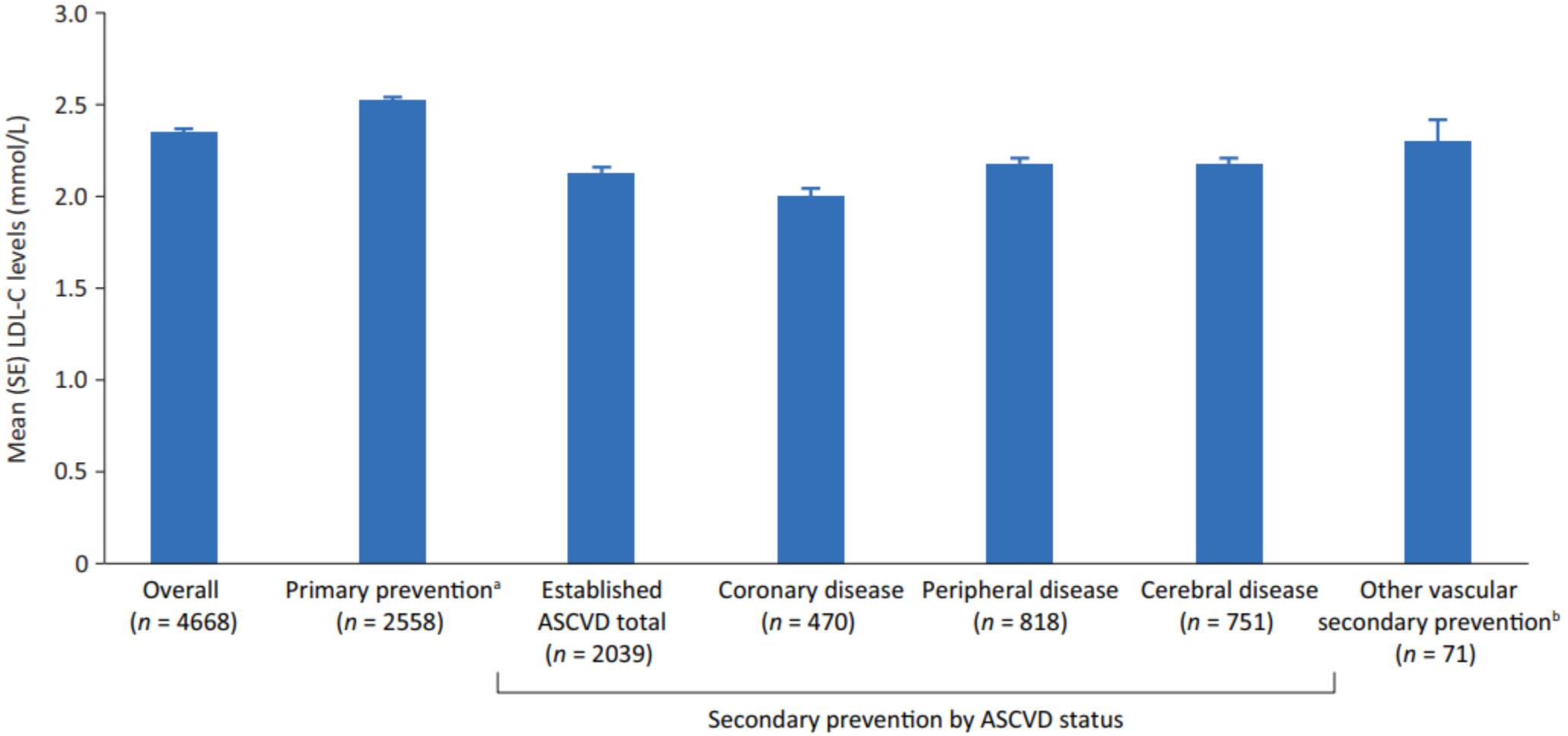
Ray KK, et al. Eur J Prev Cardiol 2021;28(11):1279-1289 .

Mean LDL-C:

Primary prevention patients: 98 mg/dL
Coronary disease: 78 mg/dL
Peripheral disease: 85 mg/dL
Cerebral disease: 84 mg/dL

Mean LDL-C:

High-intensity statin monotherapy: 84 mg/dL
Moderate-intensity statin monotherapy: 89 mg/dL



Ray KK, et al. Eur J Prev Cardiol 2021;28(11):1279-1289 .

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JAMA | Original Investigation

Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease

A Randomized Clinical Trial LODESTAR

Objective: 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 (a head-to-head comparison).

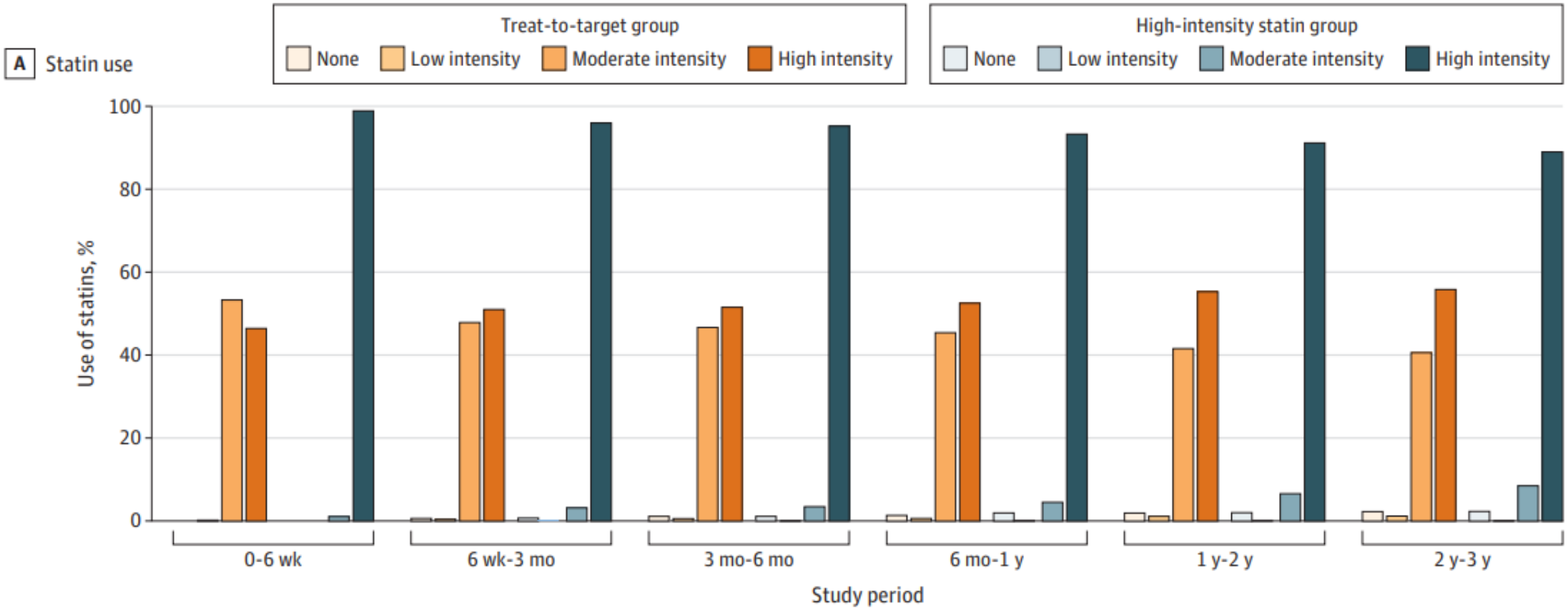
Design, Setting, and Participants: A randomized, multicenter, noninferiority trial in 4400 patients with a CAD treated at 12 centers in South Korea.

Interventions: Either the LDL-C target strategy, with an LDL-C level between 50 and 70 mg/dL as the target, or high-intensity statin treatment (rosuvastatin, 20 mg, or atorvastatin, 40 mg).

Main Outcomes and Measures: A 3-year composite of death, myocardial infarction, stroke, or coronary revascularization with a non-inferiority margin of 3%.

Hong SJ, et al. JAMA. 2023 Apr 4;329(13):1078-1087.

In the treat-to-target group, taking the high-intensity statin:
1 year: 53%
2 year: 55%
3 year: 56%

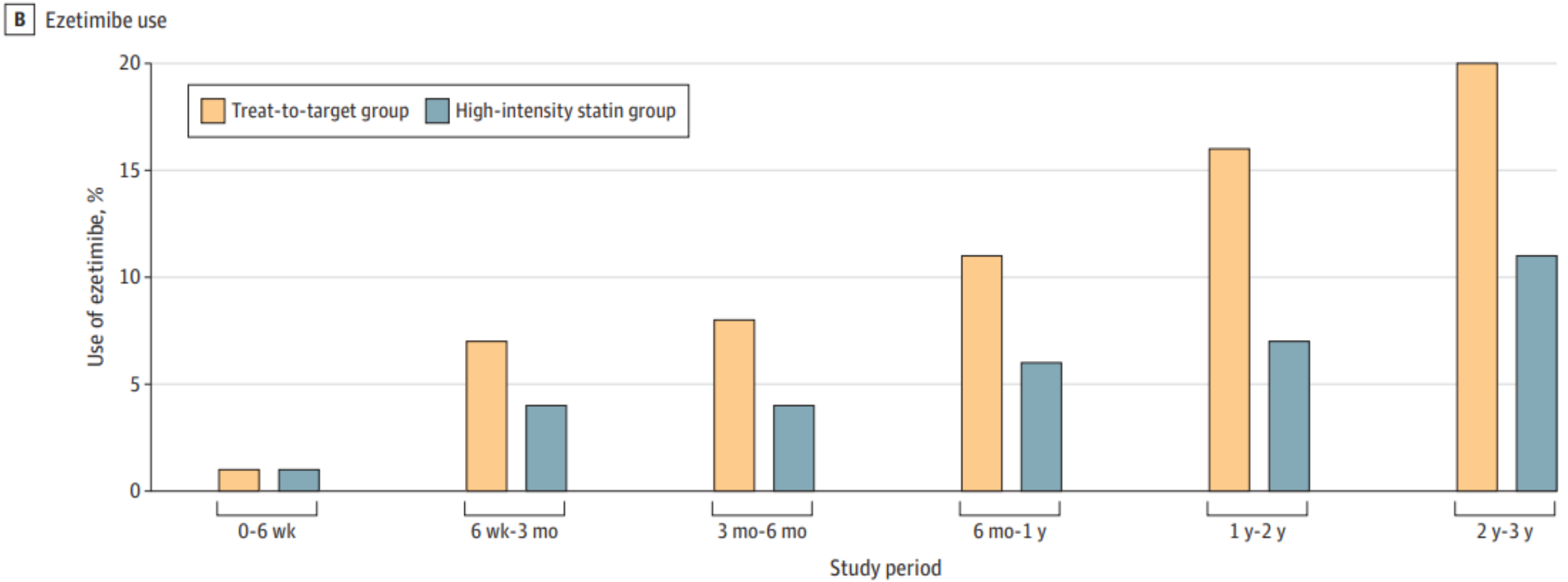


Hong SJ, et al. JAMA. 2023 Apr 4;329(13):1078-1087.

Ezetimibe use at 3 years:

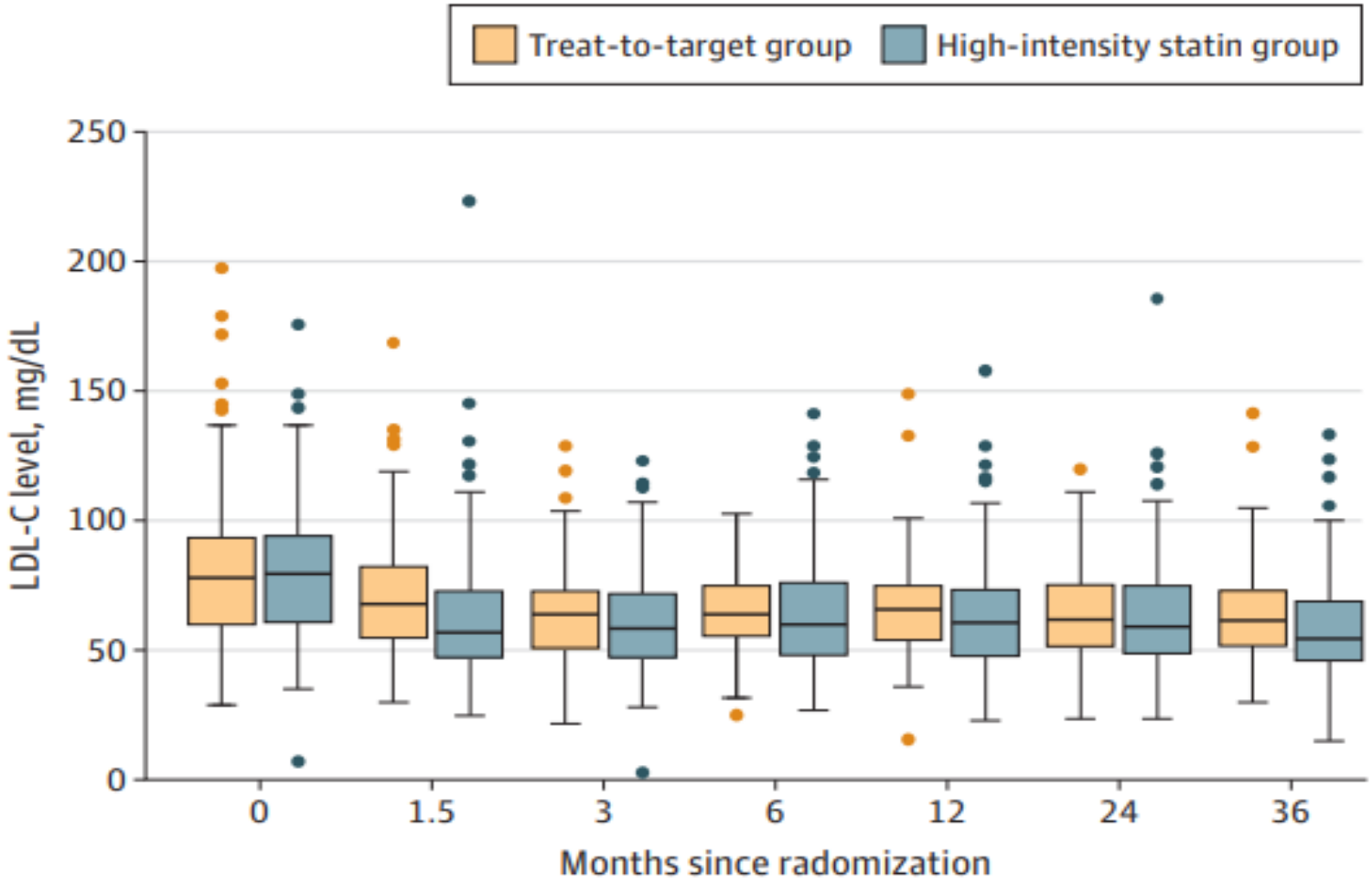
Treat-to-target group: 20%

High-intensity statin group: 11%



Hong SJ, et al. JAMA. 2023 Apr 4;329(13):1078-1087.

After 6 weeks, the LDL-C levels did not differ between the groups.

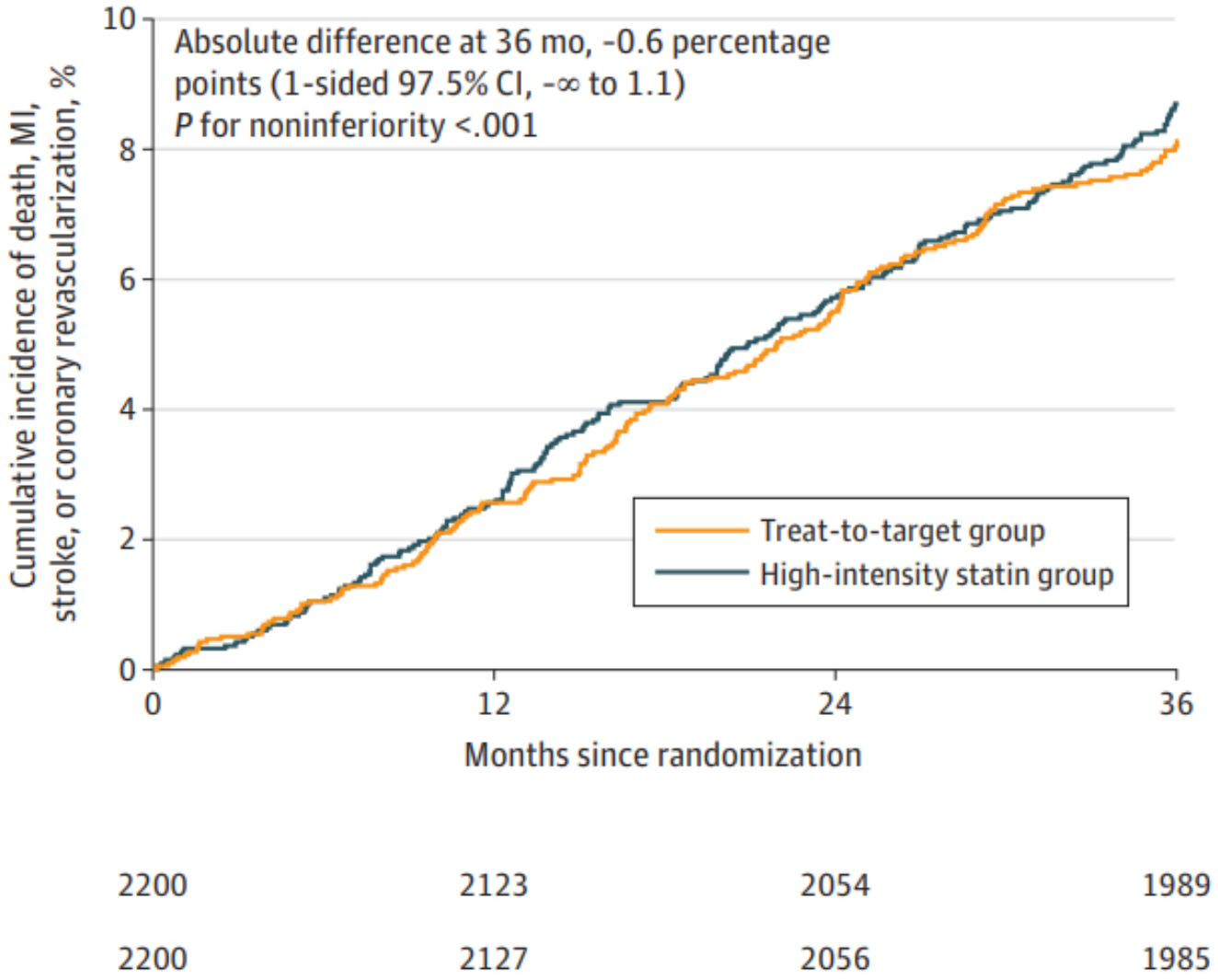


No. at risk

Treat-to-target group	2200	1598	441	1074	1862	1654	1560
High intensity statin group	2200	1601	397	1092	1854	1679	1554

- Only approximately 60% in the treat-to-target strategy group achieved an LDL-C <70 mg/dL.

Hong SJ, et al. JAMA 2023 Apr 4;329(13):1078-1087.



- **The primary end point:**

  - The treat-to-target group: 177 patients (8.1%)

  - The high-intensity statin group: 190 patients (8.7%)

  - Absolute difference: – 0.6%

Hong SJ, et al. JAMA 2023 Apr 4;329(13):1078-1087.

JAMA

QUESTION Is treatment to a goal low-density lipoprotein cholesterol (LDL-C) level between 50 and 70 mg/dL noninferior to a strategy using high-intensity statin therapy among patients with coronary artery disease?

CONCLUSION This randomized clinical trial found that the treat-to-target LDL-C strategy was noninferior to the high-intensity statin strategy for major clinical outcomes.

POPULATION

3172 Men
1228 Women

Adults with clinically diagnosed coronary artery disease (ie, stable ischemic heart disease or acute coronary syndrome)

Mean age: 65.1 years

LOCATIONS

12
Centers in South Korea

INTERVENTION

Treat to target
Titrated-intensity statin therapy, with an LDL-C level between 50 and 70 mg/dL as the target

High-intensity statin
Rosuvastatin, 20 mg, or atorvastatin, 40 mg, once daily

PRIMARY OUTCOME

3-Year composite of death, myocardial infarction, stroke, or coronary revascularization with a noninferiority margin of 3.0 percentage points

FINDINGS

Primary end point

Treat to target
8.1% (177 of 2200 patients)

High-intensity statin
8.7% (190 of 2200 patients)

Treat-to-target LDL-C strategy was noninferior to high-intensity statin strategy:

Absolute difference,
-0.6 percentage points
(1-sided 97.5% CI, −∞ to 1.1)

Hong SJ, Lee YJ, Lee SJ, et al; LODESTAR Investigators. Treat-to-target or high-intensity statin in patients with coronary artery disease: a randomized clinical trial. *JAMA*. Published March 6, 2023. doi:10.1001/jama.2023.2487

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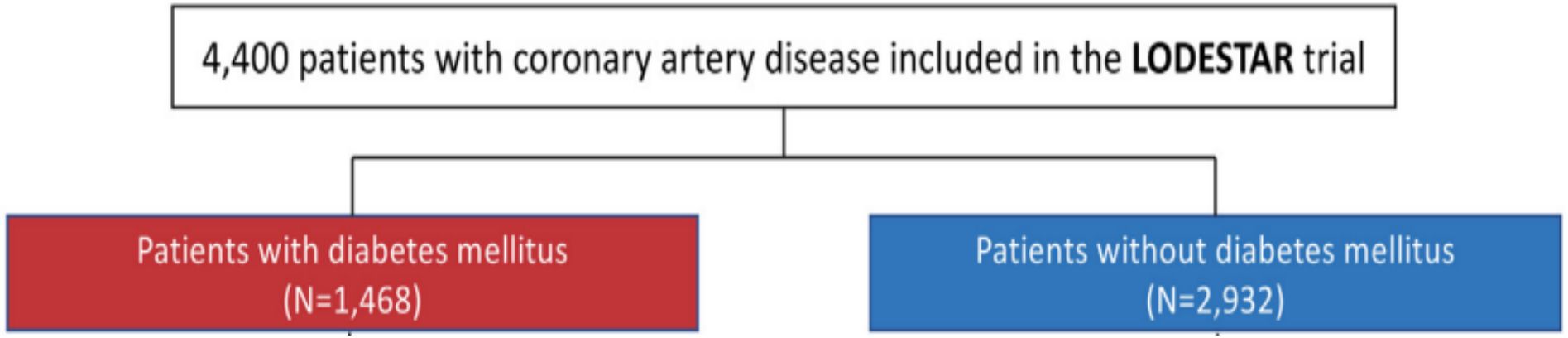
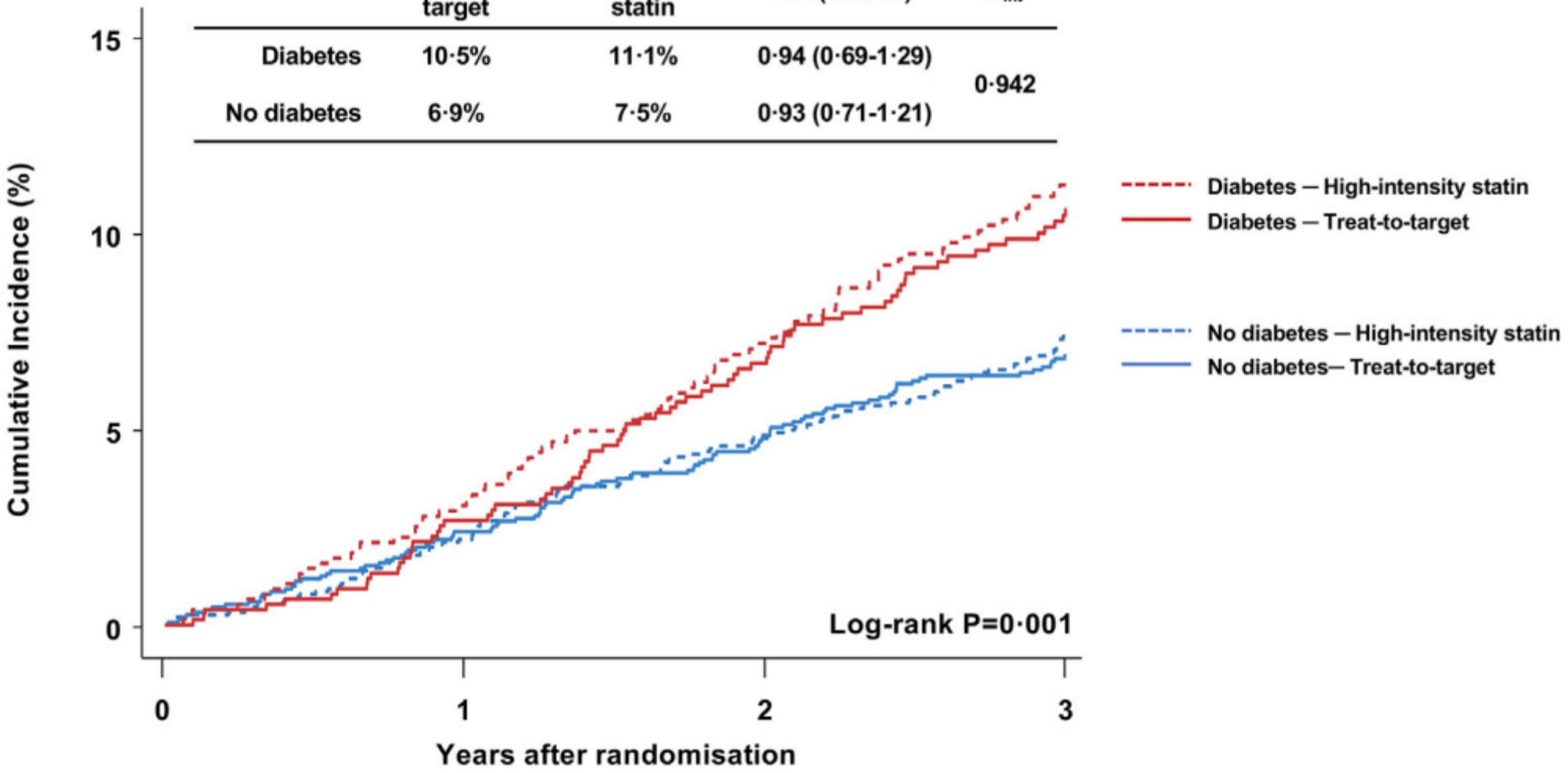
Treat-to-target versus high-intensity statin treatment in patients with or without diabetes mellitus: a pre-specified analysis from the LODESTAR trial



Lee SJ, et al. eClinicalMedicine 2023;64:102227.

In patients with CAD, a treat-to-target LDL-C strategy of 50-70 mg/dL as the goal was comparable to high-intensity statin therapy in terms of 3-year clinical efficacy and safety outcomes **regardless of the presence of DM**.

	Treat-to-target	High-intensity statin	HR (95% CI)	P_{int}
Diabetes	10·5%	11·1%	0·94 (0·69-1·29)	0·942
No diabetes	6·9%	7·5%	0·93 (0·71-1·21)	



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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

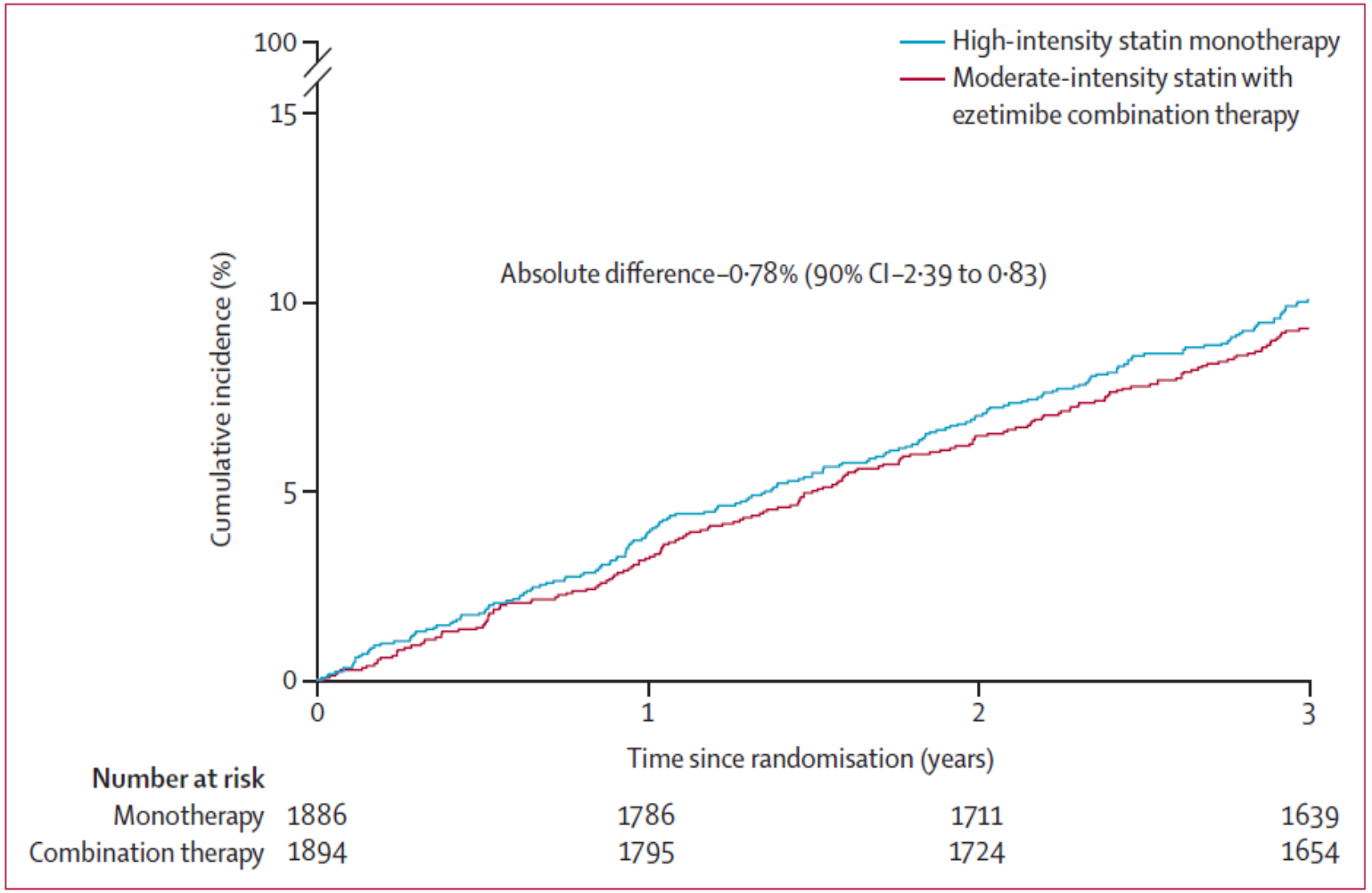
Objective: To compare 3-year clinical efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients who are at very high risk for cardiovascular diseases.

Participants: 3780 patients with ASCVD at 26 clinical centers in South Korea.

Interventions: Moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg).

Primary endpoint: 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%.

Kim BK, et al. Lancet 2022;400:380-90.

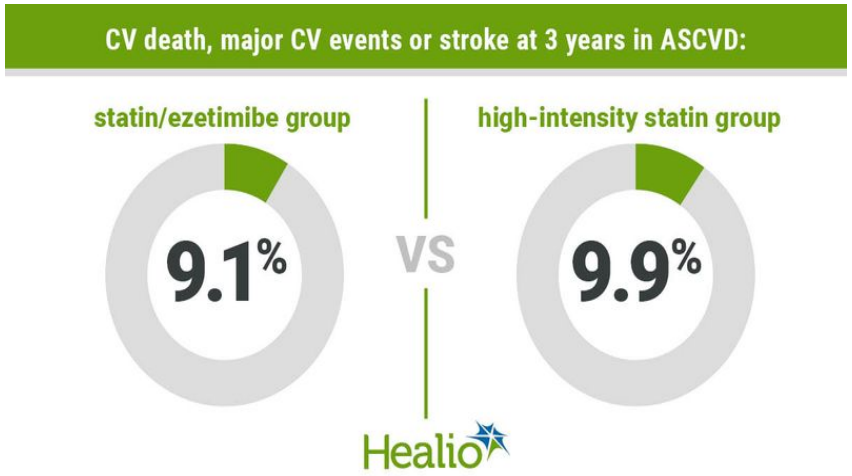


- **The primary endpoint:**

- Combination therapy group: 172 patients (9·1%)

- High-intensity statin group: 186 patients (9·9%)

- Absolute difference: −0·78%; 90% CI −2·39 to 0·83



Kim BK, et al. Lancet 2022;400:380-90.

Proportions of the patients with LDL-C <70 mg/dL
in the intention-to-treat population

	Moderate-intensity statin with ezetimibe combination therapy	High-intensity statin monotherapy	Absolute differences in proportions, % (95% CI)
1 year			
Number of patients	1675	1673	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1217 (73%)	923 (55%)	17·5 (14·2 to 20·7)
LDL cholesterol concentration (mg/dL)	58 (47–71)	67 (55–80)	..
2 years			
Number of patients	1558	1539	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1168 (75%)	924 (60%)	14·9 (11·6 to 18·2)
LDL cholesterol concentration (mg/dL)	57 (45–70)	65 (53–79)	..
3 years			
Number of patients	1349	1315	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	978 (72%)	759 (58%)	14·8 (11·1 to 18·4)
LDL cholesterol concentration (mg/dL)	58 (47–71)	66 (54–80)	..

Data are number of patients (%) or median (IQR).

Kim BK, et al. Lancet 2022;400:380-90.

Conclusions (RACING trial)

- Among patients with ASCVD, moderate-intensity statin with ezetimibe was non-inferior to high-intensity statin for the 3-year composite outcomes with a higher proportion of patients with LDL-C <70 mg/dL and lower intolerance-related drug discontinuation or dose reduction.

- Our results support recommending the addition of ezetimibe for patients who are taking moderate-intensity statins at a maximal tolerance. Ezetimibe combination therapy might be considered earlier in the use of moderate-intensity statin therapy rather than doubling the statin dose for patients at high risk of adverse effects or statin intolerance with high-intensity statin therapy.

Kim BK, et al. Lancet 2022;400:380-90.

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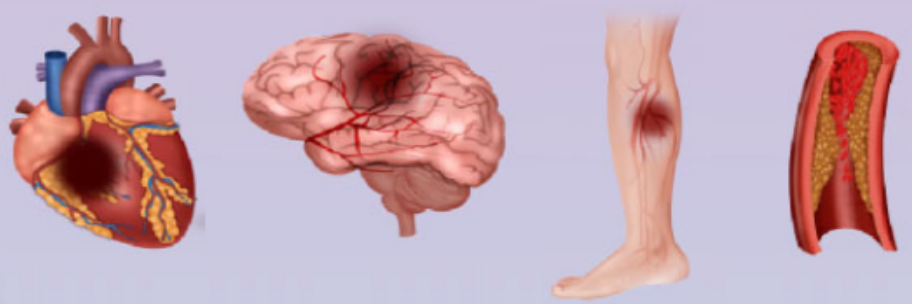
A pre-specified subgroup analysis of the randomized RACING trial

1,398 DM patients with ASCVD included in the RACING trial



Moderate-intensity statin+ezetimibe combination therapy — 701

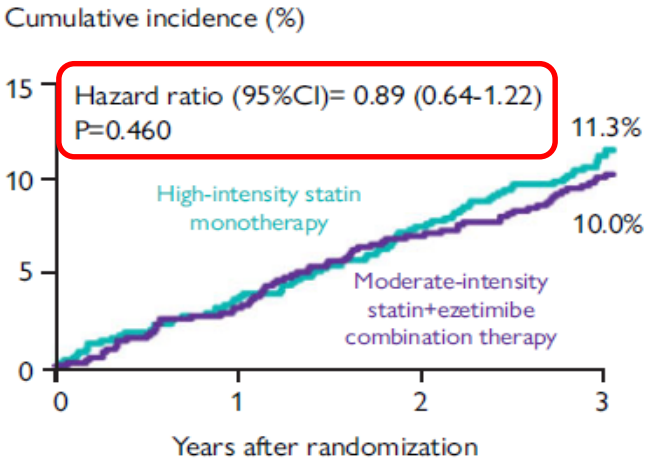
High-intensity statin monotherapy — 697

Composite of cardiovascular death, major cardiovascular events, or nonfatal stroke at 3 years

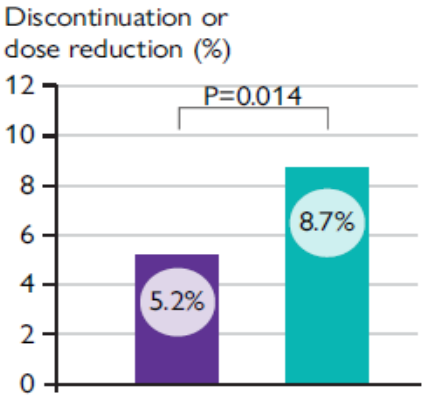
Intolerance-related drug discontinuation or dose reduction

Proportion of patients with LDL cholesterol levels <70 mg/dL

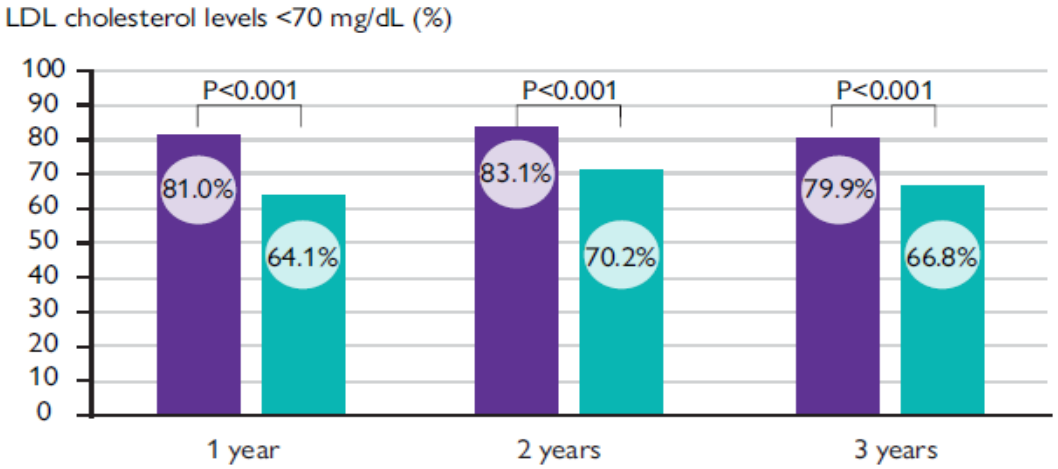
Composite cardiovascular outcomes



Intolerance



LDL cholesterol reduction



Lee YJ, et al. Eur Heart J 2023;44:972-983.

Conclusions

- The findings of the LODESTAR trial suggest that either a treat-to-target or a high-intensity statin approach is reasonable for patients with coronary artery disease.

Conclusions

Lowering LDL cholesterol in clinical practice: time for change?

- Is it time for a paradigm shift in the management of lipids toward an approach with combination therapy as an initial treatment option that is more similar to the treatment of hypertension?

- This therapeutic inertia might be overcome through early initiation of combination lipid-lowering therapy (probably with a treat-to-target strategy), leading to a greater proportion of patients with ASCVD meeting the LDL-C goal.

Adopted from Abushamat LA, Ballantyne CM. Lancet 2022 Jul 30;400(10349):341-343.

Thanks for your patience

Photo by Majid Valizadeh, MD