Rosuvastatin vs. Atorvastatin Treatment in LODESTAR Trial

Randomized comparison of rosuvastatin vs. atorvastatin treatment in patients with coronary artery disease: a secondary analysis of the randomized LODESTAR trial

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Background

- **Statins in coronary artery disease**
  - Intensive lowering of low-density lipoprotein (LDL) cholesterol levels is recommended in patients with coronary artery disease (CAD).
  - Among the various lipid-lowering drugs, statins are the cornerstone of therapy and high-intensity statins are generally used as the first-line therapy in patients with CAD.
  - Physicians make decisions for not only statin intensity but also statin type.

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

  - However, few RCTs have directly compared the long-term clinical outcomes of the two most potent statins (rosuvastatin versus atorvastatin) in patients with CAD.

- **Aims**
  - To compare the long-term efficacy and safety between the rosuvastatin and atorvastatin treatment in patients with CAD

Study design

- LODESTAR :A randomised, open-label, multicenter trial (Hong SJ, et al. JAMA 2023;329:1078-1087)
- 2-by-2 factorial randomization (statin type and statin intensity strategy)
- Enrollment period: September 9, 2016 and November 27, 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

Rosuvastatin treatment	**Atorvastatin treatment**
N=2204	**N=2196**

Clinical follow-up at 3 years
Composite of all-cause death, myocardial infarction, stroke, or any coronary revascularization

Trial Registration: Clinicaltrial.gov Identifier: NCT02579499

Statistical analysis

- The sample size estimation for the LODESTAR trial was performed on the basis of determining the primary objective of the study: to compare the treat-to-target strategy (target LDL cholesterol, 50-70mg/dL) with the high-intensity statin strategy in terms of 3-year occurrence of the primary outcome.

  Hong SJ, et al. *JAMA* 2023;329:1078-1087

- A 2-by-2 factorial randomization was prespecified, nevertheless, the sample size estimation was not performed for comparing the randomized statin types.

- Interaction between statin type and statin intensity strategy regarding the primary outcome was estimated, and there was no significant interaction.

- **This study focused on the randomized statin types in the LODESTAR trial**
  → 3-year clinical outcomes between the rosuvastatin and atorvastatin treatment in patients with CAD were evaluated

Study flow

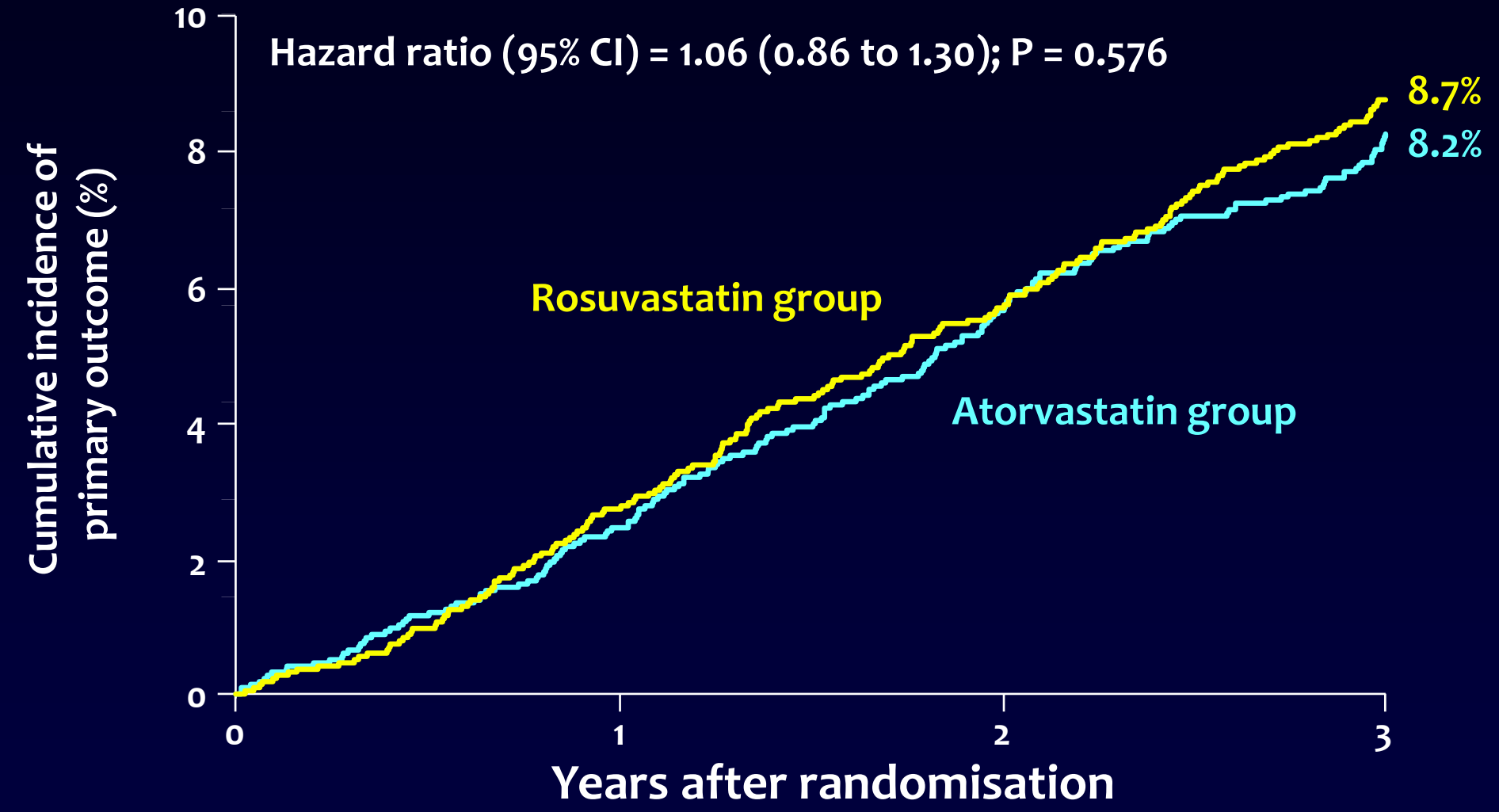
4400 underwent randomization

2204 Were assigned to receive rosuvastatin	**2196 Were assigned to receive atorvastatin**
1935 Received rosuvastatin as randomized	1898 Received atorvastatin as randomized
49 Did not complete statin therapy	46 Did not complete statin therapy
40 Due to adverse events	37 Due to adverse events
9 Due to poor compliance	9 Due to poor compliance
229 Did not receive rosuvastatin	252 Did not receive atorvastatin
21 Due to adverse events	30 Due to adverse events
18 Due to patients' request	16 Due to patients' request
5 Due to physicians' decision	11 Due to physicians' decision
170 Failure to comply with protocol	187 Failure to comply with protocol
6 Others	8 Others
16 Withdrew consent 13 Lost to follow-up 57 Died	14 Withdrew consent 12 Lost to follow-up 51 Died
2204 Included in the primary analysis	2196 Included in the primary analysis

Baseline clinical characteristics

	Rosuvastatin group (N=2204)	Atorvastatin group (N=2196)
Age, mean (SD), years	65 (10)	65 (10)
Female sex	602 (27)	626 (29)
Body-mass index, mean (SD), kg/m^2	24.8 (3.0)	24.7 (2.8)
Hypertension	1498 (68)	1439 (66)
Diabetes	725 (33)	743 (34)
Chronic kidney disease	149 (7)	170 (8)
Previous stroke	140 (6)	123 (6)
Previous PCI	1258 (57)	1199 (55)
Previous CABG	167 (8)	167 (8)
Clinical presentation at randomization		
Acute myocardial infarction within 1 year	175 (8)	163 (7)
Unstable angina or revascularization within 1 year	404 (18)	384 (18)
>1 year after myocardial infarction	322 (15)	353 (16)
>1 year after unstable angina or revascularization	906 (41)	878 (40)
Detection of CAD at screening without symptoms	397 (18)	418 (19)
Lipid lowering therapy before randomization		
Statin		
None	351 (16)	327 (15)
Low-intensity statin	43 (2)	50 (2)
Moderate-intensity statin	1277 (58)	1247 (57)
High-intensity statin	533 (24)	572 (26)
Ezetimibe	259 (12)	220 (10)
LDL cholesterol, mean (SD), mg/dL	86 (33)	87 (32)

Primary outcome



Rosuvastatin	2204	2126	2059	1984
Atorvastatin	2196	2124	2051	1990

Primary outcomes

	Rosuvastatin group (N=2204)	Atorvastatin group (N=2196)	Absolute difference (95% CI)	Hazard ratio (95% CI)	P Value
Primary outcome					
Death, myocardial infarction, stroke, or coronary revascularization	**189 (8.7)**	**178 (8.2)**	**0.5 (-1.2 to 2.1)**	**1.06 (0.86 to 1.30)**	**0.576**
Components of primary outcome					
Death	57 (2.6)	51 (2.3)	0.3 (-0.7 to 1.2)	1.12 (0.77 to 1.63)	0.570
Cardiac death	14	15			
Myocardial infarction	34 (1.5)	26 (1.2)	0.3 (-0.4 to 1.0)	1.27 (0.76 to 2.12)	0.366
Stroke	24 (1.1)	20 (0.9)	0.2 (-0.4 to 0.8)	1.20 (0.66 to 2.17)	0.549
Ischemic stroke	16	16			
Hemorrhagic stroke	8	4			
Coronary revascularization	115 (5.3)	111 (5.2)	0.2 (-1.2 to 1.5)	1.03 (0.80 to 1.34)	0.812

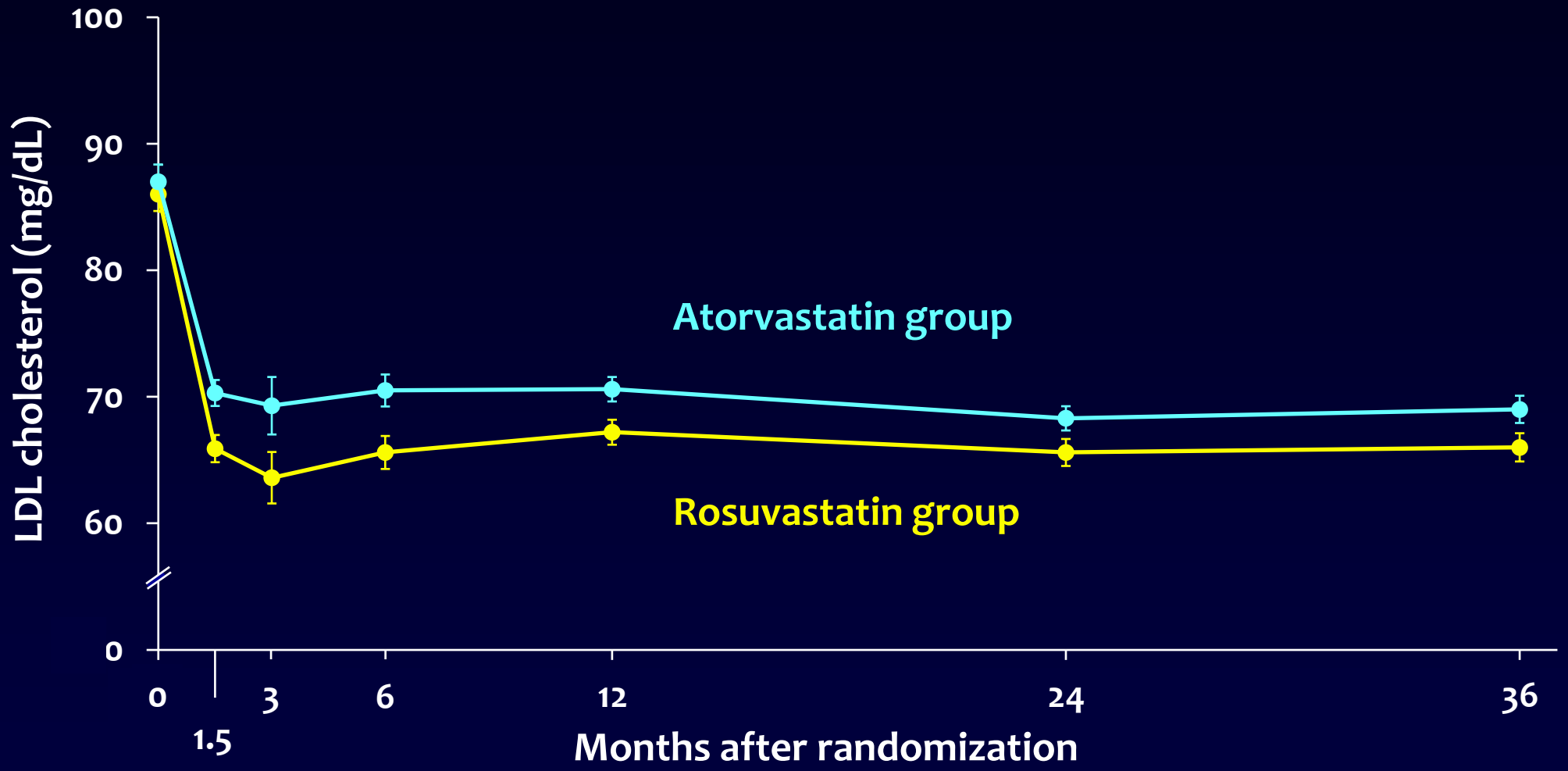
Secondary outcomes

	Rosuvastatin group (N=2204)	Atorvastatin group (N=2196)	Absolute difference (95% CI)	Hazard ratio (95% CI)	P Value
New-onset diabetes	**152 (7.1)**	**119 (5.5)**	**1.5 (0.1 to 3.0)**	**1.29 (1.01 to 1.63)**	**0.040**
New-onset diabetes among patients without diabetes at baseline	**152/1479 (10.4)**	**119/1453 (8.4)**	**2.1 (-0.0 to 4.2)**	**1.26 (0.99 to 1.60)**	**0.058**
Initiation of anti-diabetic medication among patients without diabetes at baseline	**104/1479 (7.2)**	**74/1453 (5.3)**	**2.0 (0.2 to 3.7)**	**1.39 (1.03 to 1.87)**	**0.031**
Hospitalization due to heart failure	12 (0.6)	8 (0.4)	0.2 (-0.2 to 0.6)	1.50 (0.61 to 3.66)	0.373
Deep vein thrombosis or pulmonary embolism	7 (0.3)	2 (0.1)	0.2 (-0.0 to 0.5)	3.50 (0.73 to 16.84)	0.096
Deep vein thrombosis	5	2			
Pulmonary embolism	3	0			
Peripheral artery revascularization	12 (0.5)	17 (0.8)	-0.3 (-0.8 to 0.2)	0.65 (0.30 to 1.38)	0.253
Aortic intervention or surgery	3 (0.1)	2 (0.1)	0.0 (-0.2 to 0.3)	1.50 (0.25 to 8.94)	0.658
Endovascular therapy	3	0			
Surgical therapy	0	2			
End-stage kidney disease	9 (0.4)	4 (0.2)	0.2 (-0.1 to 0.6)	2.25 (0.69 to 7.30)	0.166
Discontinuation of statin therapy	40 (1.8)	37 (1.7)	0.1 (-0.7 to 0.9)	1.08 (0.69 to 1.69)	0.741
Cataract operation	**53 (2.5)**	**32 (1.5)**	**1.0 (1.4 to 1.8)**	**1.66 (1.07 to 2.58)**	**0.022**
Composite of laboratory abnormalities	26 (1.2)	22 (1.0)	0.2 (-0.4 to 0.8)	1.24 (0.70 to 2.20)	0.466
Aminotransferase elevation	10	10			
Creatine kinase elevation	5	6			
Creatinine elevation	11	7			

Lipid-lowering therapy during the study period

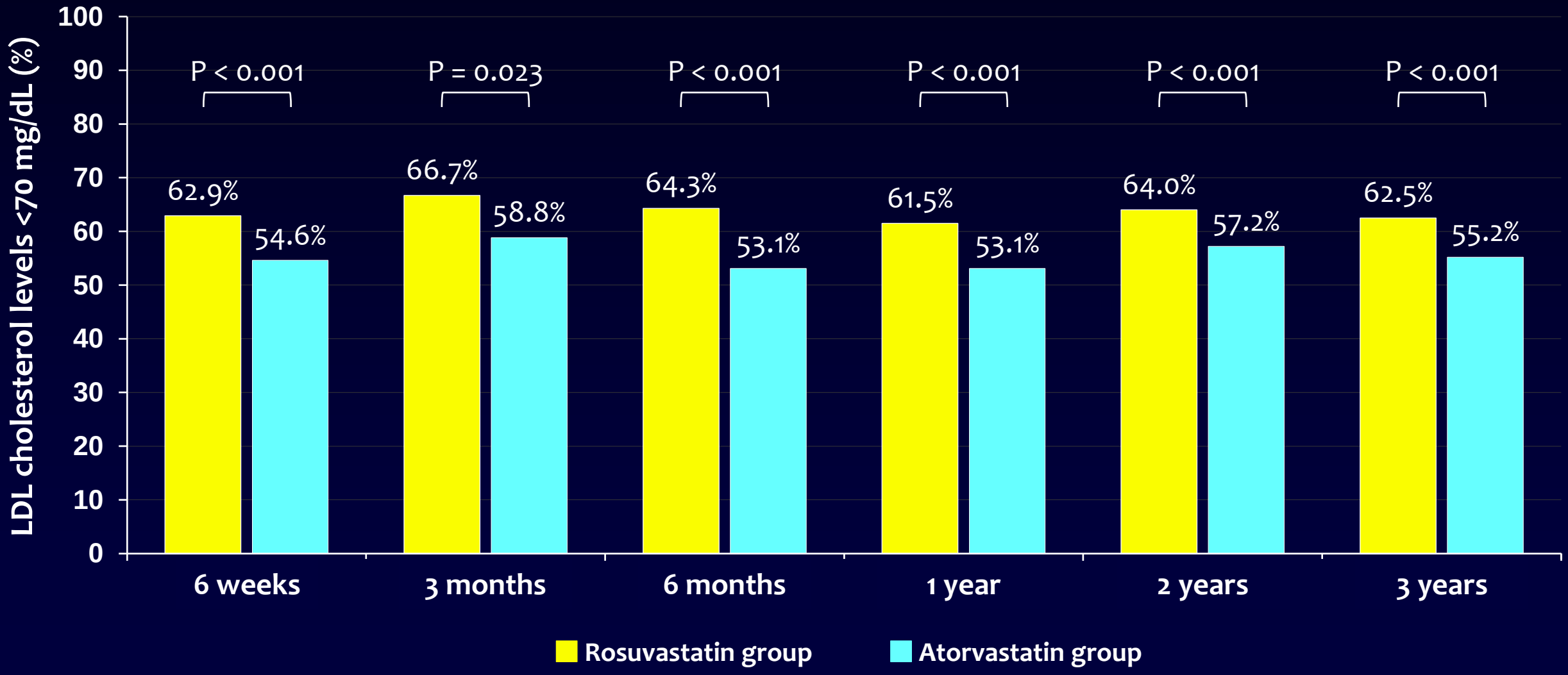
	Rosuvastatin group	Atorvastatin group	Absolute difference (95% CI)	P-value
High-intensity statins				
0 – 6 weeks	1602 / 2204 (72.7)	1596 / 2196 (72.7)	0.0 (-2.6 to 2.6)	1.000
6 week – 3 months	1599 / 2190 (73.0)	1616 / 2184 (74.0)	-1.0 (-3.6 to 1.6)	0.484
3 months – 6 months	1587 / 2189 (72.5)	1618 / 2177 (74.3)	-1.8 (-4.4 to 0.8)	0.184
6 months – 1 year	1569 / 2184 (71.8)	1611 / 2175 (74.1)	-2.2 (-4.9 to 0.4)	0.105
1 year – 2 years	1557 / 2167 (71.9)	1615 / 2163 (74.7)	-2.8 (-5.4 to -0.2)	0.040
2 years – 3 years	1517 / 2141 (70.9)	1580 / 2134 (74.0)	-3.2 (-5.9 to -0.5)	0.022
Ezetimibe				
0 – 6 weeks	18 / 2204 (0.8)	13 / 2196 (0.6)	0.2 (-0.3 to 0.7)	0.477
6 week – 3 months	97 / 2190 (4.4)	137 / 2184 (6.3)	-1.8 (-3.2 to -0.5)	0.008
3 months – 6 months	110 / 2189 (5.0)	148 / 2177 (6.8)	-1.8 (-3.2 to -0.4)	0.016
6 months – 1 year	150 / 2184 (6.9)	215 / 2175 (9.9)	-3.0 (-4.7 to -1.4)	<0.001
1 year – 2 years	200 / 2167 (9.2)	295 / 2163 (13.6)	-4.4 (-6.3 to -2.5)	<0.001
2 years – 3 years	252 / 2141 (11.8)	402 / 2134 (18.8)	-7.1 (-9.2 to -4.9)	<0.001

LDL cholesterol levels



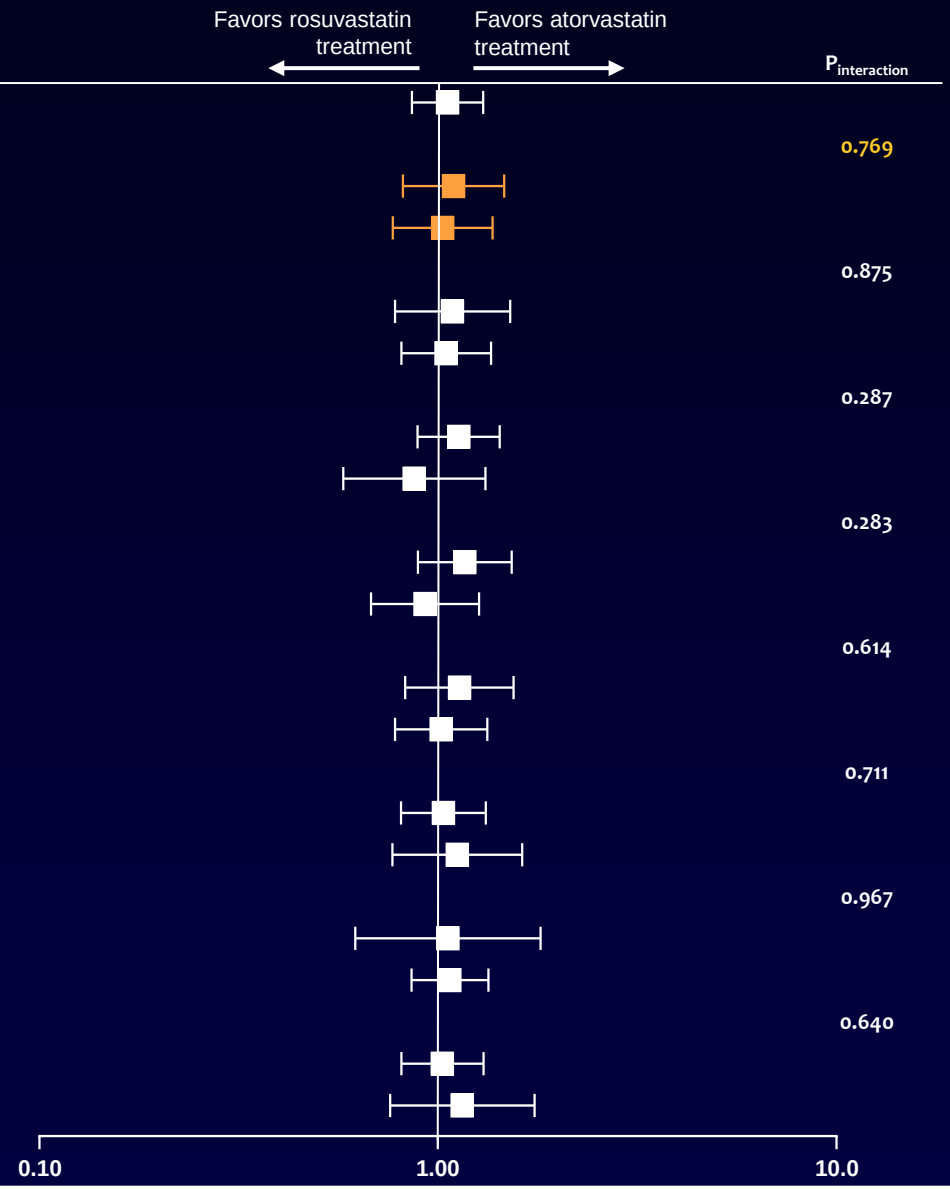
Rosuvastatin	2204	1570	447	1098	1875	1673	1582
Atorvastatin	2196	1629	391	1068	1841	1660	1532
Difference		-4.4	-5.7	-4.9	-3.4	-2.7	-3.0

LDL cholesterol levels below 70 mg/dL



Subgroup analyses for primary outcome

Subgroup	No. / Total (%) Rosuvastatin group	Atorvastatin group	HR (95% CI)	$P_{interaction}$
All patients	189/2204 (8.7)	178/2196 (8.2)	1.06 (0.86-1.30)	
Statin intensity strategy				0.769
Treat-to-target	92/1098 (8.5)	85/1102 (7.8)	1.09 (0.82-1.47)	
High-intensity statin	97/1106 (8.8)	93/1094 (8.6)	1.03 (0.77-1.37)	
Age, years				0.875
<65	73/1018 (7.2)	65/990 (6.6)	1.09 (0.78-1.52)	
≥65	116/1186 (9.9)	113/1206 (9.5)	1.05 (0.81-1.36)	
Sex				0.287
Male	148/1602 (9.3)	129/1570 (8.3)	1.13 (0.89-1.43)	
Female	41/602 (6.7)	49/626 (7.8)	0.87 (0.58-1.32)	
Body mass index, kg/m²				0.283
<25	112/1232 (9.2)	99/1266 (7.9)	1.17 (0.89-1.53)	
≥25	77/972 (8.0)	79/930 (8.6)	0.93 (0.68-1.27)	
Diabetes mellitus				0.614
Yes	82/725 (11.5)	75/743 (10.2)	1.13 (0.83-1.55)	
No	107/1479 (7.3)	103/1453 (7.2)	1.02 (0.78-1.33)	
Hypertension				0.711
Yes	133/1498 (9.0)	124/1439 (8.7)	1.03 (0.81-1.32)	
No	56/706 (8.0)	54/757 (7.2)	1.12 (0.77-1.63)	
Chronic kidney disease				0.967
Yes	26/149 (17.6)	28/170 (16.6)	1.06 (0.62-1.81)	
No	163/2055 (8.0)	150/2026 (7.5)	1.07 (0.86-1.34)	
Baseline LDL cholesterol, mg/dL				0.640
<100	144/1606 (9.0)	136/1555 (8.8)	1.03 (0.81-1.30)	
≥100	45/598 (7.7)	42/641 (6.7)	1.15 (0.76-1.75)	



Conclusion

- To our knowledge, this study is the first randomised trial comparing 3-year clinical outcomes of rosuvastatin treatment versus atorvastatin treatment in patients with CAD.

- The 3-year composite of all-cause death, MI, stroke, or any coronary revascularization did not differ between the rosuvastatin and atorvastatin treatment.

- Rosuvastatin treatment was associated with lower LDL cholesterol levels, but it also carried a higher risk of new-onset diabetes mellitus requiring anti-diabetic medication and cataract operation, compared with atorvastatin treatment.


Dreams will
come true