Comparison Between Targeted LDL Cholesterol Level Based Versus High-Intensity Statin Therapy in Patients with Coronary Artery Disease

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Disclosure

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Background

Statin intensity in coronary artery disease

- Intensive lowering of low-density lipoprotein (LDL) cholesterol levels with statins is recommended in patients with coronary artery disease.

Mach F, et al. Eur Heart J 2020;41:111-188
Grundy SM, et al. J Am Coll Cardiol 2019;73:e285-350

- However, clinically effective strategies for the choice of statin intensity remain unclear.
  1) Statin intensity can be titrated to meet a target LDL cholesterol level ⇨ **Treat-to-target strategy**
  2) High intensity statin can be initiated as well as maintained without monitoring of LDL cholesterol level ⇨ **High-intensity statin strategy**

Hypothesis

- The treat-to-target strategy with a target LDL cholesterol level between 50 and 70 mg/dL is noninferior to the high-intensity statin strategy as for the 3-year clinical outcomes in patients with coronary artery disease.

Study design

- A randomized, open-label, noninferiority, multi-center trial
- At 12 centers in Korea
- Enrollment period: September 2016 and November 2019

- Key inclusion criteria
  - Patients ≥19 years old
  - Patients clinically diagnosed with coronary artery disease: stable angina, unstable angina, acute non-ST elevation myocardial infarction, and acute ST elevation myocardial infarction
  - Patients with signed informed consent

- Key exclusion criteria
  - Pregnant women or women with potential childbearing during the study period
  - Patients with severe adverse events or hypersensitive to statin
  - Patients receiving drug that interacts with statin (strong inhibitor of cytochrome p-450 3A4 or 2C9)
  - Patients with risk factors for myopathy, hereditary muscle disorder, hypothyroidism, alcohol use disorder, severe hepatic dysfunction (3 times the normal reference values), or rhabdomyolysis
  - Life expectancy <3 years
  - Patients who could not be followed for more than 1 year
  - Patients who could not understand the consent form

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

Methods (statin dose)

In the treat-to-target group

<u>At randomization</u>

The target LDL-C level chosen was the lowest recommended LDL-C level for our population in the latest guidelines at the time of trial design (August 2015), which was below 70 mg/dL.

The statin intensity was titrated as follows.
For statin naïve patients, moderate-intensity statin therapy was initiated.
For those who were already taking a statin, an equivalent intensity was maintained when the LDL-C level was below 70 mg/dL, and the intensity was up-titrated when LDL-C ≥70 mg/dL.

<u>During follow-up</u>

up-titration for patients with LDL-C ≥70 mg/dL,
maintenance of the same intensity for those with LDL-C between 50 and 70 mg/dL
down-titration for those with LDL-C <50 mg/dL

In the high-intensity statin group

The initiation as well as maintenance of high-intensity statin therapy was recommended without adjustment regardless of follow-up LDL-C levels during the study period.

Statistical analysis

● Sample size calculation

Primary aim: Non-inferiority regarding clinical outcomes

- **High-intensity statin therapy** was regarded as the standard therapy and **treat-to-target strategy** was considered as the experimental therapy.

- Based on previous studies, the expected event rate of the primary endpoint was 4% per year in the high-intensity statin strategy group. Assuming that the two strategies had equivalent efficacy, the expected event rate of the primary endpoint at 3 years was estimated to be 12% in each group.

- **Non-inferiority hypothesis of a 3.0% margin** with giving the study a power of 80%, one-sided alpha error rate of 2.5%, follow-up loss of 15%, and balancing the two types of statins (rosuvastatin and atorvastatin)
  → A sample size of **4,400 patients** (2,200 patients in each group) was required.

- Non-inferiority would be declared if the upper limit of the one-sided 97.5% CI for the difference in primary endpoint incidences between groups was <3.0%.

Cannon CP, et al. N Engl J Med 2004;350:1495-1504
Gibson CM, et al. J Am Coll Cardiol 2009;54:2290-2295

Study flow

4400 underwent randomization

Treat-to-target strategy group

2200 Were assigned to treat-to-target strategy group

2030 Received titrated-intensity statin therapy

44 Did not complete statin therapy
- 31 Due to adverse events
- 13 Due to poor compliance

126 Did not meet a target but was not up-titrated
- 47 Due to adverse events
- 48 Due to patient or physician choice
- 22 Failure to comply protocol
- 9 Others

16 Withdrew consent
14 Lost to follow-up
54 Died

2200 Included in primary analysis

High-intensity statin therapy group

2200 Were assigned to high-intensity statin therapy group

1980 Received high-intensity statin therapy

51 Did not complete statin therapy
- 46 Due to adverse events
- 5 Due to poor compliance

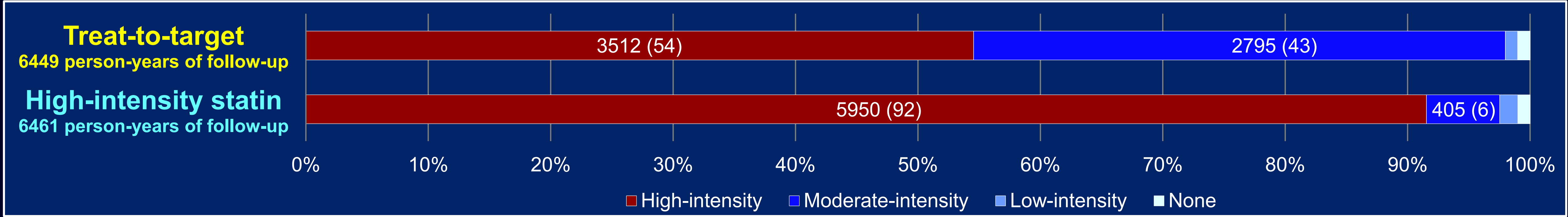
169 Did not maintain high-intensity statin therapy
- 80 Due to adverse events
- 74 Due to patient or physician choice
- 5 Failure to comply protocol
- 10 Others

14 Withdrew consent
11 Lost to follow-up
54 Died

2200 Included in primary analysis

Baseline clinical characteristics

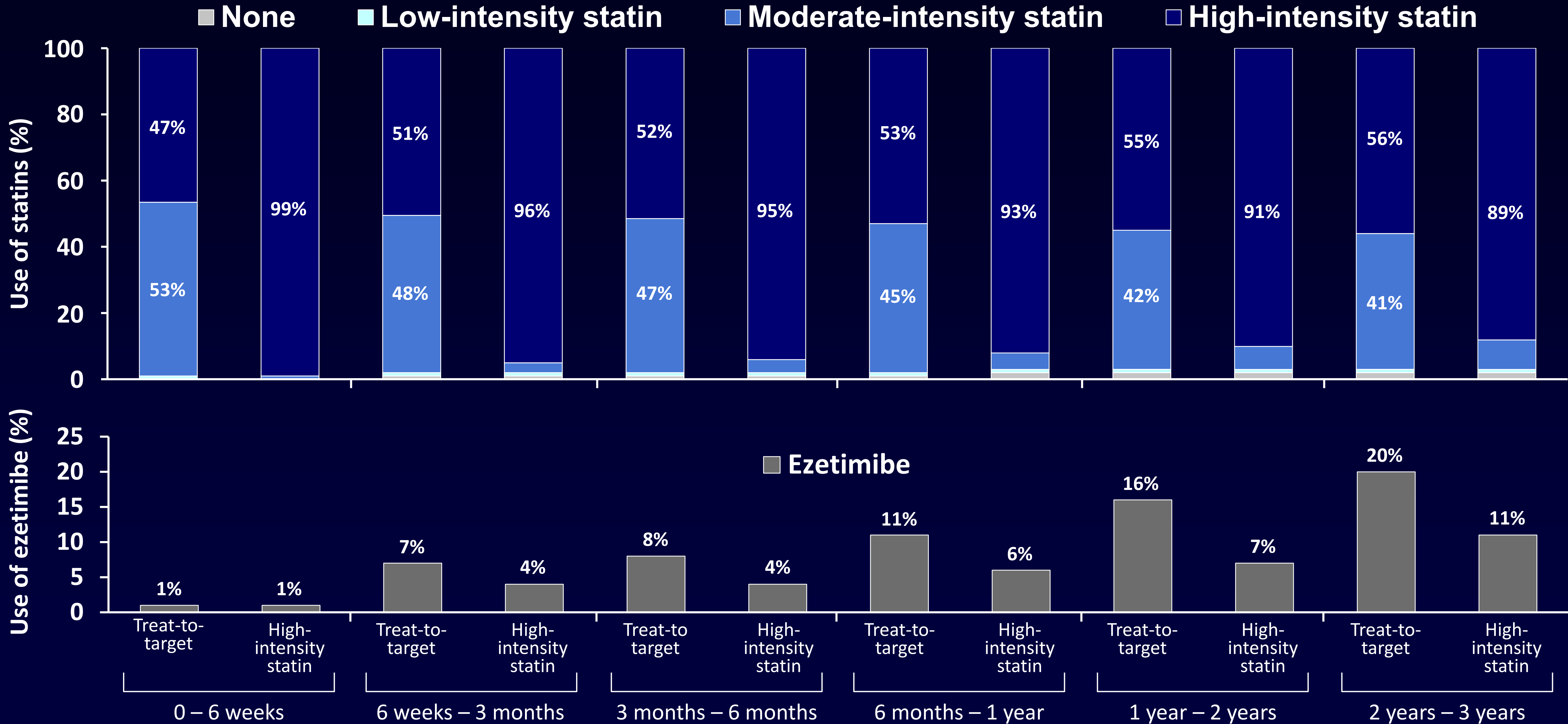
	Treat-to target strategy (N=2200)	High-intensity statin strategy (N=2200)
Age, mean (SD), years	65 (10)	65 (10)
Female sex	626 (29)	602 (27)
Body-mass index, mean (SD), kg/m^2	24.7 (2.9)	24.7 (2.9)
Hypertension	1473 (67)	1464 (67)
Diabetes	735 (33)	733 (33)
Chronic kidney disease	153 (7)	166 (8)
Previous stroke	135 (6)	128 (6)
Previous PCI	1243 (57)	1214 (55)
Previous CABG	154 (7)	180 (8)
Clinical presentation at randomization		
Acute myocardial infarction within 1 year	159 (7)	179 (8)
Unstable angina or revascularization within 1 year	381 (17)	407 (19)
>1 year after myocardial infarction	338 (15)	337 (15)
>1 year after unstable angina or revascularization	910 (41)	874 (40)
Detection of CAD at screening without symptoms	412 (19)	403 (18)
Lipid lowering therapy before randomization		
Statin		
None	334 (16)	334 (16)
Low-intensity statin	53 (2)	40 (2)
Moderate-intensity statin	1284 (58)	1240 (56)
High-intensity statin	529 (24)	576 (26)
Ezetimibe	253 (12)	226 (10)
LDL cholesterol, mean (SD), mg/dL	86 (33)	87 (31)



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)

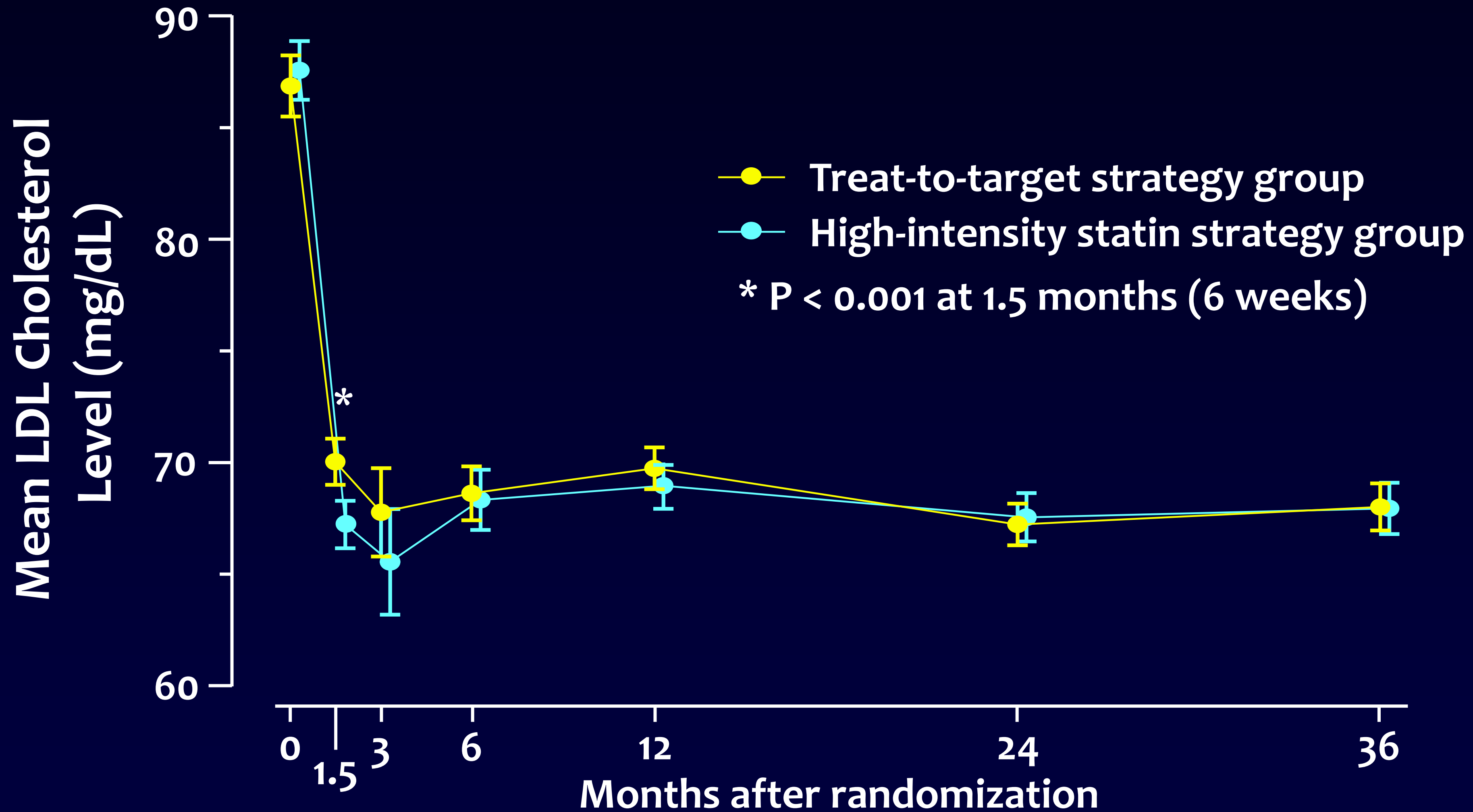
Lipid-lowering therapy during the study period



LDL-cholesterol levels below 70 mg/dL during the study period

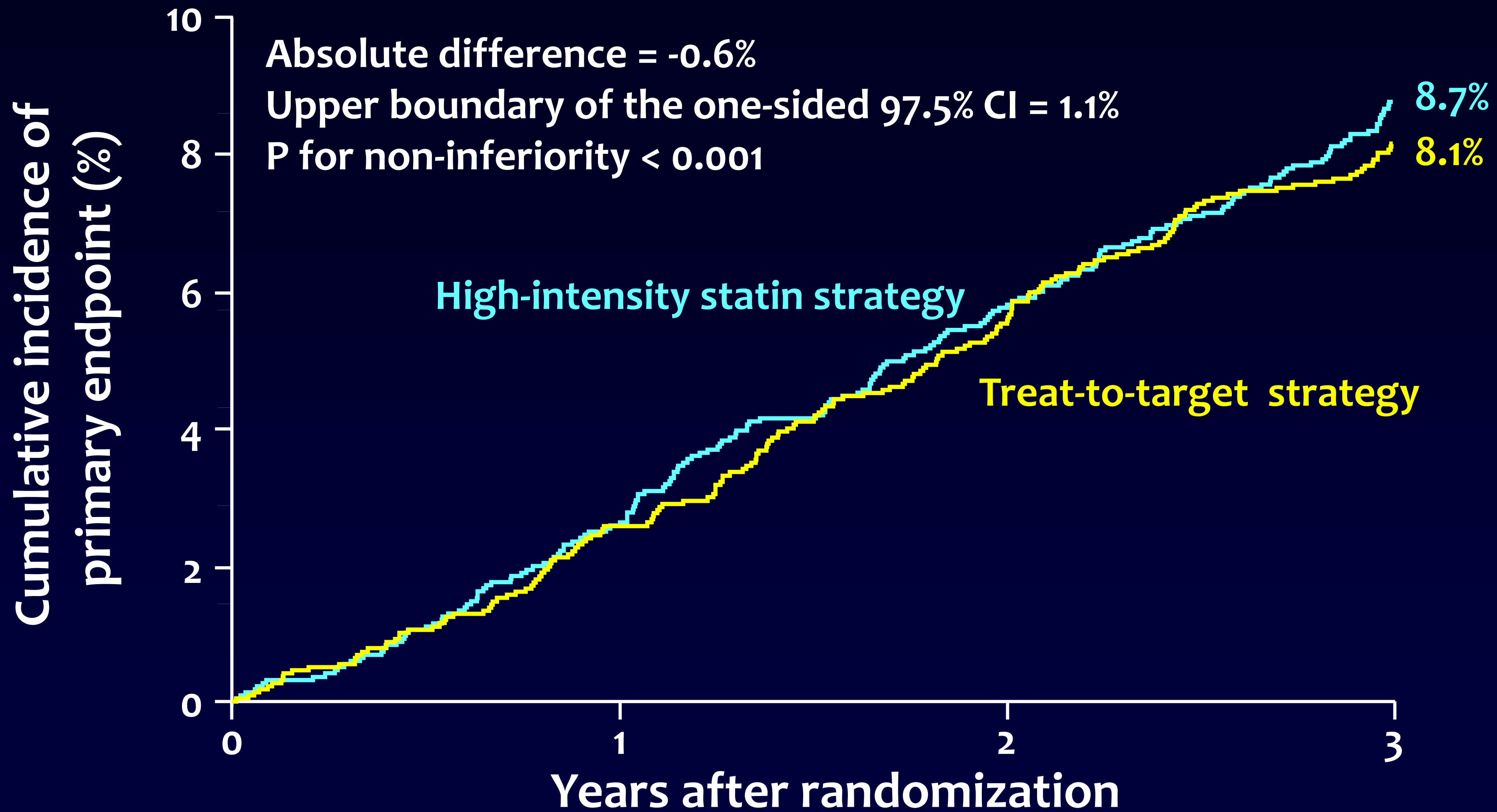
	Treat-to-target (N=2200)	High-intensity statin (N=2200)	Absolute difference (95% CI)	P Value
6 weeks				
No. of patients	1598	1601		
Patients with LDL-C levels <70 mg/dL (%)	890 (55.7)	987 (61.6)	-6.0 (-9.4 to -2.5)	<0.001
3 months				
No. of patients	441	397		
Patients with LDL-C levels <70 mg/dL (%)	261 (59.2)	267 (67.3)	-8.1 (-15.6 to -5.3)	0.02
6 months				
No. of patients	1074	1092		
Patients with LDL-C levels <70 mg/dL (%)	620 (57.7)	653 (59.8)	-2.1 (-5.8 to 1.7)	0.33
1 year				
No. of patients	1862	1854		
Patients with LDL-C levels <70 mg/dL (%)	1038 (55.7)	1092 (58.9)	-3.2 (-6.3 to 0.0)	0.05
2 years				
No. of patients	1654	1679		
Patients with LDL-C levels <70 mg/dL (%)	1005 (60.8)	1015 (60.4)	0.3 (-3.0 to 3.6)	0.86
3 years				
No. of patients	1560	1554		
Patients with LDL-C levels <70 mg/dL (%)	908 (58.2)	927 (59.7)	-1.4 (-4.9 to 2.0)	0.41

LDL cholesterol levels



	0	1.5	3	6	12	24	36
Treat-to-target	2200	1598	441	1074	1862	1654	1560
High-intensity statin	2200	1601	397	1092	1854	1679	1554
Difference	-0.7	2.8	2.2	0.3	0.8	-0.3	0.1

Primary endpoint



	0	1	2	3
Treat-to-target	2200	2123	2054	1989
High-intensity statin	2200	2127	2056	1985

Primary endpoint

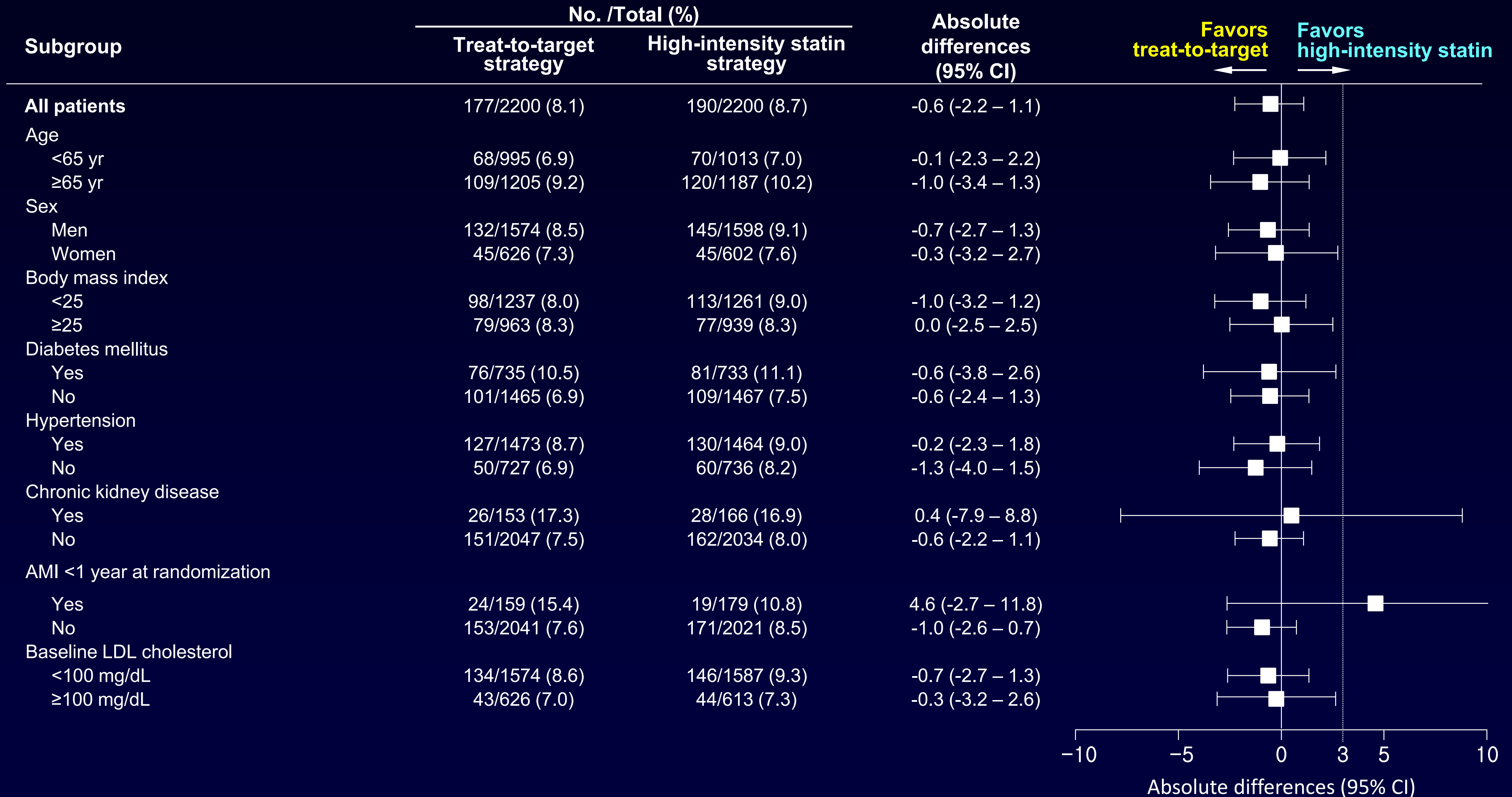
	Treat-to-target strategy (N=2200)	High-intensity statin strategy (N=2200)	Difference (95% CI)	P Value
	No. of Patients (%)		*Percentage Points*	
Primary endpoint				
Death, myocardial infarction, stroke, or coronary revascularization	177 (8.1)	190 (8.7)	-0.6*	<0.001*
Components of primary endpoint				
Death	54 (2.5)	54 (2.5)	<0.1 (-0.9 to 0.9)	0.99
Cardiac death	16	13		
Myocardial infarction	34 (1.6)	26 (1.2)	0.4 (-0.3 to 1.1)	0.23
Stroke	17 (0.8)	27 (1.3)	-0.5 (-1.1 to 0.1)	0.13
Ischemic stroke	12	20		
Hemorrhagic stroke	5	7		
Coronary revascularization	112 (5.2)	114 (5.3)	-0.1 (-1.4 to 1.2)	0.89

*The P value for noninferiority is for an upper boundary of the 97.5% confidence interval of the between-group difference in the primary endpoint, which was 1.1%.

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		

Subgroup analyses for primary endpoint



Subgroup	No. /Total (%) Treat-to-target strategy	No. /Total (%) High-intensity statin strategy	Absolute differences (95% CI)
All patients	177/2200 (8.1)	190/2200 (8.7)	-0.6 (-2.2 – 1.1)
Age			
<65 yr	68/995 (6.9)	70/1013 (7.0)	-0.1 (-2.3 – 2.2)
≥65 yr	109/1205 (9.2)	120/1187 (10.2)	-1.0 (-3.4 – 1.3)
Sex			
Men	132/1574 (8.5)	145/1598 (9.1)	-0.7 (-2.7 – 1.3)
Women	45/626 (7.3)	45/602 (7.6)	-0.3 (-3.2 – 2.7)
Body mass index			
<25	98/1237 (8.0)	113/1261 (9.0)	-1.0 (-3.2 – 1.2)
≥25	79/963 (8.3)	77/939 (8.3)	0.0 (-2.5 – 2.5)
Diabetes mellitus			
Yes	76/735 (10.5)	81/733 (11.1)	-0.6 (-3.8 – 2.6)
No	101/1465 (6.9)	109/1467 (7.5)	-0.6 (-2.4 – 1.3)
Hypertension			
Yes	127/1473 (8.7)	130/1464 (9.0)	-0.2 (-2.3 – 1.8)
No	50/727 (6.9)	60/736 (8.2)	-1.3 (-4.0 – 1.5)
Chronic kidney disease			
Yes	26/153 (17.3)	28/166 (16.9)	0.4 (-7.9 – 8.8)
No	151/2047 (7.5)	162/2034 (8.0)	-0.6 (-2.2 – 1.1)
AMI <1 year at randomization			
Yes	24/159 (15.4)	19/179 (10.8)	4.6 (-2.7 – 11.8)
No	153/2041 (7.6)	171/2021 (8.5)	-1.0 (-2.6 – 0.7)
Baseline LDL cholesterol			
<100 mg/dL	134/1574 (8.6)	146/1587 (9.3)	-0.7 (-2.7 – 1.3)
≥100 mg/dL	43/626 (7.0)	44/613 (7.3)	-0.3 (-3.2 – 2.6)

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.

Dreams will
come true
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이루어진다