Statin treatment for ASCVD from RACING and LODESTAR trials

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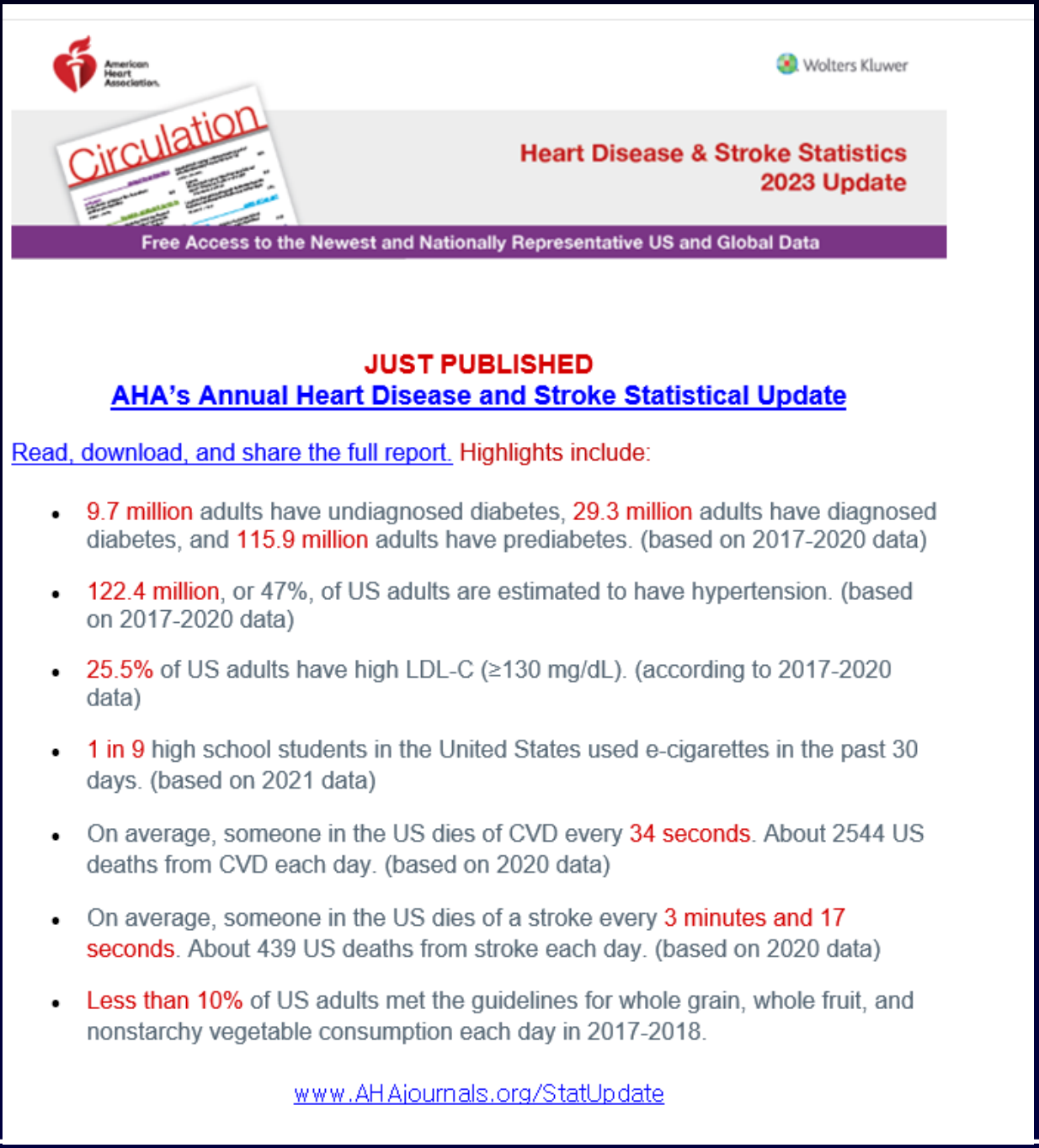
Disclosure

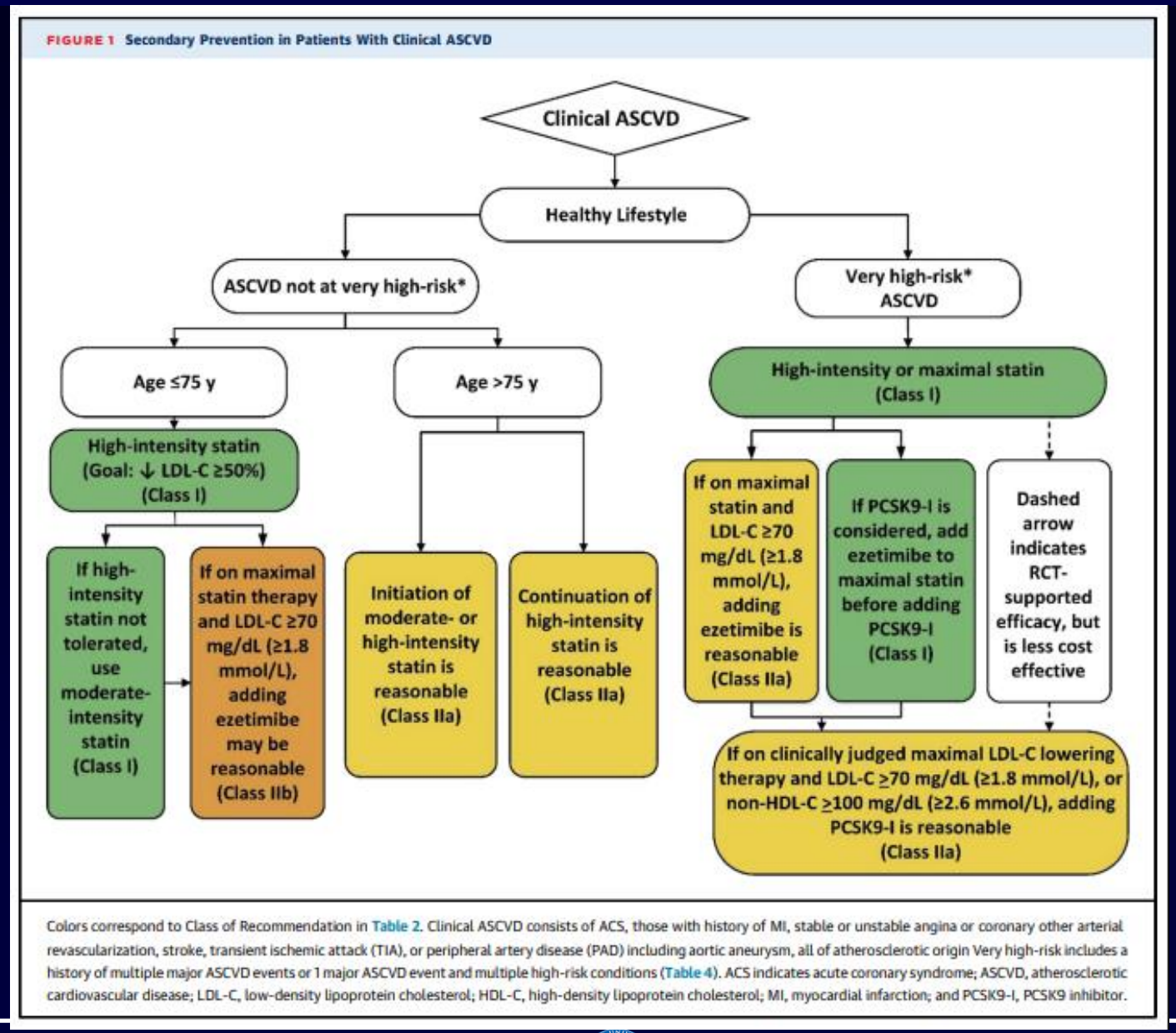
Funded by Hanmi (Pharmaceutical), Sam Jin (Pharmaceutical) and Chong Kun Dang (Pharmaceutical)



Statin therapy is the key treatment for patients with ASCVD

Which statin treatment is right for these patients?

2018 ACC/AHA dyslipidemia guideline: High-intensity statin therapy



Colors correspond to Class of Recommendation in Table 2. Clinical ASCVD consists of ACS, those with history of MI, stable or unstable angina or coronary other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4). ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9-I, PCSK9 inhibitor.

2019 ESC/EAS dyslipidemia guideline: Target LDL level based statin therapy

Recommendations for treatment goals for low-density lipoprotein cholesterol

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

[a]Class of recommendation.

[b]Level of evidence.

[c]For definitions see *Table 4*.

[d]The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

Benefits and adverse effects of statin therapy

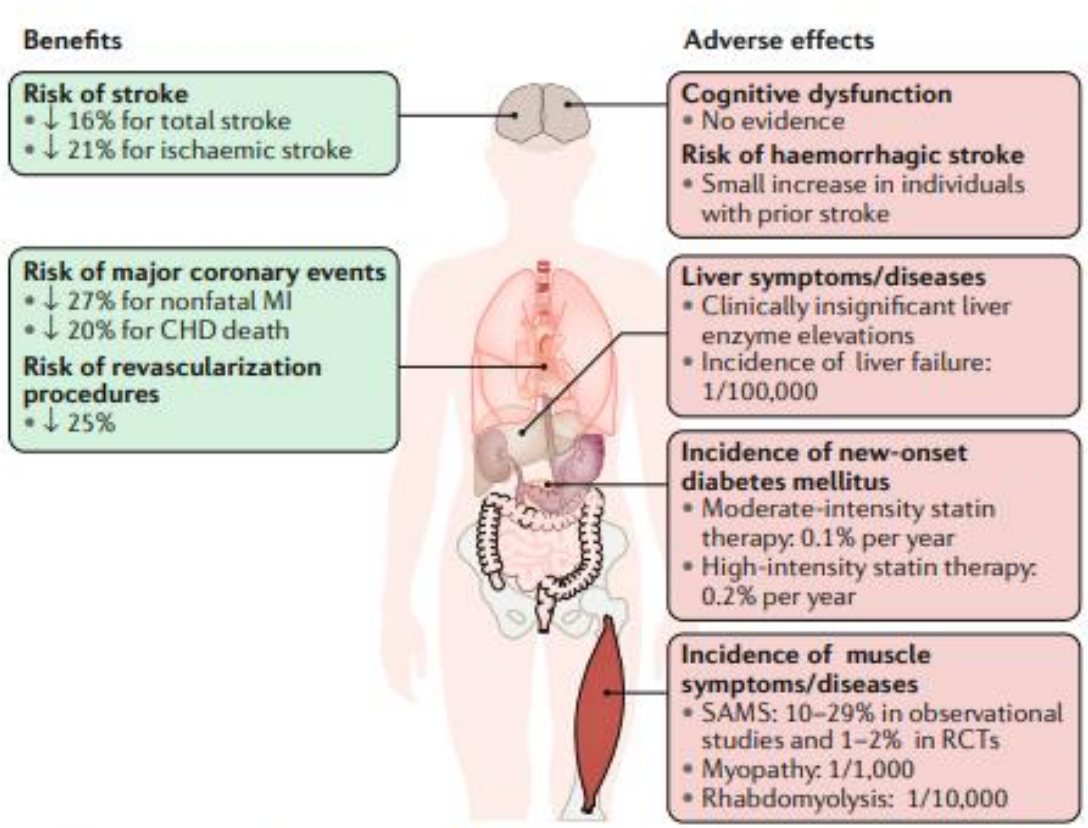


Fig. 1 | **Clinical benefits and potential adverse effects of statin therapy.** The cardiovascular benefits, including the reduction in the risk of major coronary events and revascularization and the reduction in the risk of stroke, associated with statin therapy far outweigh the potential risks. Given this clinical benefit, providers should work diligently with patients to ensure that patients adhere to therapy in a shared-decision model. CHD, coronary heart disease; MI, myocardial infarction; RCT, randomized controlled trial; SAMS, statin-associated muscle symptoms.

Adhyaru BB and Jacobson TA. *Nat Rev Cardiol* 2018

Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy: RACING trial

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

Byeong-Keuk Kim*, Sung-Jin Hong*, Yong-Joon Lee, Soon Jun Hong, Kyeong Ho Yun, Bum-Kee Hong, Jung Ho Heo, Seung-Woon Rha, Yun-Hyeong Cho, Seung-Jun Lee, Chul-Min Ahn, Jung-Sun Kim, Young-Guk Ko, Donghoon Choi, Yangsoo Jang, Myeong-Ki Hong, on behalf of the RACING investigators†

Lancet 2022; 400: 380–90

Summary

Background Drug combinations rather than increasing doses of one drug can achieve greater efficacy and lower risks.

Kim BK, Hong SJ, Jang Y (corresponding) and Hong MK (corresponding), *Lancet* 2022;400:380-390

Study design of RACING trial

Patients with documented cardiovascular diseases
N=3780

1:1 Randomization

Stratified by baseline LDL-C <100 mg/dL and DM

Moderate-intensity statin with ezetimibe combination therapy
Rosuvastatin 10 mg / Ezetimibe 10 mg
N=1890

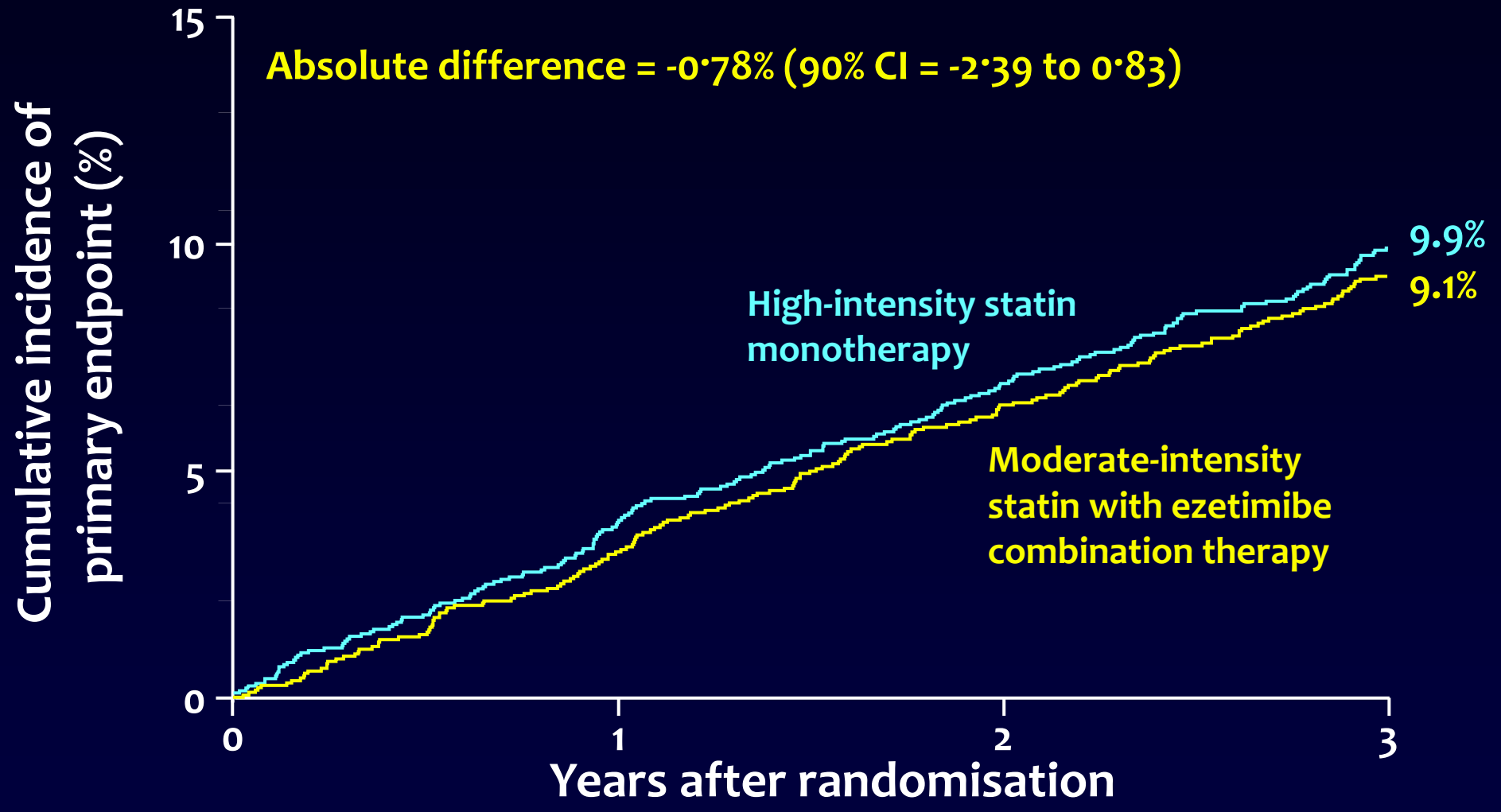
High-intensity statin monotherapy
Rosuvastatin 20 mg
N=1890

Clinical follow-up at 3 years
Composite of cardiovascular death, major cardiovascular events* (any revascularization and hospitalization for cardiovascular events), and nonfatal stroke

*Any coronary or peripheral revascularization and hospitalization for any cardiovascular events including ischemic heart disease, heart failure, or peripheral artery disease

Trial Registration: Clinicaltrial.gov Identifier: NCT03044665

Primary endpoint



Monotherapy	1886	1786	1711	1639
Combination therapy	1894	1795	1724	1654

Kim BK, Hong SJ, Jang Y (corresponding) and Hong MK (corresponding), ***Lancet*** 2022;400:380-390

LDL-cholesterol level during the study period

	Moderate-intensity statin with ezetimibe combination therapy (N=1894)	High-intensity statin monotherapy (N=1886)	Absolute difference in proportions, % (95% confidence interval)
1 year			
No. of patients	1675	1673	
No. of pts with LDL-C levels <70 mg/dL (%)	1217 (73)	923 (55)	17 (14 to 21)
LDL-C level (mg/dL)	58 (47–71)	67 (55–80)	
2 years			
No. of patients	1558	1539	
No. of pts with LDL-C levels <70 mg/dL (%)	1168 (75)	924 (60)	15 (12 to 18)
LDL-C level (mg/dL)	57 (45–70)	65 (53–79)	
3 years			
No. of patients	1349	1315	
No. of pts with LDL-C levels <70 mg/dL (%)	978 (73)	759 (58)	15 (11 to 18)
LDL-C level (mg/dL)	58 (47–71)	66 (54–80)	

Kim BK, Hong SJ, Jang Y (corresponding) and Hong MK (corresponding), ***Lancet*** 2022;400:380-390

Secondary safety endpoint (1)

	Moderate-intensity statin with ezetimibe combination therapy (N=1894)	High-intensity statin monotherapy (N=1886)	Absolute difference (95% confidence interval)
Serious adverse event			
Death	26 (1·4)	22 (1·1)	0·21 (-5·88 to 1·01)
Adverse events			
Discontinuation or dose reduction of study drug due to intolerance	88 (4.8)	150 (8.2)	-3·42 (-5·07 to -1·80)
Reported symptoms			
Dizziness or general weakness	10	21	
Chest discomfort or headache	7	12	
Gastrointestinal symptom	4	9	
Urticaria or itching sensation	6	7	
Myalgia	7	22	
Other	5	3	
Physician discretion			
Liver enzyme elevation	15	32	
Creatine kinase elevation	25	33	
Fasting glucose level elevation	5	6	
Other	4	5	

Conclusion

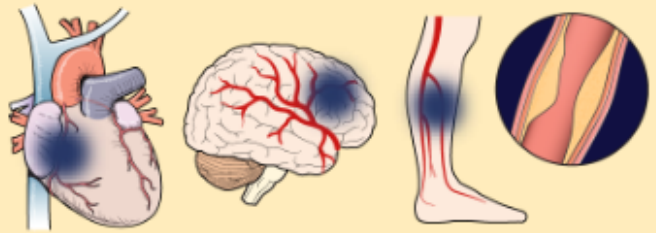
- To our knowledge, this study is the first randomised trial comparing 3-year clinical outcomes of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease.

- Moderate-intensity statin with ezetimibe combination therapy was noninferior to high-intensity statin monotherapy for the 3-year composite outcomes with a higher proportion of patients with LDL cholesterol level <70 mg/dL and lower intolerance-related drug discontinuation or dose reduction.

Diabetes Mellitus (DM) in RACING trial

Effect of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy among patients with DM and ASCVD: *a pre-specified, stratified subgroup analysis of the randomised RACING trial*

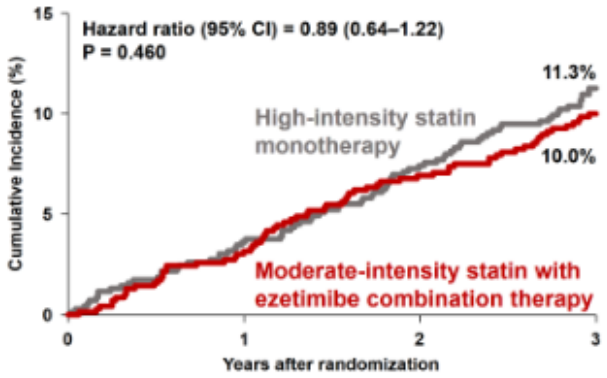
1398 DM patients with ASCVD included in the RACING trial



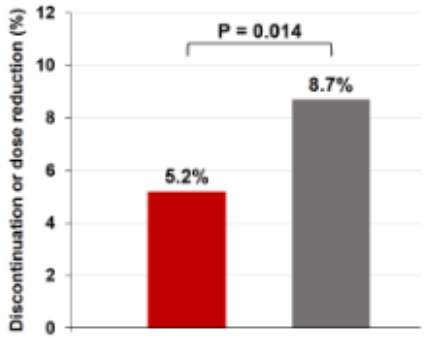
- **Moderate-intensity statin + ezetimibe combination therapy (n=701)**
- **High-intensity statin monotherapy (n=697)**

- 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

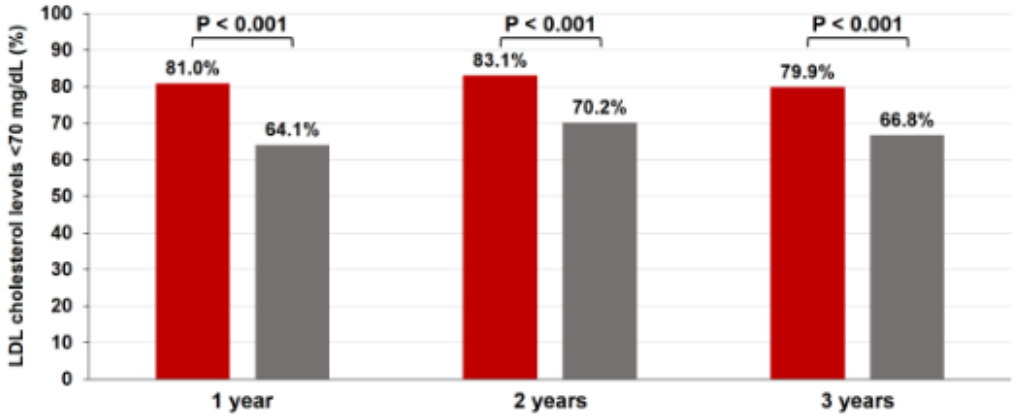
Composite cardiovascular outcomes



Intolerance



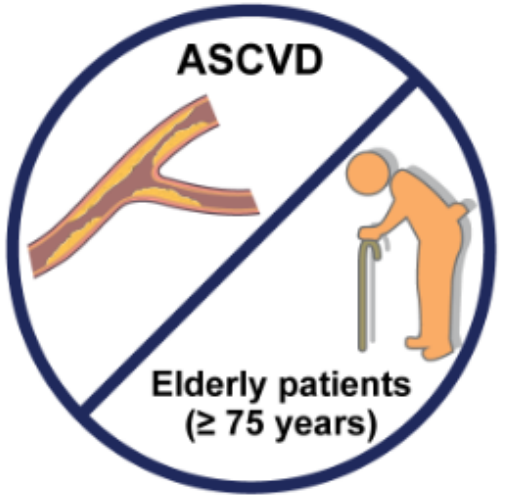
LDL cholesterol reduction

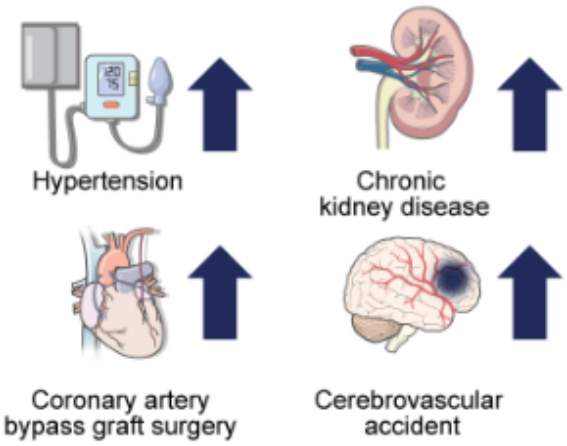


Eur Heart J 2023;44:954-968

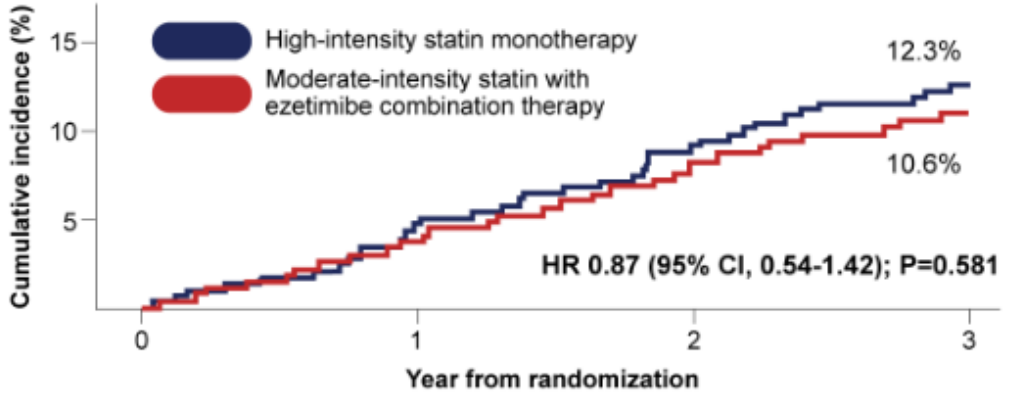
Elderly Patients (age> 75 years) in RACING trial

Impact of moderate-intensity statin with ezetimibe combination therapy for elderly versus younger patients with atherosclerotic cardiovascular disease: *Age-stratified substudy of the randomized RACING trial*

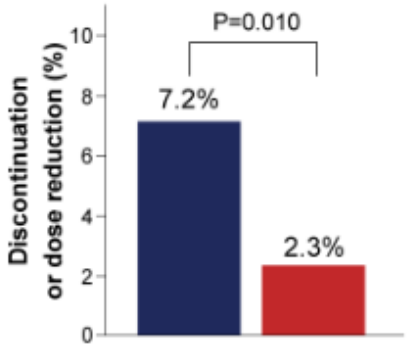




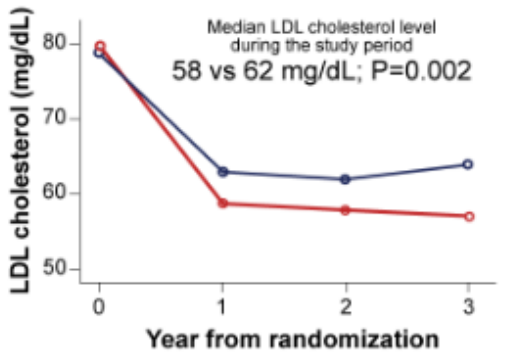
3-year composite cardiovascular events



Drug discontinuation or dose reduction

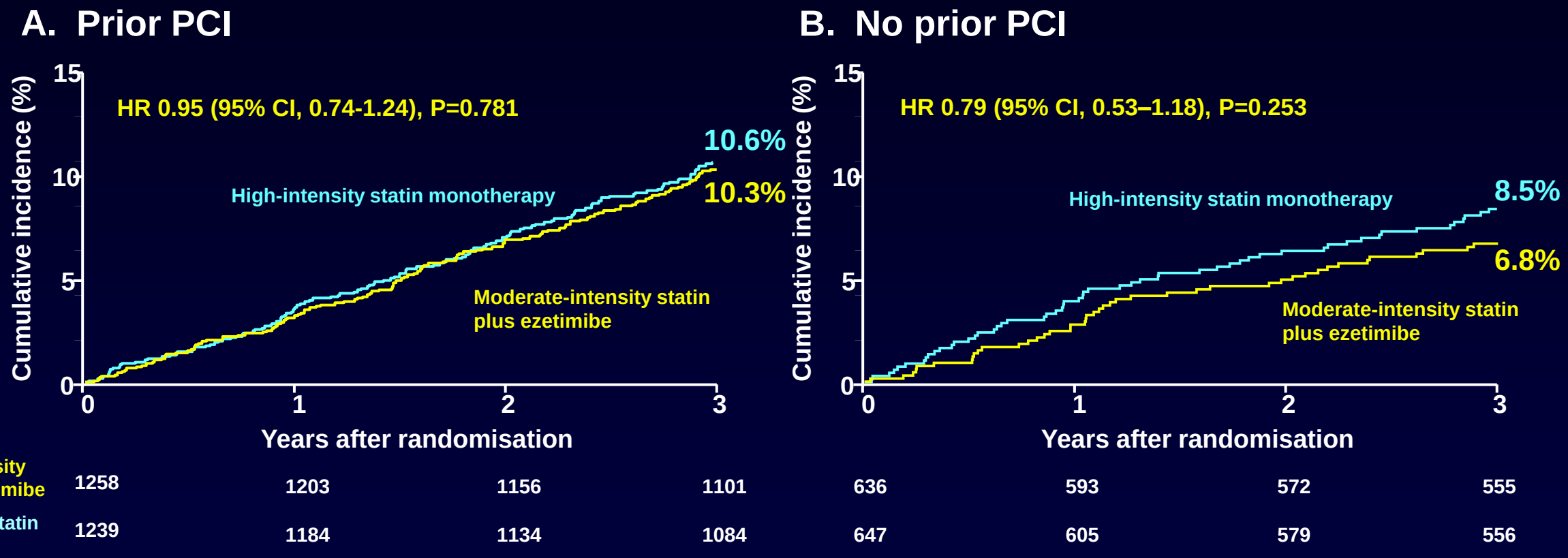


LDL cholesterol levels



JACC 2023;81:1339-1349

Primary endpoint according to treatment strategy and prior PCI status



Moderate-Intensity Statin plus ezetimibe	1258	1203	1156	1101	636	593	572	555
High-intensity statin monotherapy	1239	1184	1134	1084	647	605	579	556

EClinicalMedicine 2023;58:101933

Treat-to-Target or High-Intensity Statin in Patients with Coronary Artery Disease: LODESTAR trial

Research

JAMA | Original Investigation

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

A Randomized Clinical Trial

Sung-Jin Hong, MD; Yong-Joon Lee, MD; Seung-Jun Lee, MD; Bum-Kee Hong, MD; Woong Chol Kang, MD; Jong-Young Lee, MD; Jin-Bae Lee, MD; Tae-Hyun Yang, MD; Junghan Yoon, MD; Chul-Min Ahn, MD; Jung-Sun Kim, MD; Byeong-Keuk Kim, MD; Young-Guk Ko, MD; Donghoon Choi, MD; Yangsoo Jang, MD; Myeong-Ki Hong, MD;
for the LODESTAR Investigators

Late Breaking Science in ACC 2023, New Orleans, USA
Hong SJ, Lee YJ, and Hong MK (corresponding), *JAMA* 2023;329:1078-1087

Study design

Patients with Coronary Artery Disease
N=4400

1:1 Randomization

Stratified by baseline LDL cholesterol <100 mg/dL, acute coronary syndrome, and diabetes mellitus

Treat-to-target strategy group
(LDL cholesterol level between 50 and 70mg/dL as the target), N=2200

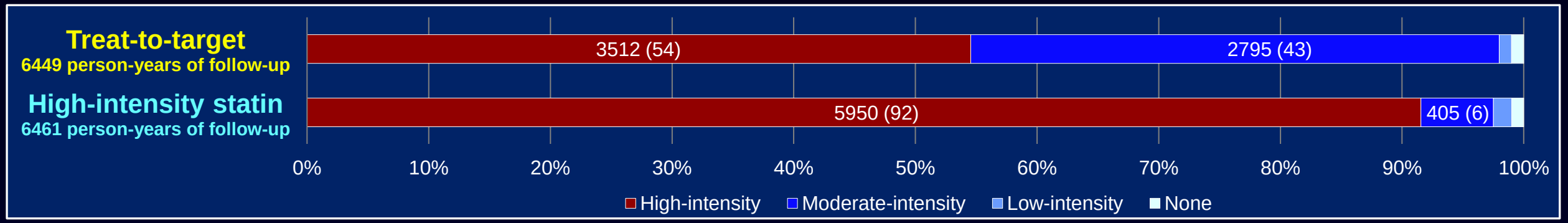
High-intensity statin strategy group,
N=2200

Primary endpoint: composite of all-cause death, MI, stroke, or coronary revascularization during 3-year clinical follow-up

*In each group, patients will be randomized in a 1:1 manner to receive two different types of statins (rosuvastatin or atorvastatin)

Trial Registration: Clinicaltrial.gov Identifier: NCT02579499

Hong SJ, Lee YJ, and Hong MK (corresponding), *JAMA* 2023;329:1078-1087

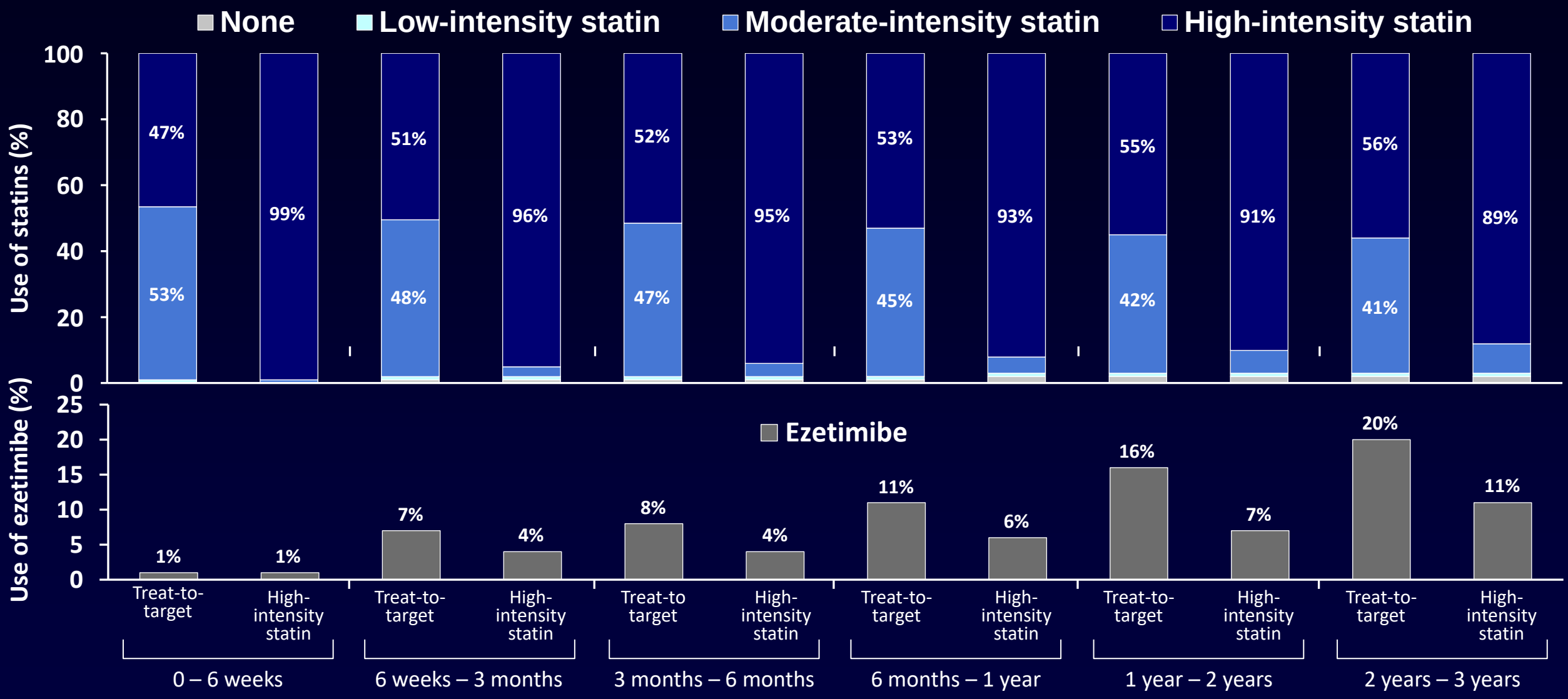


Changes in statin intensity in the treat-to-target group

	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)

Hong SJ, Lee YJ, and Hong MK (corresponding), *JAMA* 2023;329:1078-1087

Lipid-lowering therapy during the study period



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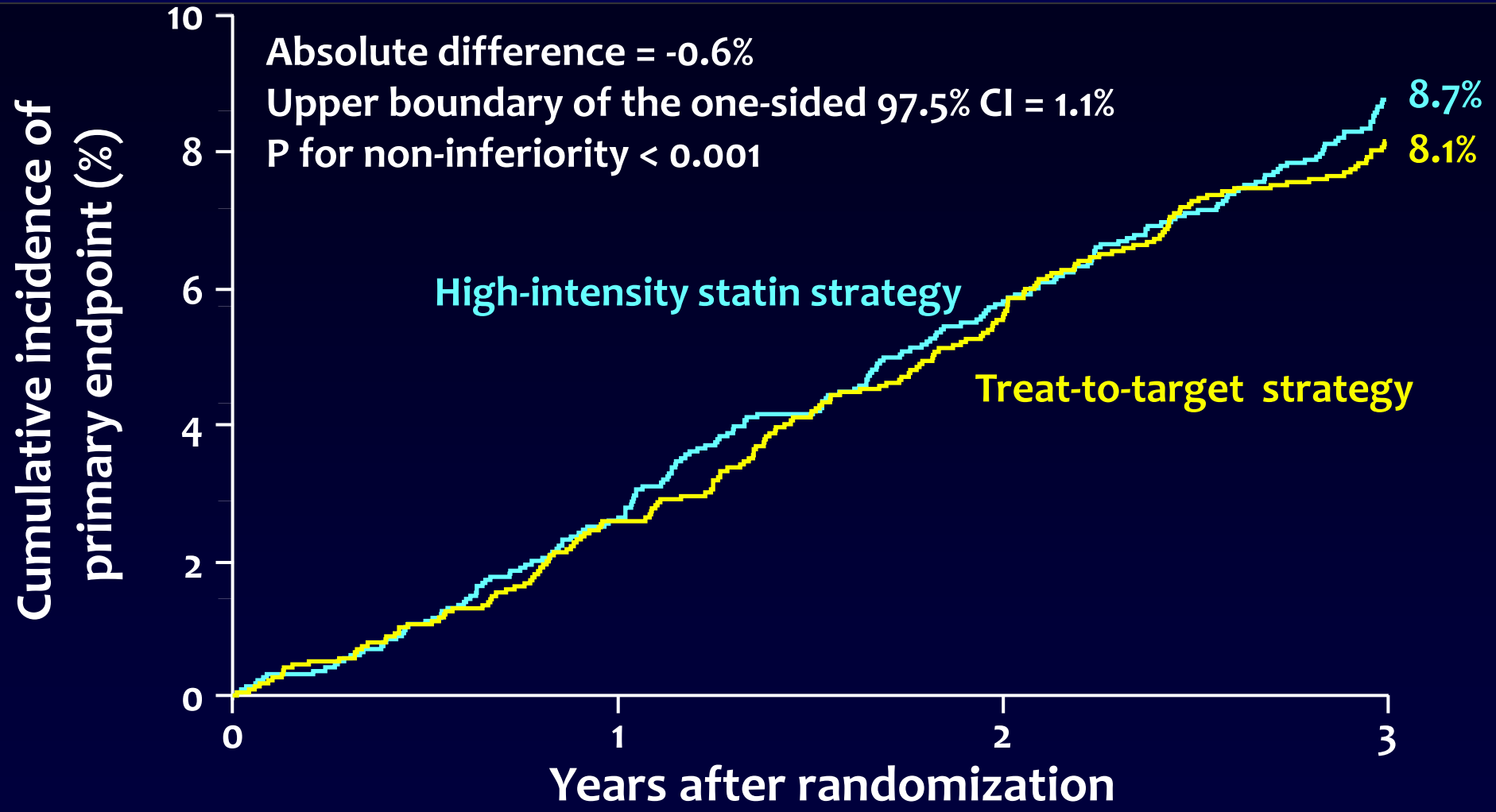
Primary endpoint



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

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Secondary endpoint

	Treat-to-target strategy (N=2200)	High-intensity statin strategy (N=2200)	Difference (95% CI)	P Value
	No. of Patients (%)		*Percentage Points*	
Secondary endpoints				
New-onset diabetes mellitus	121 (5.6)	150 (7.0)	-1.3 (-2.8 to 0.1)	0.07
Initiation of anti-diabetic medication	73	105		
Hospitalization due to heart failure	13 (0.6)	7 (0.3)	0.3 (-0.1 to 0.7)	0.17
Deep vein thrombosis or pulmonary embolism	4 (0.2)	5 (0.2)	<0.1 (-0.3 to 0.2)	0.74
Deep vein thrombosis	2	5		
Pulmonary embolism	3	0		
Peripheral artery revascularization	12 (0.6)	17 (0.8)	-0.2 (-0.8 to 0.3)	0.35
Aortic intervention or surgery	2 (0.1)	3 (0.1)	NR	
Endovascular therapy	1	2		
Surgical therapy	1	1		
End-stage kidney disease	3 (0.1)	10 (0.5)	-0.3 (-0.7 to 0.0)	0.05
Discontinuation of statin therapy	31 (1.5)	46 (2.2)	-0.7 (-1.5 to 0.1)	0.09
Cataract operation	43 (2.0)	42 (1.9)	0.1 (-0.8 to 0.9)	0.90
Composite of laboratory abnormalities	18 (0.8)	30 (1.3)	-0.5 (-1.1 to 0.1)	0.11
Aminotransferase elevation	8	12		
Creatine kinase elevation	3	8		
Creatinine elevation	7	11		

Hong SJ, Lee YJ, and Hong MK (corresponding), *JAMA* 2023;329:1078-1087

Conclusion

- To our knowledge, this study is the first randomized trial comparing 3-year clinical outcomes of treat-to-target strategy with a target LDL cholesterol level between 50 and 70 mg/dL versus high-intensity statin strategy with high-intensity statin therapy in patients with coronary artery disease.

- The treat-to-target strategy was noninferior to the high-intensity statin strategy in terms of a 3-year composite of all-cause death, myocardial infarction, stroke, or any coronary revascularization.