Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplementary methods for definition of secondary endpoints

New-onset diabetes mellitus was defined as a fasting plasma glucose level ≥126 mg/dL or new initiation of antidiabetic drugs.[1,2] Hospitalization due to heart failure was defined as a hospitalization requiring at least an overnight stay in the hospital due to substantial worsening of heart failure symptoms or signs requiring the augmentation of oral drugs or the new administration of intravenous heart failure therapy, including diuretics, inotropes, or vasodilators.[3] Deep vein thrombosis was diagnosed when thrombi in deep veins of the lower extremity were found by imaging studies such as compression ultrasonography or computed tomography.[4] Pulmonary thromboembolism was defined as the appearance of a thrombus in the pulmonary arteries in a ventilation-perfusion lung scan, pulmonary angiography, or computed tomography.[4] Aortic intervention or surgery involved any endovascular procedure or surgery to treat aorta disease. End stage kidney disease was defined as stage 5 according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of chronic kidney disease or disease requiring dialysis, irrespective of the glomerular filtration rate.[5] The composite of laboratory abnormalities considered elevation in aminotransferase (>baseline level and >3 times the upper limit of reference), creatine kinase (>baseline level and >5 times the upper limit of reference), and creatinine levels (>50% increase from baseline level and greater than the upper limit of reference). In this study, a composite of new-onset diabetes mellitus, aminotransferase or creatine kinase elevation, or end-stage kidney disease was also assessed as a post hoc.

References

1. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015;38 Suppl:S8-S16.
2. Dormuth CR, Filion KB, Paterson JM, et al. Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. BMJ 2014;348:g3244.
3. Zannad F, Garcia AA, Anker SD, et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. Eur J Heart Fail 2013;15(10):1082-1094.
4. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003;362(9383):523-526.
5. Levin A, Stevens PE. Summary of KDIGO 2012 CKD guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int 2014;85(1):49-61.

eTable 1. Inclusion and exclusion criteria

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

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

eTable 2. Changes in statin intensity in the treat-to-target strategy 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)

Data are numbers (percentages). When patients underwent ≥2 intensity changes for a given period, the initial and final intensity were considered as the overall change in statin intensity.

eTable 3. Statin intensity between groups

	Treat-to-target	High-intensity statin
Total person-years of follow-up[a]	**6449**	**6461**
None	79 (1)	96 (1)
Low-intensity statin	63 (<1)	10 (<1)
Moderate-intensity statin	2795 (43)	405 (6)
High-intensity statin	3512 (54)	5950 (92)
0 – 6 weeks		
Number of patients	2200	2200
Low-intensity statin	5 (<1)	0
Moderate-intensity statin	1173 (53)	24 (1)
High-intensity statin	1022 (47)	2176 (99)
6 week – 3 months		
Number of patients	2187	2187
None	14 (1)	16 (1)
Low-intensity statin	10 (1)	2 (<1)
Moderate-intensity statin	1047 (48)	70 (3)
High-intensity statin	1116 (51)	2099 (96)
3 months – 6 months		
Number of patients	2182	2184
None	25 (1)	25 (1)
Low-intensity statin	13 (1)	3 (<1)
Moderate-intensity statin	1019 (47)	76 (4)
High-intensity statin	1125 (52)	2080 (95)
6 months – 1 year		
Number of patients	2177	2182
None	30 (1)	43 (2)
Low-intensity statin	14 (1)	4 (<1)
Moderate-intensity statin	989 (45)	99 (5)
High-intensity statin	1144 (53)	2036 (93)
1 year – 2 years		
Number of patients	2164	2166
None	42 (2)	44 (2)
Low-intensity statin	25 (1)	4 (<1)
Moderate-intensity statin	900 (42)	143 (7)
High-intensity statin	1197 (55)	1975 (91)
2 years – 3 years		
Number of patients	2137	2138
None	49 (2)	50 (2)
Low-intensity statin	26 (1)	3 (<1)
Moderate-intensity statin	868 (41)	182 (9)
High-intensity statin	1194 (56)	1903 (89)

[a] Data are presented as person-years (%) and others are numbers (percentages).

eTable 4. Lipid-lowering therapy

	0 – 6 weeks		6 weeks – 3 months		3 – 6 months		6 months – 1 year		1 – 2 years		2 – 3 years	
	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin
No. of patients	**2200**	**2200**	**2187**	**2187**	**2182**	**2184**	**2177**	**2182**	**2164**	**2166**	**2137**	**2138**
Statin therapy												
High-intensity statin												
No. of patients	1022	2176	1116	2099	1125	2080	1144	2036	1197	1975	1194	1903
Atorvastatin 80 mg	3 (<1)	4 (<1)	8 (1)	7 (<1)	8 (1)	7 (<1)	8 (1)	7 (<1)	38 (3)	21 (1)	43 (4)	22 (1)
Atorvastatin 40 mg	532 (52)	1079 (50)	586 (53)	1025 (49)	594 (52)	1016 (49)	601 (53)	1000 (49)	605 (51)	955 (48)	600 (50)	911 (48)
Rosuvastatin 20 mg	487 (48)	1093 (50)	522 (47)	1067 (51)	523 (47)	1057 (51)	535 (47)	1029 (51)	554 (46)	999 (51)	551 (46)	970 (51)
Moderate-intensity statin												
No. of patients	1173	24	1047	70	1019	76	989	99	900	143	868	182
Atorvastatin 20 or 10 mg	557 (48)	14 (58)	481 (46)	36 (51)	461 (45)	38 (50)	442 (44)	49 (49)	387 (43)	67 (47)	362 (42)	79 (43)
Rosuvastatin 10 or 5 mg	615 (52)	9 (38)	561 (53)	28 (40)	554 (54)	33 (44)	541 (55)	47 (47)	504 (56)	65 (45)	498 (57)	89 (49)
Simvastatin 40 or 20 mg	1 (<1)	0	3 (<1)	0	2 (<1)	0	4 (<1)	0	5 (1)	1 (1)	0	0
Pitavastatin 4, 2 or 1 mg	0	1 (<)	1 (<1)	4 (6)	1 (<1)	3 (4)	1 (<1)	1 (1)	3 (<1)	9 (6)	7 (1)	13 (7)
Fluvastatin XL 80 mg	0	0	0	2 (3)	0	2 (3)	0	2 (2)	1 (<1)	1 (1)	1 (<1)	1 (1)
Pravastatin 40 mg	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	0	0	0	0
Low-intensity statin												
No. of patients	5	0	10	2	13	3	14	4	25	4	26	3
Simvastatin 10 mg	1 (20)	0	2 (20)	1 (50)	2 (15)	2 (67)	1 (7)	2 (50)	0	2 (50)	0	0
Rosuvastatin 2.5 mg	2 (40)	0	2 (20)	0	2 (15)	0	2 (14)	0	4 (16)	0	3 (12)	1 (33)
Atorvastatin 5 mg	2 (40)	0	4 (40)	1 (50)	7 (54)	1 (33)	9 (64)	2 (50)	19 (76)	2 (50)	20 (77)	2 (67)
Pravastatin 20 or 10 mg	0	0	2 (20)	0	2 (15)	0	2 (14)	0	2 (8)	0	3 (12)	0
Discontinuation of statin												
No. of patients	0	0	14	16	25	25	30	43	42	44	50	49
Non-statin therapy												
Ezetimibe	21 (1)	10 (1)	155 (7)	79 (4)	163 (8)	95 (4)	242 (11)	123 (6)	336 (16)	158 (7)	422 (20)	232 (11)
Ezetimibe only without statin	0	0			1		3	0	1	1	1	2
With low-intensity statin	1	0	2	1	2	2	1	2	0	2		
With moderate-intensity statin	6	0	13	3	17	7	22	11	35	28	56	46
With high-intensity statin	14	10	140	75	143	86	216	110	300	127	365	184

Data are numbers (percentages).

eTable 5. Cardiovascular medications

	0 – 6 weeks		6 weeks – 3 months		3 – 6 months		6 months – 1 year		1 – 2 years		2 – 3 years	
	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin	Treat-to-target	High-intensity statin
No. of patients	**2200**	**2200**	**2187**	**2187**	**2182**	**2184**	**2177**	**2182**	**2164**	**2166**	**2137**	**2138**
Aspirin	1592 (72)	1625 (74)	1548 (71)	1582 (72)	1527 (70)	1561 (72)	1494 (69)	1522 (70)	1344 (62)	1372 (63)	1242 (58)	1247 (58)
Clopidogrel	1049 (48)	1029 (47)	1041 (48)	1022 (47)	1040 (48)	1017 (47)	1019 (47)	1033 (46)	1066 (49)	1035 (48)	1057 (50)	1030 (48)
Prasugrel or Ticagrelor	153 (7)	168 (8)	142 (7)	154 (7)	135 (6)	144 (7)	125 (6)	126 (6)	44 (2)	44 (2)	17 (1)	16 (1)
Warfarin	15 (1)	12 (1)	16 (1)	13 (1)	15 (1)	13 (1)	14 (1)	14 (1)	17 (1)	15 (1)	15 (1)	12 (1)
New oral anticoagulant	40 (2)	49 (2)	42 (2)	49 (2)	48 (2)	49 (2)	56 (3)	56 (3)	57 (3)	56 (3)	64 (3)	73 (3)
Beta-blocker	1227 (56)	1209 (55)	1225 (56)	1214 (56)	1229 (56)	1210 (55)	1220 (56)	1205 (55)	1187 (55)	1175 (54)	1158 (54)	1150 (54)
ACE inhibitor or ARB	1220 (56)	1213 (55)	1207 (55)	1226 (56)	1211 (56)	1226 (56)	1195 (55)	1218 (56)	1189 (55)	1198 (55)	1182 (55)	1205 (56)
Calcium channel blocker	134 (6)	145 (7)	133 (6)	136 (6)	139 (6)	132 (6)	141 (7)	136 (6)	132 (6)	128 (6)	140 (7)	128 (6)
Thiazide	134 (6)	145 (7)	133 (6)	136 (6)	139 (6)	132 (6)	141 (7)	136 (6)	132 (6)	128 (6)	140 (7)	128 (6)
Loop diuretics	126 (6)	131 (6)	123 (6)	122 (6)	116 (5)	128 (6)	111 (5)	121 (6)	110 (5)	112 (5)	105 (5)	113 (5)
Spironolactone	55 (3)	63 (3)	51 (2)	59 (3)	49 (2)	59 (3)	47 (2)	54 (3)	39 (2)	54 (3)	44 (2)	53 (3)

Data are numbers (percentages).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

eTable 6. Serial changes in lipid profiles

	Treat-to-target	High-intensity statin	Absolute Difference (95% confidence interval)	P Value
Lipid profile, mean (SD), mg/dl				
At 6 weeks				
No. of patients	1598	1601		
LDL-C	69.6 (21.2)	66.8 (21.8)	2.8 (1.3 to 4.3)	<.001
Total-C	136.1 (26.7)	135.9 (28.1)	0.1 (-1.8 to 2.0)	.91
Triglyceride	127.1 (65.0)	127.3 (67.5)	-0.2 (-4.8 to 4.4)	.95
HDL-C	47.2 (11.5)	47.4 (11.5)	-0.1 (-0.9 to 0.7)	.78
At 3 months				
No. of patients	441	397		
LDL-C	67.3 (21.1)	65.1 (24.0)	2.2 (-0.8 to 5.3)	.16
Total-C	135.9 (27.8)	135.4 (29.8)	0.6 (-3.1 to 4.3)	.76
Triglyceride	133.8 (85.3)	143.6 (106.2)	-9.8 (-22.9 to 3.3)	.14
HDL-C	46.4 (12.4)	45.8 (11.7)	0.6 (-1.0 to 2.3)	.46
At 6 months				
No. of patients	1074	1092		
LDL-C	68.2 (20.3)	67.9 (22.8)	0.3 (-1.5 to 2.1)	.76
Total-C	137.8 (26.9)	137.6 (29.2)	0.2 (-2.1 to 2.5)	.87
Triglyceride	131.6 (72.6)	128.8 (72.2)	2.8 (-3.3 to 9.0)	.37
HDL-C	47.4 (12.0)	47.5 (11.5)	-0.1 (-1.1 to 0.9)	.84
At 1 year				
No. of patients	1862	1854		
LDL-C	69.3 (20.6)	68.5 (22.7)	0.8 (-0.6 to 2.2)	.28
Total-C	137.1 (27.4)	136.7 (27.4)	0.3 (-1.4 to 2.1)	.72
Triglyceride	132.0 (78.8)	130.4 (75.4)	1.6 (-3.4 to 6.5)	.54
HDL-C	47.8 (11.8)	47.6 (11.9)	0.2 (-0.6 to 1.0)	.59
At 2 years				
No. of patients	1654	1679		
LDL-C	66.8 (19.5)	67.1 (22.5)	-0.3 (-1.7 to 1.1)	.66
Total-C	136.3 (26.3)	135.7 (26.5)	0.6 (-1.2 to 2.4)	.49
Triglyceride	128.9 (72)	125.3 (71.3)	3.6 (-1.3 to 8.5)	.15
HDL-C	47.6 (11.6)	47.1 (11.8)	0.5 (-0.3 to 1.3)	.19
At 3 years				
No. of patients	1560	1554		
LDL-C	67.6 (21.2)	67.5 (23.0)	0.1 (-1.5 to 1.6)	.93
Total-C	135.2 (26.7)	136.4 (27.1)	-1.2 (-3.1 to 0.7)	.21
Triglyceride	128.3 (73.1)	126.9 (81.3)	1.5 (-4 to 6.9)	.60
HDL-C	46.3 (11.5)	47.0 (11.5)	-0.7 (-1.5 to 0.1)	.10

Data are numbers (percentages).

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Total-C, total cholesterol.

eTable 7. Patients with LDL-C below 70 mg/dL

	Treat-to-target	High-intensity statin	Absolute Difference (95% confidence interval)	P Value
At randomization	712/2200 (32.4)	655/2200 (29.8)	2.6 (-0.1 to 5.3)	.06
At 6 weeks	890/1598 (55.7)	987/1601 (61.6)	-6.0 (-9.4 to -2.5)	<.001
At 3 months	261/441 (59.2)	267/397 (67.3)	-8.1 (-15.6 to -5.3)	.02
At 6 months	620/1074 (57.7)	653/1092 (59.8)	-2.1 (-5.8 to 1.7)	.33
At 1 year	1038/1862 (55.7)	1092/1854 (58.9)	-3.2 (-6.3 to 0.0)	.05
At 2 years	1005/1654 (60.8)	1015/1679 (60.4)	0.3 (-3.0 to 3.6)	.86
At 3 years	908/1560 (58.2)	927/1554 (59.7)	-1.4 (-4.9 to 2.0)	.41

Data are presented as number of patients / total number of patients (percentages).

Abbreviations: LDL-C, low-density lipoprotein cholesterol.

eTable 8. Patients excluded from the per-protocol population

	Treat-to-target (n=92)	High-intensity statin (n=94)
Discontinuation of statin therapy by patient's poor compliance	13	5
Did not undergo up-titration despite non-achievement of the goal in the treat-to-target strategy group		
Patient choice	34	
Physician choice	14	
Failure to comply with protocol	22	
Other	9	
Did not maintain high-intensity statin in the high-intensity statin strategy group		
Patient choice		48
Physician choice		26
Failure to comply with protocol		5
Other		10

Data are presented as number of patients.

eTable 9. Primary and secondary endpoints in the per-protocol population[a]

Outcome	Treat-to-target (N=2108)	High-intensity statin (N=2106)	Difference (95% CI)[b]	P Value
	no. of patients (%)		*percentage points*	
Primary endpoint				
Death, myocardial infarction, stroke, or coronary revascularization	173 (8.3)	177 (8.5)	-0.2 (-∞ to 1.5)[c]	<.001[d]
Components of primary endpoint				
Death	54 (2.6)	49 (2.3)	0.3 (-0.7 to 1.2)	.61
Cardiac death	16	12		
Myocardial infarction	34 (1.6)	24 (1.1)	0.5 (-0.2 to 1.3)	.14
Stroke	16 (0.8)	26 (1.3)	-0.5 (-1.1 to 0.1)	.12
Ischemic stroke	11	19		
Hemorrhagic stroke	5	7		
Coronary revascularization[e]	109 (5.3)	107 (5.2)	0.1 (-1.3 to 1.5)	.89
Secondary endpoints				
New-onset diabetes mellitus	116 (5.6)	145 (7.0)	-1.4 (-2.9 to 0.1)	.07
Initiation of anti-diabetic medication	70	102		
Cataract operation	42 (2.0)	41 (2.0)	0.1 (-0.8 to 0.9)	.90
Discontinuation of statin therapy	31 (1.5)	46 (2.3)	-0.7 (-1.6 to 0.1)	.09
Composite of laboratory abnormalities[f]	17 (0.8)	22 (1.1)	-0.2 (-0.8 to 0.4)	.43
Aminotransferase elevation	7	8		
Creatine kinase elevation	3	6		
Creatinine elevation	7	8		
Peripheral artery revascularization	12 (0.6)	16 (0.8)	-0.2 (-0.7 to 0.3)	.45
Hospitalization due to heart failure	13 (0.6)	5 (0.2)	0.4 (-0.0 to 0.8)	.06
End-stage kidney disease	3 (0.1)	7 (0.3)	-0.2 (-0.5 to 0.1)	.21
Deep vein thrombosis or pulmonary embolism	4 (0.2)	5 (0.2)	<0.1 (-0.3 to 0.2)	.74
Deep vein thrombosis	2	5		
Pulmonary embolism	3	0		
Aortic intervention or surgery	2 (0.1)	3 (0.1)	NR	
Endovascular therapy	1	2		
Surgical therapy	1	1		
Composite of new-onset diabetes mellitus, aminotransferase or creatine kinase elevation, or end-stage kidney disease (post hoc)	126 (6.1)	165 (8.0)	-1.9 (-3.4 to -0.4)	.015

[a] The listed percentages were estimated using the Kaplan-Meier method, so the values might not calculate mathematically. Differences in event rates are not reported (NR) for aortic intervention because of the low numbers of events.

[b] The between-group difference was measured in the treat-to-target group compared with the high-intensity statin group. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

[c] A 1-sided 97.5% CI was calculated for the primary end point.

[d] The P value for noninferiority is for the upper boundary of the 97.5% confidence interval of the between-group difference in primary endpoint, which was 1.5 percentage points. Other P values were two-sided.

[e] All coronary revascularizations were clinically indicated: an invasive angiographic percent diameter stenosis ≥50% with ischemic symptoms or signs, or ≥70% even without symptoms or signs.

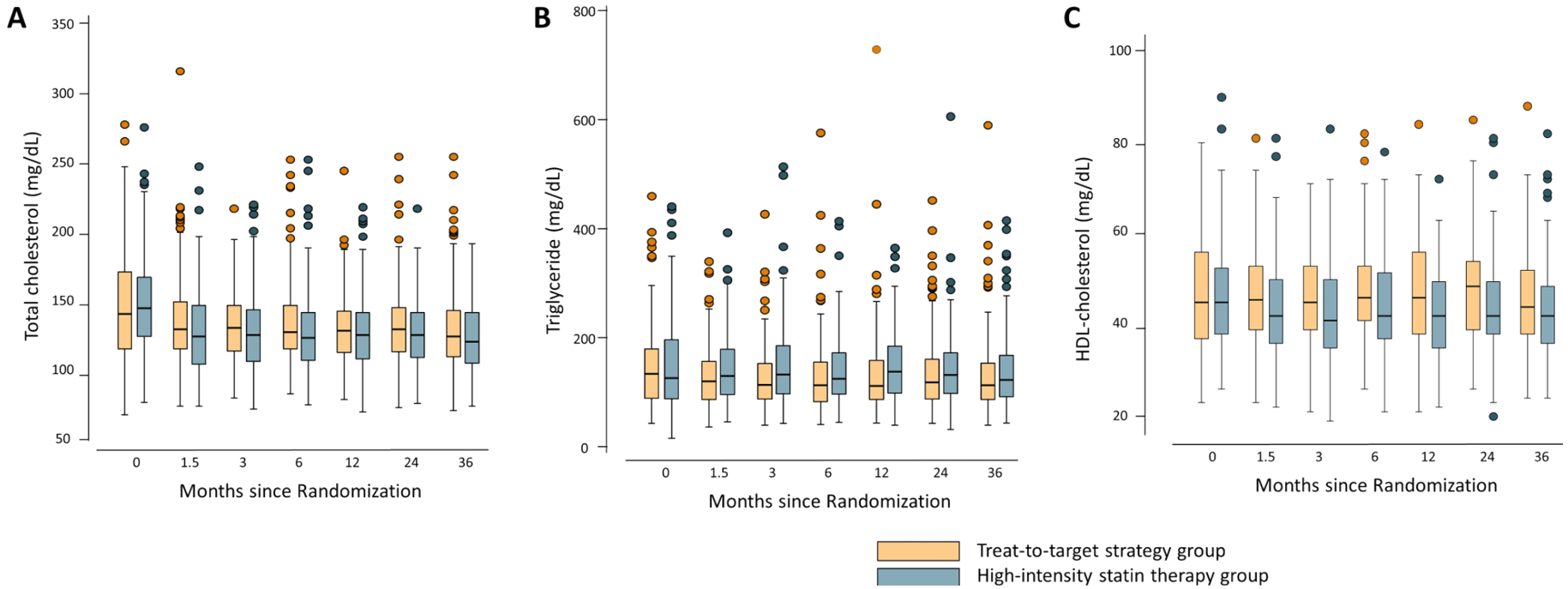
[f] Aminotransferase elevation was defined as >baseline level and >3 times the upper limit of reference; creatine kinase elevation was defined as >baseline level and >5 times the upper limit of reference; creatinine level elevation was defined as >50% increase from baseline and greater than the upper limit of reference. Reference values may vary based on lab and location.

eTable 10. Reasons for discontinuing statin therapy by adverse effect

	Treat-to-target (n=31)	High-intensity statin (n=46)
General weakness	9 (29)	17 (37)
Gastrointestinal symptoms	9 (29)	9 (20)
Muscle symptoms	5 (16)	9 (20)
Itching or urticaria	1 (3)	1 (2)
Dizziness or peripheral numbness	2 (4)	2 (4)
Creatine kinase elevation	1 (3)	5 (11)
Liver enzyme elevation	1 (3)	1 (2)
Other	3 (10)	2 (4)

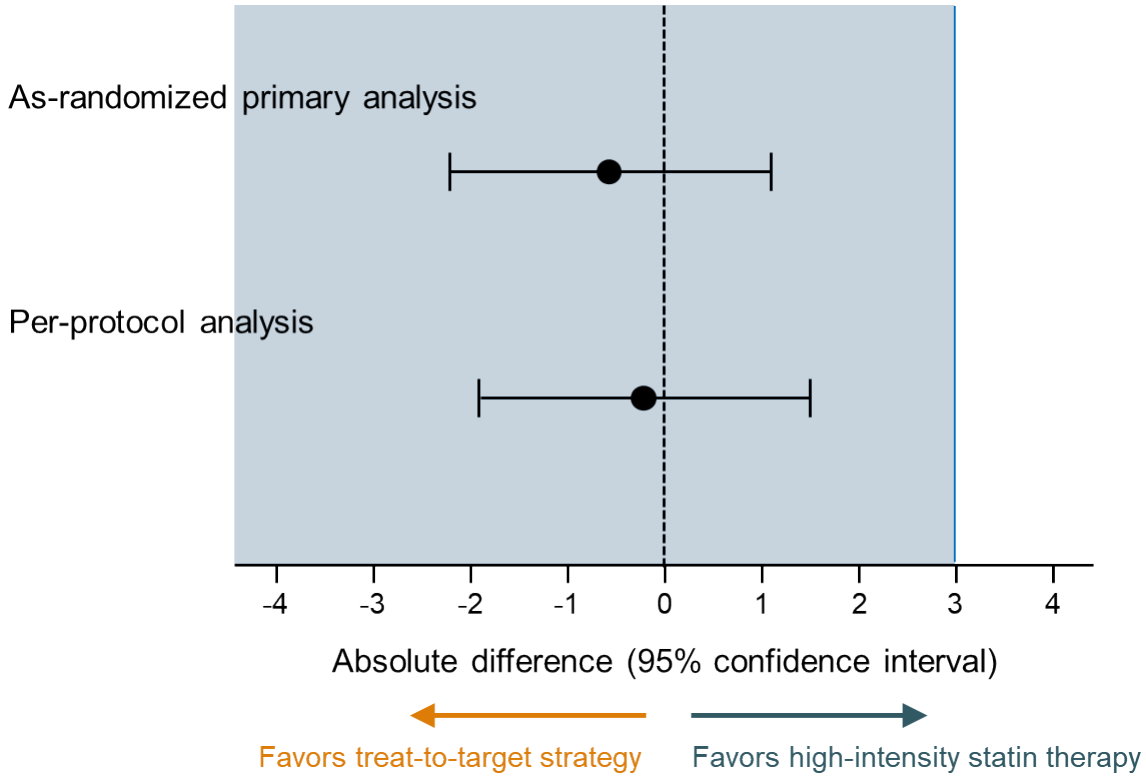
Data are numbers (percentages).

eFigure 1. Lipid profiles during study period



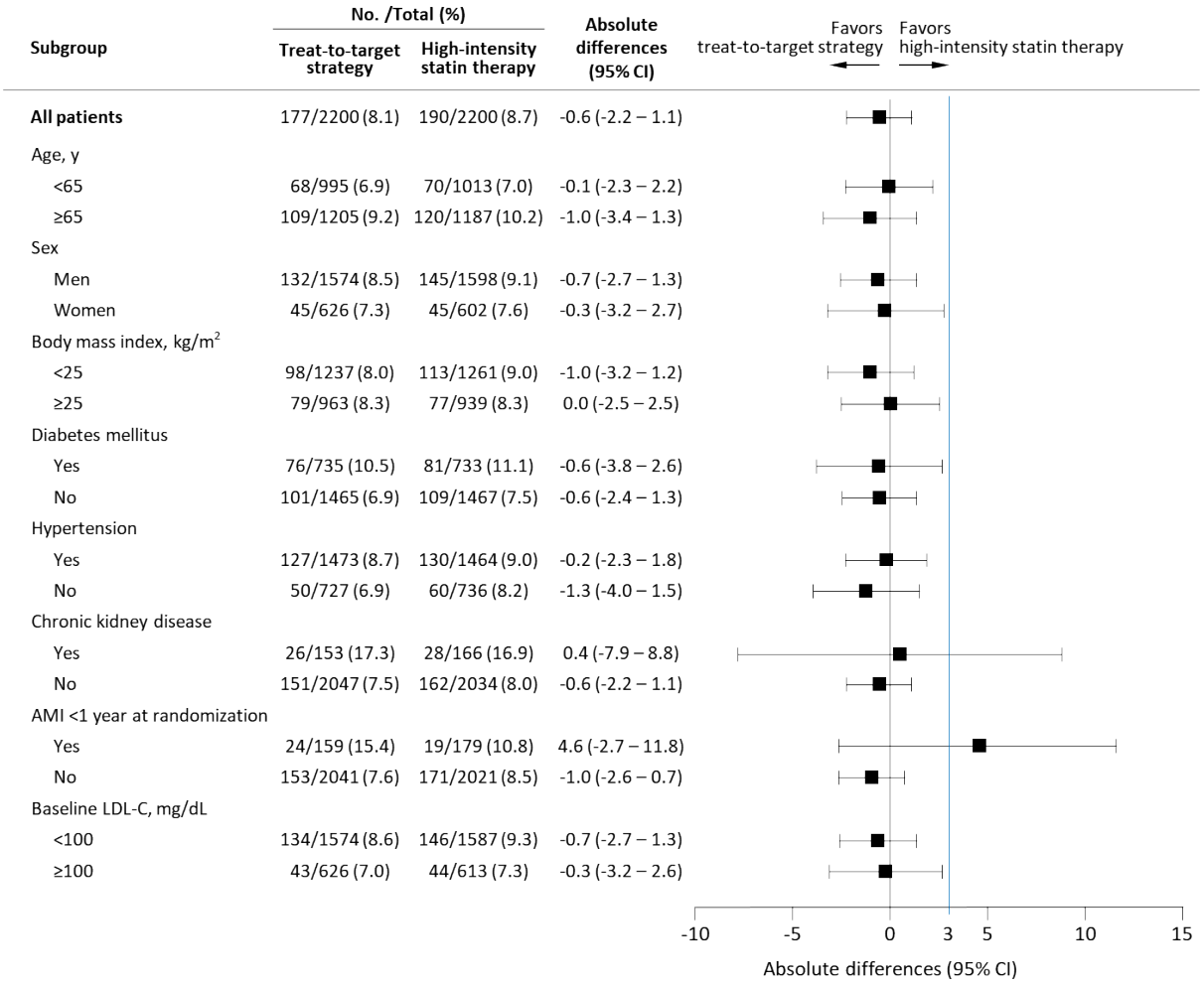
Box plots are shown in which the middle line represents the median value, boxes represent the interquartile range, whiskers extend to the most extreme observed values with 1.5 × the interquartile range of the nearer quartile, and dots represent observed values outside that range. Reference values may vary based on lab and location. HDL indicates high-density lipoprotein.

eFigure 2. Treatment difference for the primary endpoint



The vertical blue line indicates the absolute difference of 3.0 percentage points prespecified as the non-inferiority margin; the blue tinted region to the left of the absolute difference of 3.0 percentage points indicates values for which a treat-to-target strategy would be considered noninferior to a high-intensity statin therapy.

eFigure 3. Subgroup analyses for the primary endpoint.



Results showing the absolute differences in the primary endpoint (death, myocardial infarction, stroke, or coronary revascularization) in prespecified subgroups of patients who received the target-to-treat strategy or high-intensity statin therapy for statin intensity. The vertical blue line indicates the absolute difference of 3.0 percentage points prespecified as the non-inferiority margin. AMI indicates acute myocardial infarction; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.