

ONLINE SUPPLEMENT

Long-term effect of pravastatin on carotid intima-media complex thickness: the Japan Statin Treatment Against Recurrent Stroke (J-STARS) Echo Study

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SUPPLEMENTARY TABLE I: Trial Offices

The office of the J-STARS Echo Study: Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center

Kazuo Minematsu (chief investigator of the J-STARS Echo Study)

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SUPPLEMENTARY TABLE II: Inclusion and Exclusion Criteria

Inclusion criteria

1. Age between 45 and 80 years of either sex
2. Clinical diagnosis of noncardioembolic ischemic stroke developing within the preceding month to 3 years
3. Serum total cholesterol maintained between 4.65 and 6.21 mmol/L (180 and 240 mg/dL) without use of statins at enrollment
4. Written consent to participate in both the J-STARS Study and J-STARS Echo Study

Exclusion criteria

1. Ischemic stroke of determined rare etiology, (e.g., vertebral artery dissection, fibromuscular dysplasia, and Moyamoya disease) or associated with catheterization or surgery
2. Co-existing coronary artery disease that needs treatment with statins
3. Hemorrhagic diathesis
4. Coagulopathy
5. Hemorrhagic diseases (e.g., intracerebral hemorrhage, subarachnoid hemorrhage, and active peptic ulcer)
6. Thrombocytopenia (platelet count $\leq 100\ 000/\text{mm}^3$)
7. Hepatic dysfunction (aspartate transaminase or alanine transaminase ≥ 100 IU/L)
8. Renal dysfunction (serum creatinine ≥ 2.0 mg/dL)
9. Scheduled surgery
10. Patients for whom carotid ultrasound would be technically problematic because of cervical tumor, torticollis, or others
11. Patients who underwent carotid endarterectomy or cervical radiotherapy

#1 to 3 of the inclusion criteria and #1 to 9 of the exclusion criteria are specific to the J-STARS Study.

SUPPLEMENTARY TABLE III. Baseline Characteristics and Lipid Profiles

	Pravastatin group (n=388)	Control group (n=405)	p value
Women, n (%)	133 (34.3)	130 (32.1)	0.52
Age, years	66.4±8.2	66.4±8.4	0.96
Hypertension, n (%)	294 (75.8)	321 (79.3)	0.24
Diabetes mellitus, n (%)	89 (22.9)	107 (26.4)	0.26
History of coronary disease, n (%)	15 (3.9)	20 (4.9)	0.46
Current and past smoking habit, n (%)	201 (51.8)	218 (53.8)	0.52
Small infarct size* on MRI or CT	302 (77.8)	297 (73.3)	0.22
Body weight, kg	60.8±9.8	60.5±10.0	0.64
Body mass index, kg/m ²	23.8±2.9	23.7±3.0	0.49
Duration after stroke onset, months	9.6±10.0	9.8±10.0	0.88
Initial NIHSS score, median (range)	0 (0-19)	1 (0-17)	0.019
Stroke subtype			
Atherothrombotic infarction, n (%)	93 (24.0)	102 (25.2)	1.00
Lacunar infarction, n (%)	251 (64.7)	275 (67.9)	
Others, n (%)	44 (11.3)	28 (6.9)	
Laboratory data			
Total cholesterol, mmol/L	5.48±0.67	5.41±0.66	0.18
LDL cholesterol, mmol/L	3.39±0.66	3.37±0.63	0.74
Triglycerides, mmol/L	1.58±0.80	1.61±0.80	0.54
HDL cholesterol, mmol/L	1.39±0.42	1.35±0.38	0.17

NIHSS, National Institutes of Health Stroke Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; * <1.5 cm in diameter

Data are represented as mean ± standard deviation unless otherwise stated

SUPPLEMENTARY TABLE IV. Temporal trends of mean intima-media complex thickness change by allocated groups

Index	Group		Follow-up timing						
			Baseline	1 year	2 years	3 years	4 years	5 years	
Mean IMT	Pravastatin	N	388	336	305	268	251	255	
		Mean (SD)	0.8871 (0.1546)	0.9024 (0.1675)	0.9138 (0.1751)	0.9057 (0.1714)	0.9051 (0.1738)	0.9066 (0.1729)	
		Median (min, max)	0.8742 (0.535, 1.647)	0.8763 (0.551, 1.592)	0.8901 (0.600, 2.055)	0.8815 (0.574, 1.793)	0.8787 (0.635, 1.857)	0.8819 (0.612, 1.962)	
		Control	N	405	346	318	281	261	265
		Mean (SD)	0.8870 (0.1515)	0.8980 (0.1635)	0.9116 (0.1691)	0.8972 (0.1468)	0.9141 (0.1692)	0.9280 (0.1828)	
	Median (min, max)	0.8739 (0.605, 1.811)	0.8697 (0.598, 2.032)	0.8765 (0.642, 1.727)	0.8793 (0.621, 1.793)	0.8811 (0.644, 2.048)	0.8906 (0.642, 2.019)		
	Mean IMT change	Pravastatin	Mean (SD)	-	0.0112 (0.0848)	0.0231 (0.1143)	0.0168 (0.1137)	0.0181 (0.1176)	0.0207 (0.1163)
			Median (min, max)	-	0.0024 (-0.254, 0.563)	0.0176 (-0.477, 0.890)	0.0063 (-0.252, 0.631)	0.0094 (-0.360, 0.688)	0.0146 (-0.236, 0.797)
			Adjusted mean (SE)	-	0.01 (0.00)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)
			Control	Mean (SD)	-	0.0084 (0.0741)	0.0197 (0.0868)	0.0174 (0.0966)	0.0299 (0.1129)
Median (min, max)			-	0.0098 (-0.423, 0.257)	0.0185 (-0.250, 0.423)	0.0125 (-0.283, 0.587)	0.0185 (-0.400, 0.759)	0.0337 (-0.254, 0.834)	
Adjusted mean (SE)	-	0.01 (0.00)	0.02 (0.00)	0.02 (0.01)	0.03 (0.01)	0.04 (0.01)			
		p*	-	0.74	0.99	0.44	0.18	0.010	

*Wilcoxon rank-sum test

IMT, intima-media complex thickness

SUPPLEMENTARY TABLE V. Incidence of stroke and TIA by allocated groups

	Event rate, %/year		Adjusted hazard ratio	95% confidence interval
	Pravastatin	Control		
Total stroke and TIA	2.58	2.89	0.91	0.61 to 1.35
Total stroke	2.27	2.66	0.87	0.58 to 1.33
Ischemic stroke	2.09	2.33	0.92	0.59 to 1.42
Atherothrombotic infarction	0.27	0.71	0.41	0.15 to 1.15
Lacunar infarction	1.20	1.14	1.07	0.59 to 1.93

Hazard ratios are adjusted for the stratification factors at randomization in the main J-STARS trial: i.e., stroke subtype (atherothrombotic infarction vs. others), high blood pressure ($\geq 150/90$ mm Hg vs. not), and diabetes mellitus (absence vs. presence).

SUPPLEMENTARY TABLE VI. Comparisons of baseline characteristics and lipid profiles between patients in the intention-to-treatment analyses and the remaining patients in the main J-STARS trial

	Patients in the intention-to-treatment analyses (n=793)	The remaining patients in the main J-STARS trial (n=785)	p value
Women, n (%)	263 (33.2)	228 (29.0)	0.077
Age, years	66.4±8.3	66.0±8.6	0.32
Hypertension, n (%)	615 (77.6)	585 (74.5)	0.16
Diabetes mellitus, n (%)	196 (24.7)	173 (22.0)	0.21
History of coronary disease, n (%)	35 (4.4)	46 (5.9)	0.17
Current and past smoking habit, n (%)	429 (52.8)	427 (54.4)	0.31
Small infarct size* on MRI or CT	599 (75.5)	573 (73.0)	0.16
Body weight, kg	60.6±9.9	61.6±10.3	0.070
Body mass index, kg/m ²	23.7±3.0	23.7±3.2	0.95
Duration after stroke onset, months	9.7±10.0	9.6±10.2	0.78
Initial NIHSS score, median (range)	1 (0-19)	1 (0-17)	0.052
Stroke subtype			
Atherothrombotic infarction, n (%)	195 (24.6)	206 (26.2)	0.22
Lacunar infarction, n (%)	502 (63.3)	504 (64.2)	
Others, n (%)	96 (12.1)	75 (9.6)	
Laboratory data			
Total cholesterol, mmol/L	5.44±0.66	5.42±0.60	0.47
LDL cholesterol, mmol/L	3.38±0.64	3.32±0.62	0.055
Triglycerides, mmol/L	1.59±0.80	1.62±0.87	0.63
HDL cholesterol, mmol/L	1.37±0.40	1.39±0.41	0.23

NIHSS, National Institutes of Health Stroke Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; * <1.5 cm in diameter

Data are represented as mean ± standard deviation unless otherwise stated

SUPPLEMENTARY TABLE VII. Temporal trends of mean intima-media complex thickness change by allocated groups using only patients with carotid ultrasonography examination at 5 years

Index	Group		Follow-up timing					
			Baseline	1 year	2 years	3 years	4 years	5 years
Mean IMT	Pravastatin	N	255	240	235	221	227	255
		Mean (SD)	0.8859 (0.1602)	0.8990 (0.1731)	0.9104 (0.1825)	0.9016 (0.1744)	0.9035 (0.1782)	0.9066 (0.1729)
		Median (min, max)	0.8670 (0.570, 1.647)	0.8656 (0.551, 1.592)	0.8857 (0.600, 2.055)	0.8787 (0.574, 1.793)	0.8737 (0.635, 1.857)	0.8819 (0.612, 1.962)
	Control	N	265	238	238	224	230	265
		Mean (SD)	0.8878 (0.1460)	0.8948 (0.1562)	0.9061 (0.1663)	0.8945 (0.1552)	0.9146 (0.1735)	0.9280 (0.1828)
		Median (min, max)	0.8752 (0.605, 1.461)	0.8605 (0.644, 1.579)	0.8757 (0.642, 1.558)	0.8790 (0.621, 1.793)	0.8840 (0.644, 2.048)	0.8906 (0.642, 2.019)
Mean IMT change	Pravastatin	Mean (SD)	-	0.0107 (0.0877)	0.0217 (0.1204)	0.0156 (0.1158)	0.0194 (0.1206)	0.0207 (0.1163)
		Median (min, max)	-	0.0022 (-0.254, 0.563)	0.0108 (-0.477, 0.890)	0.0083 (-0.252, 0.631)	0.0101 (-0.360, 0.688)	0.0146 (-0.236, 0.797)
		Adjusted mean (SE)	-	0.01 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)
	Control	Mean (SD)	-	0.0067 (0.0770)	0.0177 (0.0921)	0.0120 (0.0979)	0.0298 (0.1167)	0.0403 (0.1182)
		Median (min, max)	-	0.0081 (-0.423, 0.243)	0.0174 (-0.250, 0.423)	0.0085 (-0.283, 0.587)	0.0188 (-0.400, 0.759)	0.0337 (-0.254, 0.834)
		Adjusted mean (SE)	-	0.01 (0.00)	0.02 (0.01)	0.02 (0.01)	0.03 (0.01)	0.04 (0.01)
		p*	-	0.80	0.98	0.87	0.29	0.010

*Wilcoxon rank-sum test

IMT, intima-media complex thickness

SUPPLEMENTARY TABLE VIII. Comparisons of baseline characteristics and lipid profiles between patients in the intention-to-treatment analyses and those without initial echographic data

	Patients in the intention-to-treatment analyses (n=793)	Patients without initial echographic data (n=71)	p value
Women, n (%)	263 (33.2)	15 (21.1)	0.038
Age, years	66.4±8.3	65.4±7.8	0.29
Hypertension, n (%)	615 (77.6)	52 (73.2)	0.41
Diabetes mellitus, n (%)	196 (24.7)	13 (18.3)	0.23
History of coronary disease, n (%)	35 (4.4)	9 (12.7)	<0.01
Current and past smoking habit, n (%)	419 (52.8)	39 (54.9)	0.42
Small infarct size* on MRI or CT	599 (75.5)	40 (56.3)	<0.01
Body weight, kg	60.6±9.9	63.7±9.6	0.017
Body mass index, kg/m ²	23.7±3.0	24.2±2.9	0.20
Duration after stroke onset, months	9.7±10.0	10.9±11.3	0.34
Initial NIHSS score, median (range)	1 (0-19)	0 (0-8)	0.42
Stroke subtype			
Atherothrombotic infarction, n (%)	195 (24.6)	29 (40.8)	<0.01
Lacunar infarction, n (%)	526 (66.3)	32 (45.1)	
Others, n (%)	72 (9.1)	10 (14.1)	
Laboratory data			
Total cholesterol, mmol/L	5.44±0.66	5.46±0.79	0.87
LDL cholesterol, mmol/L	3.38±0.64	3.29±0.66	0.29
Triglycerides, mmol/L	1.59±0.80	1.82±1.45	0.043
HDL cholesterol, mmol/L	1.37±0.40	1.33±0.32	0.42

NIHSS, National Institutes of Health Stroke Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; * <1.5 cm in diameter

Data are represented as mean ± standard deviation unless otherwise stated

SUPPLEMENTARY TABLE IX. Comparisons of baseline characteristics and lipid profiles between patients with and without follow-up at 5 years

	Patients with follow-up at 5 years (n=520)	Patients without follow-up at 5 years (n=344)	p value
Women, n (%)	171 (32.9)	107 (31.1)	0.58
Age, years	66.0±8.2	66.9±8.3	0.11
Hypertension, n (%)	401 (77.1)	266 (77.3)	0.94
Diabetes mellitus, n (%)	115 (22.1)	94 (27.3)	0.08
History of coronary disease, n (%)	22 (4.2)	22 (6.4)	0.15
Current and past smoking habit, n (%)	266 (51.2)	192 (55.8)	0.10
Small infarct size* on MRI or CT	398 (76.5)	241 (70.1)	0.090
Body weight, kg	61.1±9.6	60.6±10.3	0.49
Body mass index, kg/m ²	23.8±2.9	23.7±3.0	0.60
Duration after stroke onset, months	9.9±10.1	9.7±10.2	0.74
Initial NIHSS score, median (range)	1 (0-14)	0 (0-19)	0.72
Stroke subtype			
Atherothrombotic infarction, n (%)	128 (24.6)	96 (27.9)	0.12
Lacunar infarction, n (%)	352 (67.7)	206 (59.9)	
Others, n (%)	40 (7.7)	42 (12.2)	
Laboratory data			
Total cholesterol, mmol/L	5.46±0.63	5.42±0.73	0.41
LDL cholesterol, mmol/L	3.39±0.63	3.34±0.68	0.28
Triglycerides, mmol/L	1.60±0.82	1.64±0.94	0.51
HDL cholesterol, mmol/L	1.39±0.42	1.34±0.35	0.084

NIHSS, National Institutes of Health Stroke Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; * <1.5 cm in diameter

Data are represented as mean ± standard deviation unless otherwise stated

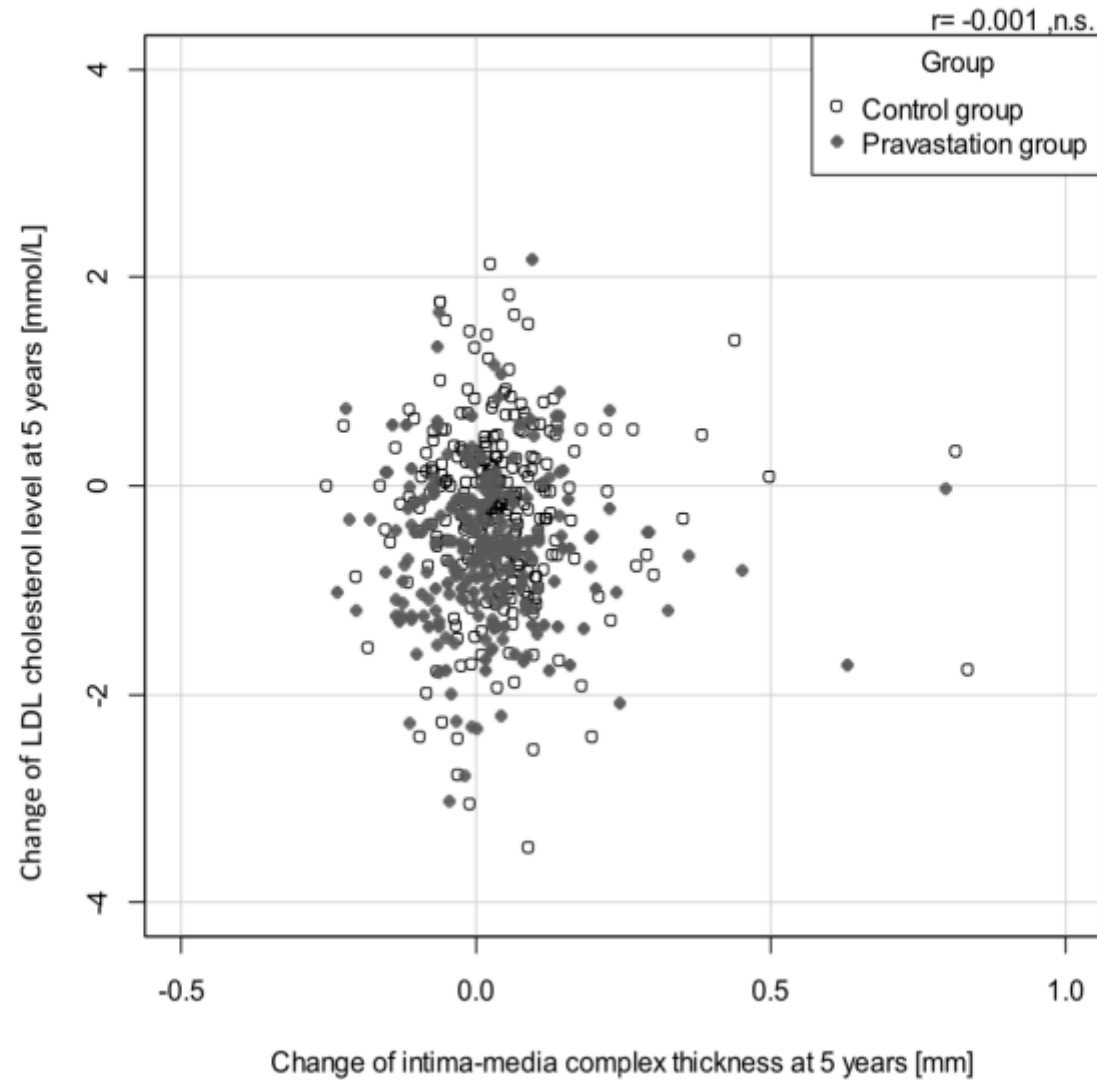
SUPPLEMENTARY FIGURE legends

SUPPLEMENTARY FIGURE I. The association between the change of intima-media complex thickness and the change of low-density lipoprotein (LDL) cholesterol level at 5 years in the pravastatin group (closed circle) and in the control group (open circle) is shown by a scattered plot.

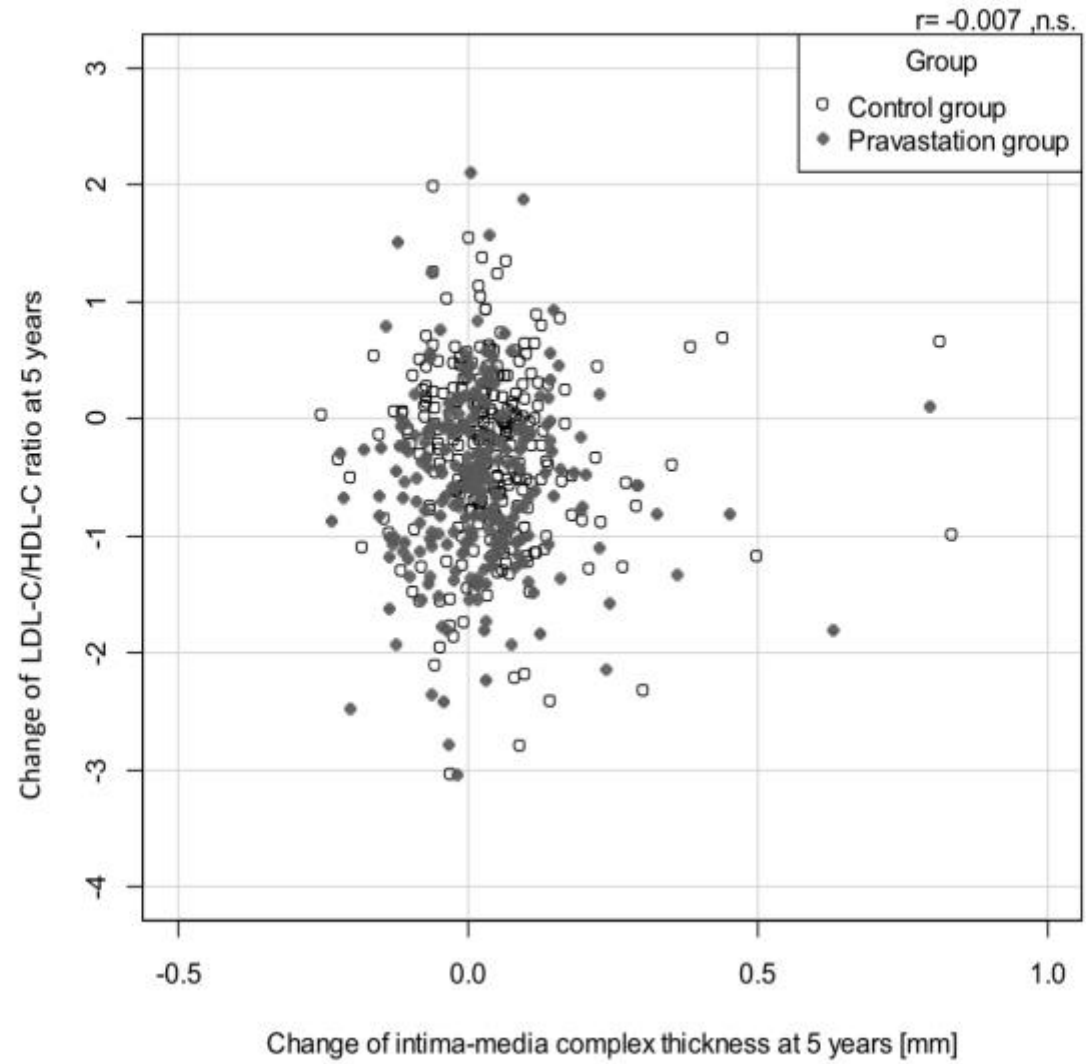
SUPPLEMENTARY FIGURE II. The association between the change of intima-media complex thickness and the change of low-density lipoprotein (LDL) cholesterol level to high density lipoprotein (HDL) cholesterol level at 5 years in the pravastatin group (closed circle) and in the control group (open circle) is shown by a scattered plot.

SUPPLEMENTARY FIGURES III. The association between the change of intima-media complex thickness and the change of log-transformed C-reactive protein level at 5 years in the pravastatin group (closed circle) and in the control group (open circle) is shown by a scattered plot.

SUPPLEMENTARY FIGURE I. A scattered plot showing the association between the change of intima-media complex thickness and the change of low density lipoprotein cholesterol level



SUPPLEMENTARY FIGURE II. A scattered plot showing the association between the change of intima-media complex thickness and the change of low density lipoprotein cholesterol level to high density lipoprotein cholesterol level ratio



SUPPLEMENTARY FIGURE III. A scattered plot showing the association between the change of intima-media complex thickness and the change of high-sensitivity C-reactive protein level

