

# ACC.26



## Intensive LDL cholesterol targeting in atherosclerotic cardiovascular disease : The Ez-PAVE randomized clinical trial

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on behalf of the Ez-PAVE Investigators

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# Disclosure

- **Speaker's name: Byeong-Keuk Kim**

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# Background



- In patients with atherosclerotic cardiovascular disease (ASCVD) at high or very high risk, recent guidelines have lowered the **low-density lipoprotein cholesterol (LDL-C) target from <70 mg/dL to <55 mg/dL.**

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- These recommendations are based on prior trials showing that high-intensity statins and combination therapies reduce LDL-C levels and cardiovascular risk, although **most did not directly evaluate specific LDL-C targets.**

	PROVE IT-TIMI 22	TNT	IMPROVE-IT	FOURIER	ODYSSEY OUTCOMES
Experimental vs. Control therapy	Atorvastatin 80 mg vs. Pravastatin 40 mg	Atorvastatin 80 mg vs. Atorvastatin 10 mg	Simva-/ezetimibe 40/10 mg vs. Simvastatin 40 mg	Evolocumab + statins vs. placebo + statins	Alirocumab + statins vs. placebo + statins

- Therefore, **randomized evidence supporting this stricter target (LDL-C <55mg/dL) remains limited.**

# Objective



- To investigate whether **LDL-C targeting <55 mg/dL (intensive targeting)** is superior to **targeting <70 mg/dL (conventional targeting)** in preventing cardiovascular events in patients with ASCVD.

# Trial design and population



- **Investigator-initiated, multicenter, randomized, open-label, superiority trial**  
(ClinicalTrials.gov number, NCT04626973)
- **Conducted at 17 sites in South Korea**
- **Enrollment period: January 2021 and July 2022**
- **Enrollment criteria**

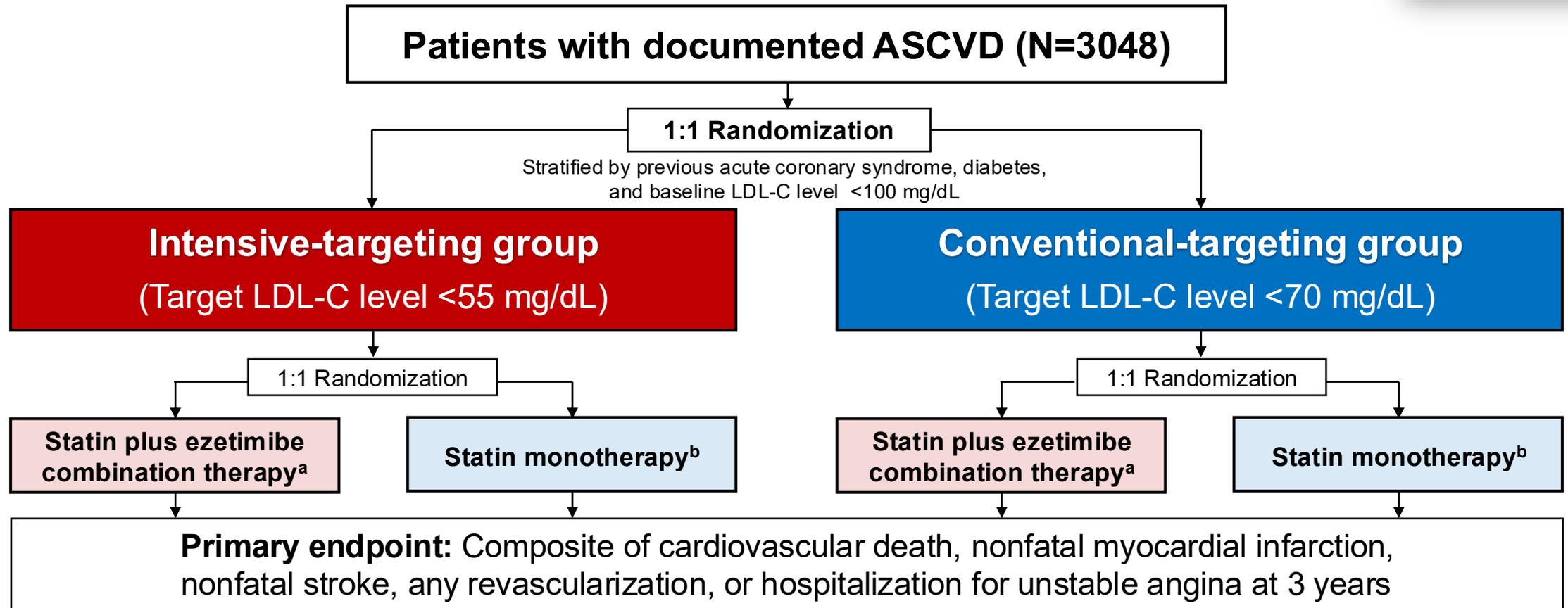
## Inclusion criteria

1. Age 19–80 years
2. **Documented ASCVD** (at least one of the following):
  - A. Previous acute coronary syndrome**
  - B. Stable angina** with imaging or functional studies
  - C. Coronary or other arterial revascularization**
  - D. Stroke or transient ischemic attack**
  - E. Peripheral artery disease**

## Exclusion criteria

1. LDL-C <70 mg/dL without statin therapy
2. Allergy or hypersensitivity to statins or ezetimibe
3. Active liver diseases or persistent elevation of aminotransferase levels >2 times UNL
4. Solid organ transplantation recipient
5. Pregnant, potent childbearing, or lactating women
6. Life expectancy <3 years
7. Inability to perform follow-up
8. No informed consent

# Randomization and follow-up



- <sup>a</sup>Combination therapy: **rosuvastatin plus ezetimibe**
- <sup>b</sup>Statin monotherapy: **rosuvastatin** or **atorvastatin** (1:1 randomization)
- Therapy titrated to achieve target LDL-C; **statin up-titration and ezetimibe** recommended before **PCSK9 inhibitors**

# Trial end points



- **Primary end point**

Composite of **cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for unstable angina at 3 years**

- **Key secondary end points**

Efficacy endpoints	Safety endpoints
<ol style="list-style-type: none"><li>1. Individual components of the primary end point</li><li>2. Prespecified composite end points</li></ol>	<ol style="list-style-type: none"><li>1. New-onset diabetes</li><li>2. Worsening of glycemic control</li><li>3. Statin-associated muscle symptoms leading to changes in therapy dose or regimen</li><li>4. Cancer diagnosis</li><li>5. Cataract surgery</li><li>6. Aminotransferase elevation</li><li>7. Creatine kinase elevation</li><li>8. Creatinine elevation</li></ol>

# Statistical considerations



## ▪ Sample size estimation

- The primary objective was to **compare LDL-C lowering therapy** with **intensive targeting vs conventional targeting** with respect to the primary endpoint under the **superiority hypothesis** of the **intensive targeting** over **conventional targeting** in patients with ASCVD.
- Assuming a 3-year incidence of 15% in the **conventional-targeting group** & 15% attrition rate, a total of **3048 patients** would provide 80% power (two-sided alpha level of 0.05) to detect a 24.75% lower relative risk of the primary endpoint in the **intensive-targeting group**.

## ▪ Statistical analysis

- Primary intention-to-treat analysis
- Cumulative incidences calculated by Kaplan–Meier method and compared with log-rank test
- Subgroup analysis according to prespecified factors

# Investigators and trial organizations



## ▪ **Participating investigators (17 sites in South Korea)**

Byeong-Keuk Kim (Severance Hospital, Severance Hospital, Yonsei University College of Medicine); Jin Won Kim (Korea University Guro Hospital, Korea University College of Medicine); Gwang-Sil Kim (Sanggye Paik Hospital, Inje University College of Medicine); Jae Hyoung Park (Korea University Anam Hospital, Korea University College of Medicine); Jin-Man Cho (Kyung Hee University Hospital at Gangdong); Woong Chol Kang (Gachon University Gil Medical Center); Hyuck-Jun Yoon (Dongsan Hospital, Keimyung University); Won Ho Kim (Eulji University Hospital); Seung-Jin Lee (Soonchunhyang University Hospital); Jin Bae Lee (Daegu Catholic University Hospital); Ji-Yong Jang (National Health Insurance Service Ilsan hospital); Sanghoon Shin (Ewha Womans University Seoul Hospital); Ik Hyun Park (Samsung Changwon Hospital, Sungkyunkwan University School of Medicine); Sung Uk Kwon (Inje University Ilsan Paik Hospital); Sunwon Kim (Korea University Ansan Hospital, Korea University College of Medicine); Ung Kim (Yeungnam University Medical Center); Jung Hoon Sung (Cha Bundang Medical Center, CHA University)

## ▪ **Executive Committee**

Byeong-Keuk Kim (Trial PI), Yong-Joon Lee, and Seung-Jun Lee

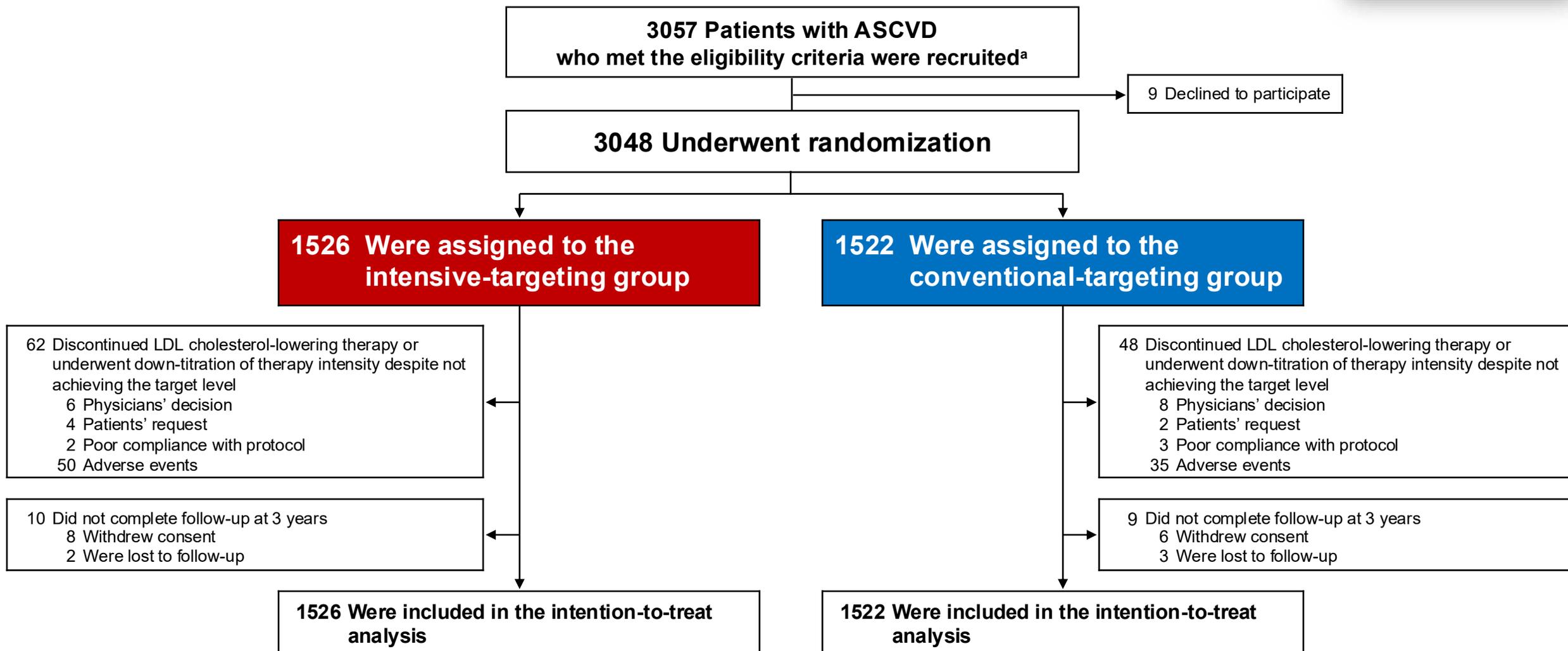
## ▪ **Clinical events adjudication committee**

Seunghwan Kim (Chair), Hyung-Bok Park, and Iksung Cho

## ▪ **Data and safety monitoring board**

Dong Ho Shin (Chair), Junbeom Park, and Jae Sun Uhm

# Patient disposition and follow-up



<sup>a</sup> Study sites were not required to provide screening logs.

# Baseline characteristics (1)



	Intensive targeting (n=1526)	Conventional targeting (n=1522)
Age, yr	64.2 ± 9.1	64.6 ± 9.0
Male sex	1204 (78.9%)	1206 (79.2%)
Body mass index, kg/m <sup>2</sup>	24.9 (23.0–26.8)	24.7 (23.1–26.8)
<b><u>Type of ASCVD</u></b>		
• <b>Previous acute coronary syndrome</b>	<b>827 (54.2%)</b>	<b>867 (57.0%)</b>
Myocardial infarction / Unstable angina	460 (30.1%) / 367 (24.0%)	481 (31.6%) / 386 (25.4%)
• <b>Stable angina with imaging or functional studies</b>	<b>744 (48.8%)</b>	<b>730 (48.0%)</b>
• <b>Coronary or other arterial revascularization</b>	<b>1015 (66.5%)</b>	<b>1034 (67.9%)</b>
Percutaneous coronary intervention	884 (57.9)	900 (59.1)
Coronary-artery bypass grafting	58 (3.8)	71 (4.7)
Other arterial revascularization	88 (5.8)	82 (5.4)
• <b>Stroke or transient ischemic attack</b>	<b>57 (3.7%)</b>	<b>60 (3.9%)</b>
• <b>Peripheral artery disease</b>	<b>132 (8.7%)</b>	<b>134 (8.8%)</b>

\*The baseline characteristics did not differ between the two groups.

# Baseline characteristics (2)

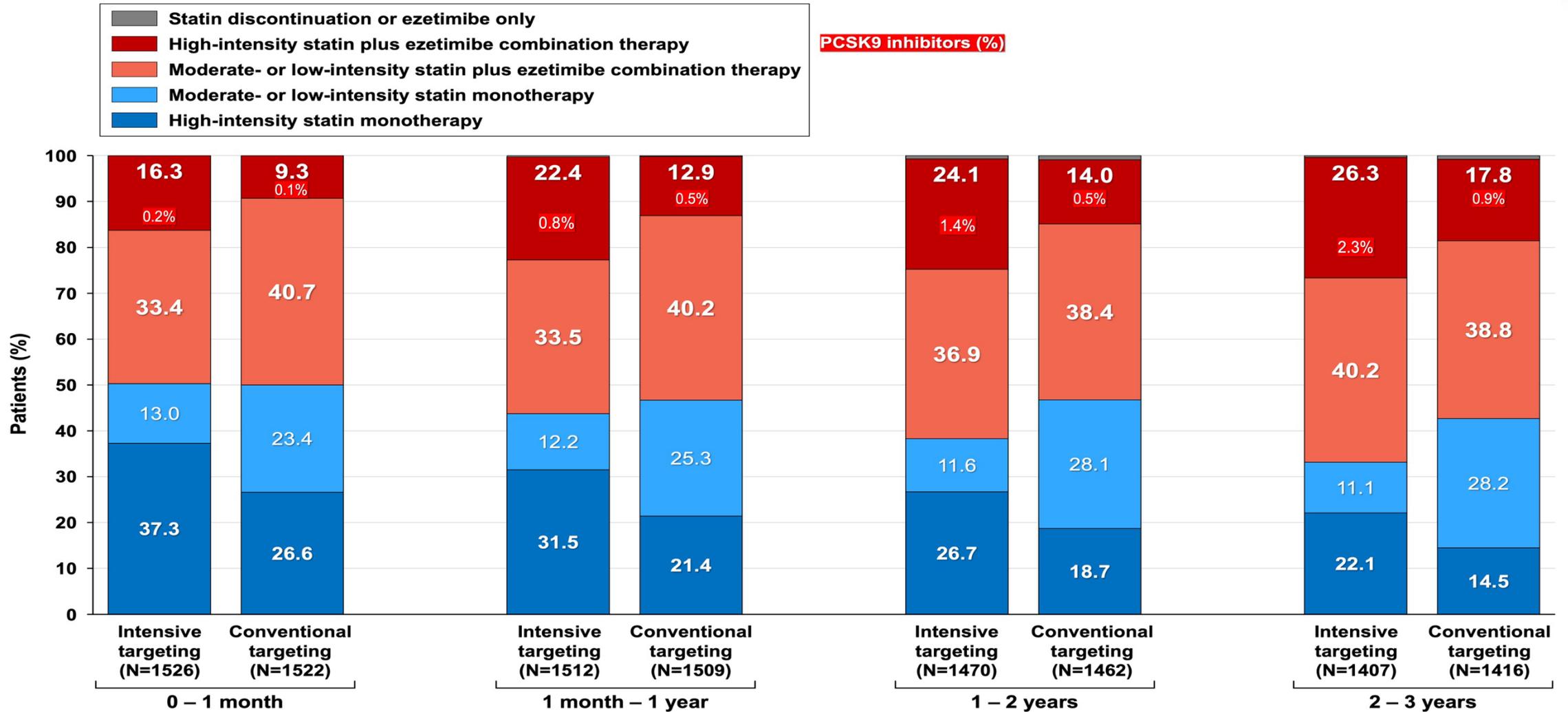


	Intensive targeting (n=1526)	Conventional targeting (n=1522)
Hypertension	1136 (74.4%)	1103 (72.5%)
<b>Diabetes</b>	<b>605 (39.6%)</b>	<b>602 (39.6%)</b>
<b>Chronic kidney disease</b>	<b>91 (6.0%)</b>	<b>87 (5.7%)</b>
<i>Lipid levels — mg/dL</i>		
<b>LDL cholesterol</b>	<b>77 (60–96)</b>	<b>75 (61–97)</b>
HDL cholesterol	46 (40–55)	47 (39–54)
Total cholesterol	143 (123–167)	143 (123–167)
Triglycerides	117 (87–159)	115 (83–163)
Statin		
High-intensity	352 (23.1%)	349 (22.9%)
Moderate-intensity	1036 (67.9%)	1038 (68.2%)
Low-intensity	10 (0.7%)	1 (0.1%)
None	128 (8.4%)	134 (8.8%)
Ezetimibe	454 (29.8%)	421 (27.7%)

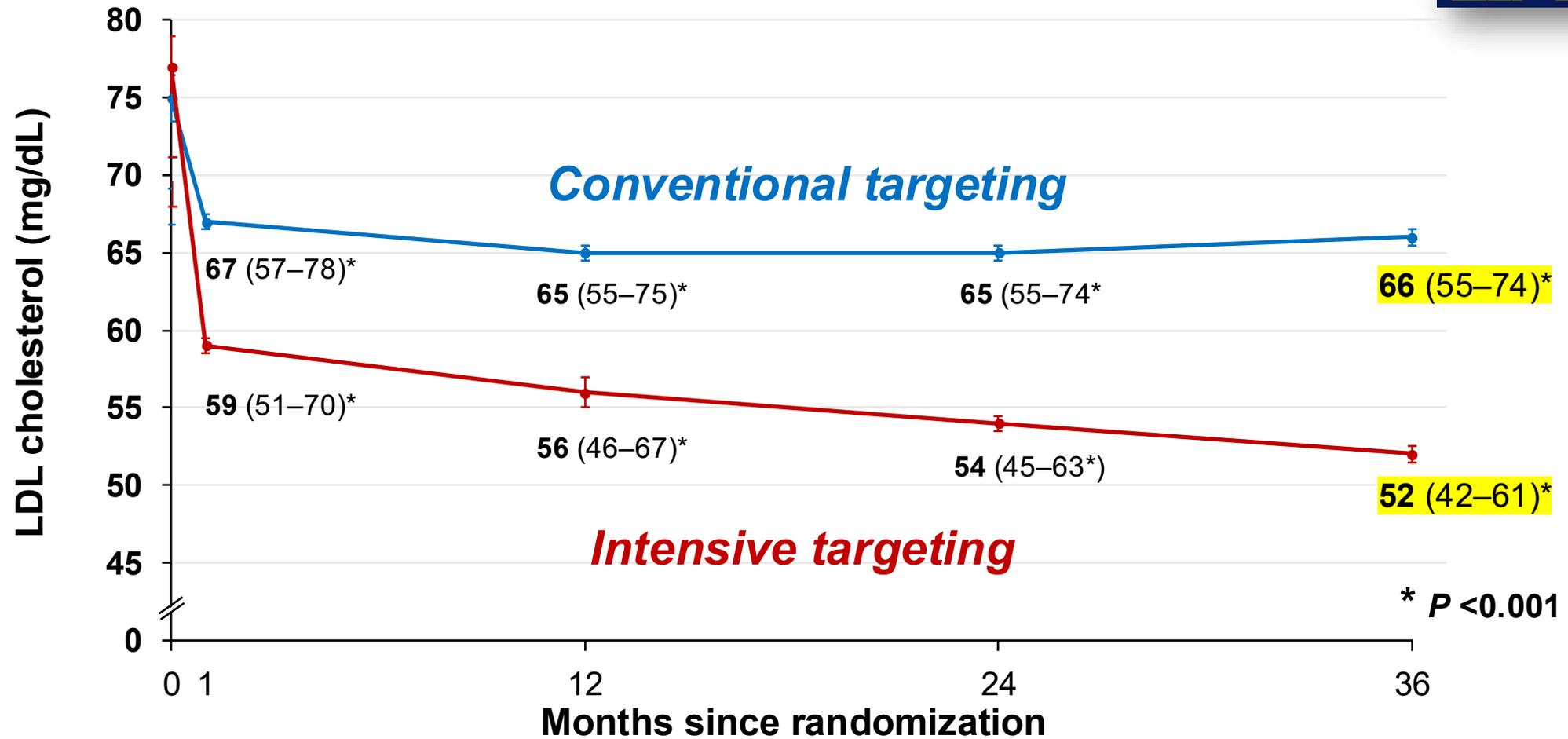
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# LDL cholesterol-lowering therapy

(Statin intensity, Ezetimibe combination, and use of PCSK9 inhibitors)



# LDL cholesterol levels : Median LDL-C level (IQR)

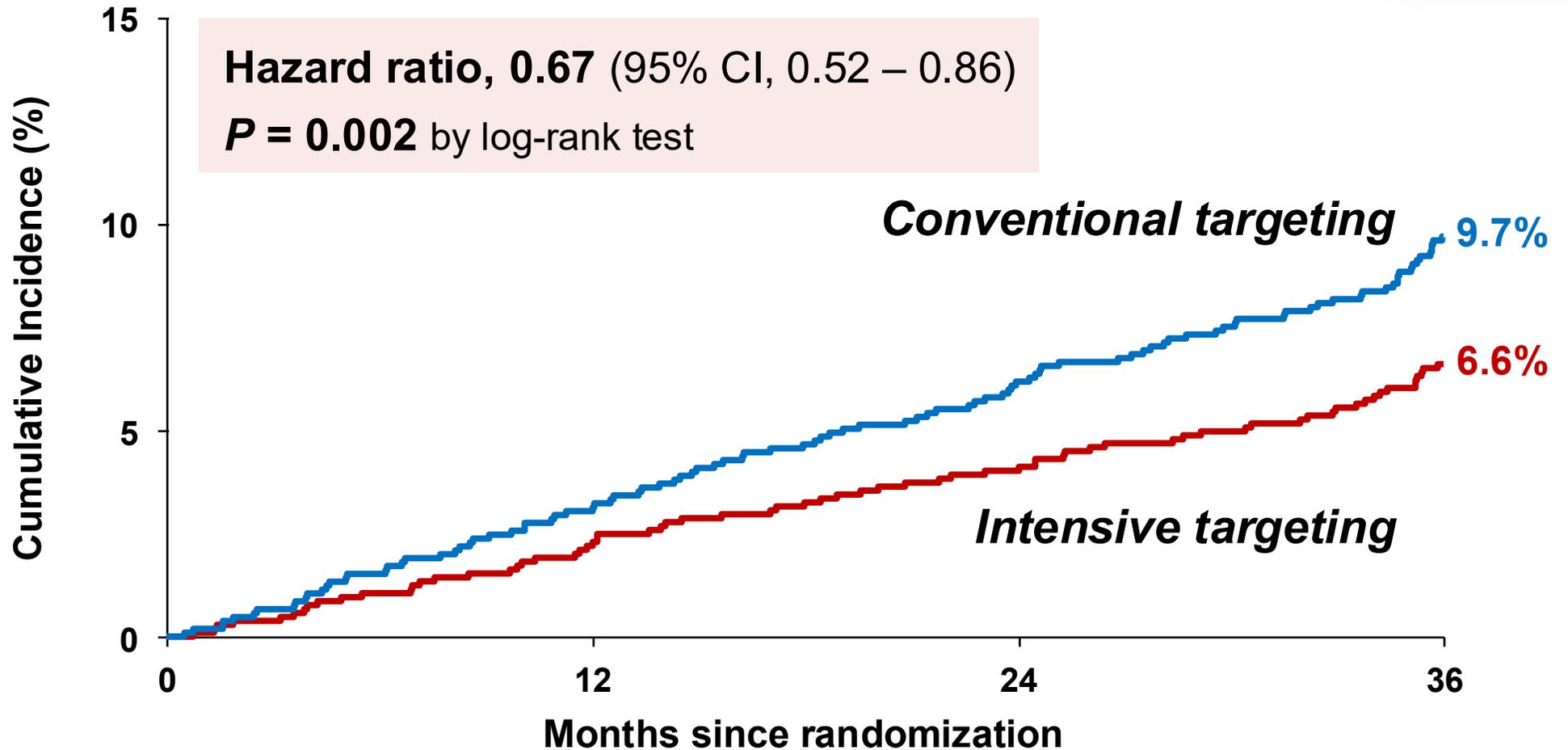


## Target achievement (%)

LDL-C <55 mg/dL	31.2% vs. 20.2%	42.9% vs. 24.9%	53.3% vs. 24.2%	60.8% vs. 24.2%
LDL-C <70 mg/dL	74.1% vs. 59.4%	78.5% vs. 67.2%	82.6% vs. 67.7%	85.2% vs. 68.1%

# Primary endpoint

Composite of cardiovascular death, nonfatal MI, nonfatal stroke, any revascularization, or hospitalization for UA at 3 years



**No. at risk**

Conventional targeting	1522	1465	1415	1358
Intensive targeting	1526	1481	1445	1402

# Secondary endpoints



	Intensive targeting (n=1526)	Conventional targeting (n=1522)	Hazard ratio (95% CI)	P value
<i>Individual events</i>				
<b>CV death</b>	<b>15 (1.0%)</b>	<b>18 (1.2%)</b>	<b>0.83 (0.42 to 1.65)</b>	<b>0.600</b>
All-cause death	31 (2.0%)	29 (1.9%)	0.1 (-0.9 to 1.1)	0.800
<b>Nonfatal MI</b>	<b>12 (0.8%)</b>	<b>26 (1.7%)</b>	<b>0.46 (0.23 to 0.91)</b>	<b>0.022</b>
Nonfatal stroke	8 (0.5%)	10 (0.7%)	0.80 (0.32 to 2.03)	0.636
<b>Any revascularization</b>	<b>72 (4.8%)</b>	<b>113 (7.5%)</b>	<b>0.63 (0.47 to 0.84)</b>	<b>0.002</b>
PCI	67 (4.5%)	99 (6.6%)	0.67 (0.49 to 0.91)	0.009
CABG	1 (0.1%)	7 (0.5%)	0.14 (0.02 to 1.15)	0.033
<b>Hospitalization for unstable angina</b>	<b>22 (1.5%)</b>	<b>36 (2.4%)</b>	<b>0.61 (0.36 to 1.03)</b>	<b>0.063</b>
<i>Composite events</i>				
<b><u>CV death, nonfatal MI, or nonfatal stroke</u></b>	<b>34 (2.3%)</b>	<b>54 (3.6%)</b>	<b>0.63 (0.41 to 0.96)</b>	<b>0.030</b>
<b>CV death, nonfatal MI, nonfatal stroke, or any revascularization</b>	<b>95 (6.3%)</b>	<b>141 (9.3%)</b>	<b>0.66 (0.51 to 0.86)</b>	<b>0.002</b>
<b>CV death, nonfatal MI, or any revascularization</b>	<b>88 (5.8%)</b>	<b>132 (8.7%)</b>	<b>0.66 (0.50 to 0.86)</b>	<b>0.002</b>

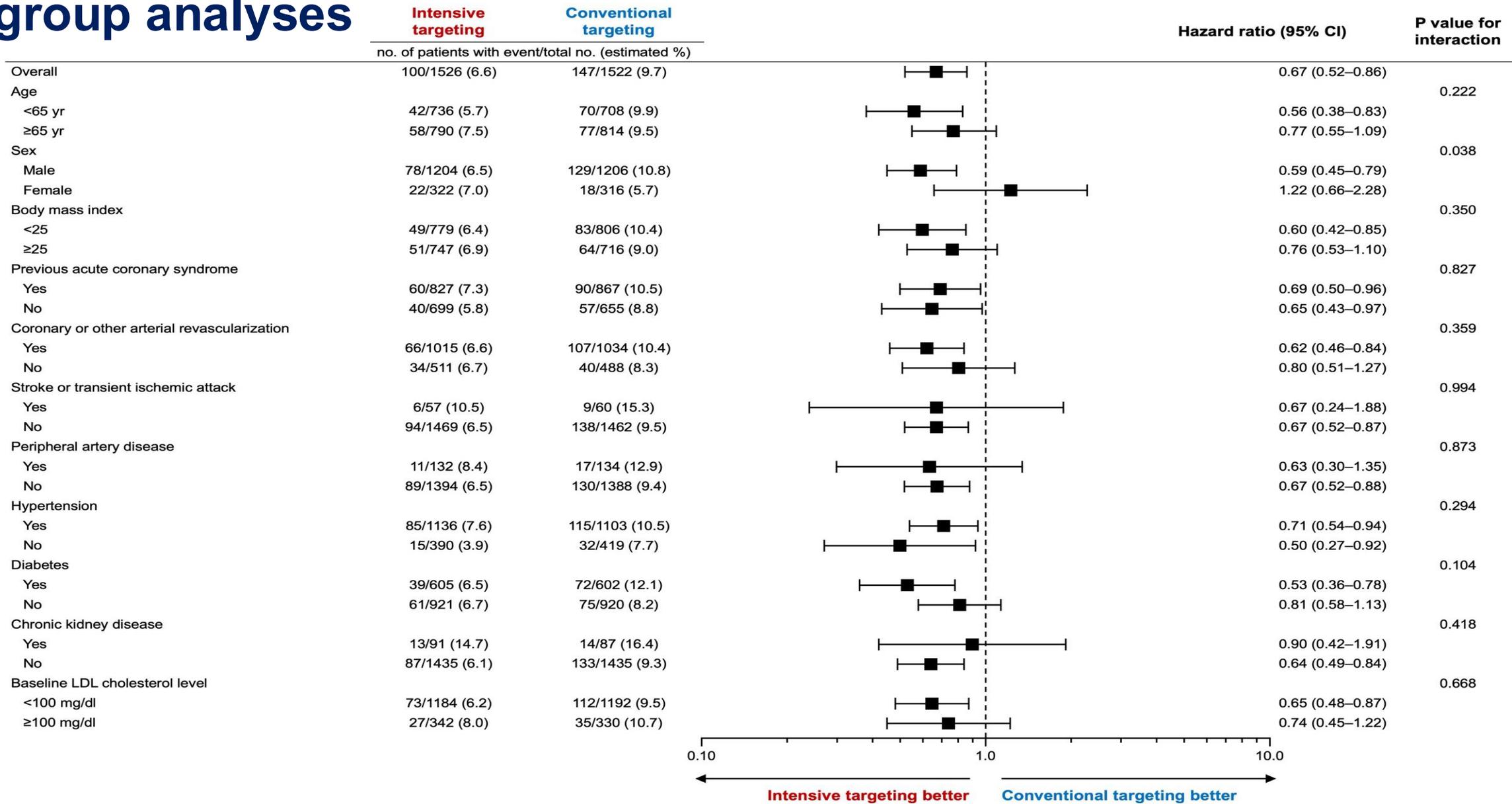
# Safety endpoints



	Intensive targeting (N=1526)	Conventional targeting (N=1522)	Difference (95% CI)	P value
<b>New-onset diabetes</b> among patients without diabetes	153/921 (16.6%)	148/920 (16.1%)	0.5 (-2.9 to 3.9)	0.809
<b>Worsening of glycemic control</b> among diabetic patients	295/605 (48.8%)	305/602 (50.7%)	-1.9 (-7.5 to 3.7)	0.546
<b>Statin-associated muscle symptoms</b> (changes in therapy dose or regimen)	15 (1.0%)	9 (0.6%)	0.4 (-0.2 to 1.0)	0.309
<b>Cancer diagnosis</b>	36 (2.4%)	40 (2.6%)	-0.3 (-1.4 to 0.8)	0.719
<b>Cataract surgery</b>	20 (1.3%)	16 (1.1%)	0.3 (-0.5 to 1.0)	0.621
Laboratory abnormalities				
<b>Aminotransferase elevation (<math>\geq 3</math> times UNL)</b>	37 (2.4%)	23 (1.5%)	0.9 (-0.1 to 1.9)	0.092
<b>Creatine kinase elevation (<math>&gt;4</math> times the UNL)</b>	4 (0.3%)	4 (0.3%)	0.0 (-0.4 to 0.4)	1.000
<b>Creatinine elevation (<math>&gt;1.5</math> times the baseline)<sup>a</sup></b>	18/1517 (1.2%)	41/1515 (2.7%)	-1.5 (-2.5 to -0.5)	0.004

<sup>a</sup> Patients who were undergoing dialysis at the start of the trial were excluded from the analysis.

# Sub-group analyses



# Study limitations



- **Unblinded trial design**, as treatment decisions required knowledge of the assigned LDL-C targets.
- **Lower-than-expected event rate**, although the superiority end point was met.
- **Despite a gradual increase in target attainment in the intensive-targeting group, 39% did not reach the LDL-C target at 3 years.**
  - **Limited use of PCSK9 inhibitors** due to stepwise treatment (reserved as the final step after statin dose adjustment and ezetimibe addition) and reimbursement constraints
  - **Absence of newer non-statin agents** (inclisiran or bempedoic acid) during the study period
- **Only East Asian participants** included
- **Relatively short follow-up period** (3 years).

# Summary of the Ez-PAVE trial



- The **first randomized trial** comparing LDL-C targets of **<55 mg/dL vs. <70 mg/dL** in **patients with ASCVD**.
- **Targeting LDL-C <55mg/dL (Intensive targeting)** was associated with a significantly lower 3-year risk of the composite endpoint (cardiovascular death, nonfatal MI, nonfatal stroke, any revascularization, or hospitalization for unstable angina) than **targeting <70 mg/dL (conventional targeting)**.
- **No major safety concerns** of intensive LDL-C targeting were observed, with similar rates of prespecified safety end points between two groups.

# Conclusion



- In the Ez-PAVE trial involving patients with ASCVD, **intensive LDL-C targeting (<55 mg/dL)** resulted in a **lower 3-year risk of cardiovascular events than conventional targeting (<70 mg/dL)**.
- These findings provide **randomized evidence supporting more intensive lipid-lowering strategies** for secondary prevention, consistent with current guideline recommendations.

# Further Details, Just Published in NEJM



The NEW ENGLAND  
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ORIGINAL ARTICLE

## Intensive LDL Cholesterol Targeting in Atherosclerotic Cardiovascular Disease

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