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Early Statins after Intravenous or Endovascular Recanalization Is Beneficial Regardless of Timing, Intensity, and Stroke Mechanism

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Dear Sir:

In the modern era of ischemic stroke treatment, stroke physicians have highly effective tools to recanalize occluded major cerebral arteries. After hyperacute treatments, deleterious effects of reperfusion into the ischemic brain, including oxidative injuries, extravasation of intravascular blood, and recurrent infarctions should be managed appropriately. Statins may be a feasible and effective therapeutic option because of their pleiotropic effects, such as the stabilization of endothelial activation, augmentation of cerebral blood flow, and anti-oxidative and anti-inflammatory effects protecting against ischemic-reperfusion injuries.[1-3] Several studies have attempted to evaluate therapeutic potential of statins to address this issue, but the majority of such studies analyzed the effect of statin medication before stroke or statin withdrawal after stroke.[4] Considering the early development of oxidative and inflammatory injuries after recanalization treatment, it may be better to initiate statins earlier to obtain the best effects. Previously, we reported on the efficacy of early statin use after recanalization treatment.[5] In this current study, we aimed to update the analysis with recent data on recanalization treatment and to determine the subgroups that benefit from early statin initiation (≤72 hours).

A total of 857 acute ischemic stroke patients treated with intravenous or endovascular recanalization between July 2007 and December 2015 were identified from a prospective clinical registry from a single center. We retrospectively obtained data on the timing and dose of statins from an electronic barcode medication administration system. Favorable shifts on the modified Rankin Scale score at 3 months and symptomatic hemorrhagic transformation were analyzed, and clustering effects by treatment year were considered. Early statins were used in 67% (n=574) of the patients, with 33% (n=191) receiving them within 12 hours. High-intensity statins (atorvastatin 40–80 mg or rosuvastatin 20 mg) were used in 73% (n=418) of patients, and low-to-moderate intensity statins were used in 27% (n=156) of patients (Supplementary Tables 1 and 2). Adjusted multivariable analyses revealed that early statin initiation within 72 hours was associated with a favorable modified Rankin Scale score shift (adjusted odds ratio 1.52; 95% confidence interval 1.13–2.03) compared with no statin therapy (Figure 1). Early statins were also associated with decreased odds of having symptomatic hemorrhagic transformation (adjusted odds ratio 0.44; 95% confidence interval 0.24–0.83). Early statins showed no substantial exposure-response relationship with time of initiation or intensity. The beneficial effects of early statin initiation maintained in subgroup analyses regarding the mode of recanalization, stroke mechanism, and statin use before the index stroke. The clinical profiles in the exposure-response and subgroup analyses are provided in Supplementary Tables 3–7. The full models of multivariable logistic regression analyses are presented in Supplementary Table 8.

This study shows that early initiation of statins may confer improved functional recovery and decrease hemorrhagic transformation after recanalization treatment for acute ischemic stroke, regardless of treatment modalities, stroke mechanisms, and pre-stroke statin use. Several studies have reported the efficacy of early statin use after recanalization treatment, but
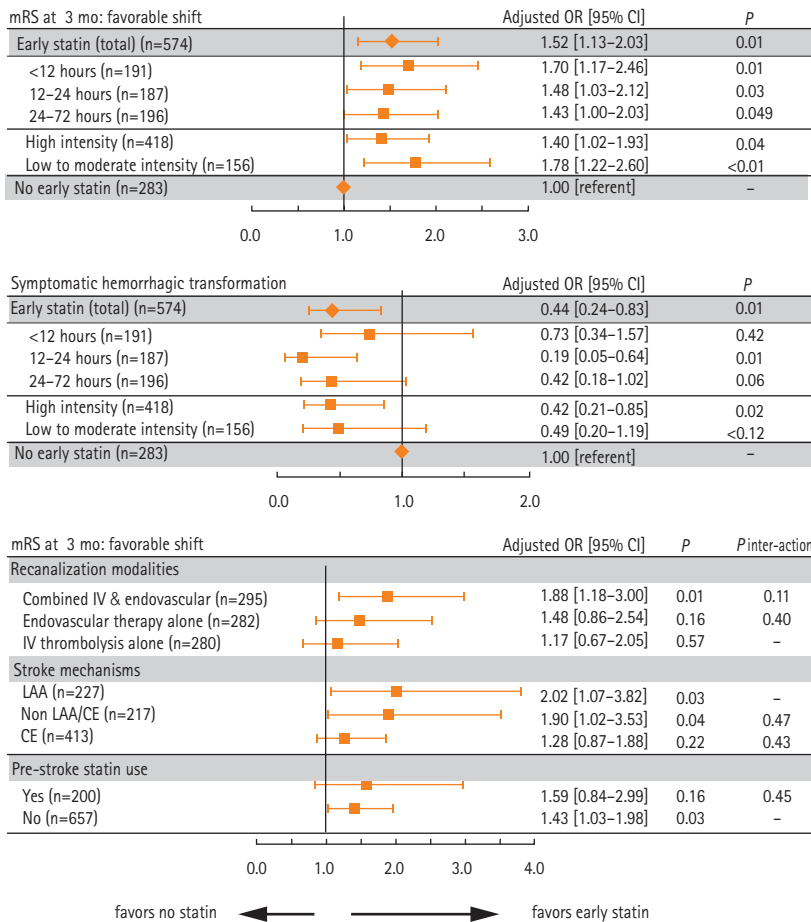
mRS at 3 mo: favorable shift	Adjusted OR [95% CI]	P
Early statin (total) (n=574)	1.52 [1.13–2.03]	0.01
<12 hours (n=191)	1.70 [1.17–2.46]	0.01
12–24 hours (n=187)	1.48 [1.03–2.12]	0.03
24–72 hours (n=196)	1.43 [1.00–2.03]	0.049
High intensity (n=418)	1.40 [1.02–1.93]	0.04
Low to moderate intensity (n=156)	1.78 [1.22–2.60]	<0.01
No early statin (n=283)	1.00 [referent]	–

Symptomatic hemorrhagic transformation	Adjusted OR [95% CI]	P
Early statin (total) (n=574)	0.44 [0.24–0.83]	0.01
<12 hours (n=191)	0.73 [0.34–1.57]	0.42
12–24 hours (n=187)	0.19 [0.05–0.64]	0.01
24–72 hours (n=196)	0.42 [0.18–1.02]	0.06
High intensity (n=418)	0.42 [0.21–0.85]	0.02
Low to moderate intensity (n=156)	0.49 [0.20–1.19]	<0.12
No early statin (n=283)	1.00 [referent]	–

mRS at 3 mo: favorable shift	Adjusted OR [95% CI]	P	P inter-action
Recanalization modalities			
Combined IV & endovascular (n=295)	1.88 [1.18–3.00]	0.01	0.11
Endovascular therapy alone (n=282)	1.48 [0.86–2.54]	0.16	0.40
IV thrombolysis alone (n=280)	1.17 [0.67–2.05]	0.57	–
Stroke mechanisms			
LAA (n=227)	2.02 [1.07–3.82]	0.03	–
Non LAA/CE (n=217)	1.90 [1.02–3.53]	0.04	0.47
CE (n=413)	1.28 [0.87–1.88]	0.22	0.43
Pre-stroke statin use			
Yes (n=200)	1.59 [0.84–2.99]	0.16	0.45
No (n=657)	1.43 [1.03–1.98]	0.03	–

favors no statin ← → favors early statin

Figure 1. The effects of early statins on functional outcome after recanalization treatment. All models (except symptomatic hemorrhagic transformation) are commonly adjusted with age, sex, premorbid mRS, NIHSS score at arrival, NIHSS score after recanalization treatment, recanalization modalities, stroke mechanism, hypertension, hyperlipidemia, atrial fibrillation, regular smoking, prestroke antithrombotics, prestroke stain, hemoglobin, HbA1c, triglycerides, low density lipoprotein-cholesterol. mRS at 3 mo, modified Rankin Scale at 3 months after stroke; OR, odds ratio; CI, confidence interval; IV, intravenous; LAA, large artery atherosclerosis; CE, cardioembolism NIHSS, National Institute of Health Stroke Scale.

they included only intravenous thrombolysis cases[6] or were mostly performed before stent-retrievers were used in a majority of patients.[5,7] In addition, the post-treatment National Institute of Health Stroke Scale score was incorporated into all models in our study as a covariate, which resulted in more accurate assessment of the effect of early statins following recanalization treatment.[8]

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2017.00836.

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Supplementary Table 1. Clinical characteristics of study patients by early statin use and the timing of statin administration

Variables	All patients (n=857)	No statins (n=283)	Early statins (n=574)	P
Demographic information				
Age	68.8±12.6	70.4±12.9	68.0±12.4	0.01
Male sex	494 (57.6)	144 (50.9)	350 (61.0)	<0.01
Premorbid mRS score=0	735 (85.8)	226 (79.9)	509 (88.7)	<0.01
Admission year, 2011–2015	592 (69.1)	158 (55.8)	434 (75.6)	<0.01
Stroke information				
NIHSS score at arrival	12 (7–19)	15 (9–20)	11 (6–18)	<0.01
Onset to treatment delay (hour)	2.8 (1.7–7.7)	2.8 (1.7–6.0)	2.9 (1.7–8.6)	0.13
Recanalization treatment				<0.01
Intravenous thrombolysis alone	280 (32.7)	71 (25.1)	209 (36.4)	
Endovascular therapy alone	282 (32.9)	88 (31.1)	194 (33.8)	
Combined	295 (34.4)	124 (43.8)	171 (29.8)	
NIHSS score after treatment	10 (4–17)	14 (6–20)	8 (4–15)	<0.01
Stroke mechanism				<0.01
Large artery atherosclerosis	227 (26.5)	44 (15.5)	183 (31.9)	
Small vessel occlusion	33 (3.9)	1 (0.4)	32 (5.6)	
Cardioembolism	413 (48.2)	172 (60.8)	241 (42.0)	
Other determined causes	41 (4.8)	19 (6.7)	22 (3.8)	
Undetermined cause	143 (16.7)	47 (16.6)	96 (16.7)	
Vascular risk factors				
Hypertension	579 (67.6)	174 (61.5)	405 (70.6)	0.01
Diabetes	232 (27.1)	70 (24.7)	162 (28.2)	0.28
Hyperlipidemia	226 (26.4)	45 (15.9)	181 (31.5)	<0.01
Atrial fibrillation	363 (42.4)	158 (55.8)	205 (35.7)	<0.01
Regular smoking	327 (38.2)	82 (29.0)	245 (42.7)	<0.01
Pre-stroke antithrombotics	378 (44.1)	153 (54.1)	225 (39.2)	<0.01
Pre-stroke statins	200 (23.3)	51 (18.0)	149 (26.0)	0.01
Laboratory information				
White cell count (μL)	8,375±3,209	8,276±3,474	8,423±3,072	0.54
Hemoglobin (g/dL)	13.6±2.0	13.4±2.0	13.7±2.0	0.02
Initial glucose (mg/dL)	137±51	137±49	137±51	0.98
HbA1c (%)	6.1±1.1	6.0±0.9	6.2±1.2	0.01
Total cholesterol (mg/dL)	168±42	160±34	172±44	<0.01
HDL cholesterol (mg/dL)	45±12	46±13	44±11	0.14
Triglycerides (mg/dL)	108±64	99±57	112±67	<0.01
LDL cholesterol (mg/dL)	102±36	95±29	105±39	<0.01
Systolic blood pressure (mmHg)	152±27	150±27	153±28	0.11
Diastolic blood pressure (mmHg)	82±18	81±16	82±18	0.19
Outcome information				
mRS score at 3 months				<0.01
0	177 (20.7)	45 (15.9)	132 (23.0)	
1	137 (16.0)	25 (8.8)	112 (19.5)	
2	120 (14.0)	36 (12.7)	84 (14.6)	
3	116 (13.5)	32 (11.3)	84 (14.6)	
4	91 (10.6)	39 (13.8)	52 (9.1)	
5	122 (14.2)	53 (18.7)	69 (12.0)	
6	94 (11.0)	53 (18.7)	41 (7.1)	
Symptomatic HT	52 (6.1)	30 (10.6)	22 (3.8)	<0.01

Values are presented as mean± standard deviation, median (interquartile range), or number (%). The admission year was divided into 2011–2015 and 2007–2010 because use of the stent-retriever started in 2011.

mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HT, hemorrhage transformation.

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Supplementary Table 2. Statin agent, dose, and time of early statin administration

	Early statins (n=574)	<12 hours (n=191)	12–24 hours (n=187)	24–72 hours (n=196)
Atorvastatin (mg)	541 (94.3)	187 (97.9)	179 (95.7)	175 (89.3)
80	313 (54.5)	139 (72.8)	100 (53.5)	74 (37.8)
40	102 (17.8)	25 (13.1)	42 (22.5)	35 (17.9)
20	32 (5.6)	7 (3.7)	12 (6.4)	13 (6.6)
10	94 (16.4)	16 (8.4)	25 (13.4)	53 (27.0)
Rosuvastatin (mg)	12 (2.1)	1 (0.5)	2 (1.1)	9 (4.6)
20	3 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
10	9 (1.6)	0 (0.0)	1 (0.5)	8 (4.1)
Simvastatin (mg)	10 (1.7)	2 (1.0)	4 (2.1)	4 (2.0)
20	7 (1.2)	2 (1.0)	3 (1.6)	2 (1.0)
10	3 (0.5)	0 (0.0)	1 (0.5)	2 (1.0)
Pitavastatin (mg)	6 (1.0)	1 (0.5)	1 (0.5)	4 (2.0)
2	6 (1.0)	1 (0.5)	1 (0.5)	4 (2.0)
Pravastatin (mg)	4 (0.7)	0 (0.0)	0 (0.0)	4 (2.0)
40	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)
10	3 (0.5)	0 (0.0)	0 (0.0)	3 (1.5)

Values are presented as number (%). High intensity statins were defined as a statin agent and dosage of atorvastatin of 40–80 mg or a dosage of rosuvastatin of 20 mg. Low to moderate intensity statins were defined as all other statin agents/doses.

Supplementary Table 3. Clinical characteristics of study patients by timing of early statin administration

Variables	Timing of early statin administration				P
	No statins (n=283)	<12 hours (n=191)	12–24 hours (n=187)	24–72 hours (n=196)	
Demographic information					
Age	70.4±12.9	68.4±11.9	67.6±13.0	68.0±12.5	0.06
Male sex	144 (50.9)	123 (64.4)	112 (59.9)	115 (58.7)	0.03
Premorbid mRS score=0	226 (79.9)	168 (88.0)	167 (89.3)	174 (88.8)	0.01
Admission year, 2011–2015	158 (55.8)	160 (83.8)	141 (75.4)	133 (67.9)	<0.01
Stroke information					
NIHSS score at arrival	15 (9–20)	11 (6–17)	11 (6–17)	11.5 (6–18)	<0.01
Onset to treatment delay (hour)	2.8 (1.7–6.0)	3.9 (1.8–11.5)	2.9 (1.6–6.9)	2.5 (1.7–5.9)	0.04
Recanalization treatment					<0.01
Intravenous thrombolysis alone	71 (25.1)	57 (29.8)	71 (38.0)	81 (41.3)	
Endovascular therapy alone	88 (31.1)	87 (45.5)	61 (32.6)	46 (23.5)	
Combined	124 (43.8)	47 (24.6)	55 (29.4)	69 (35.2)	
NIHSS score after treatment	14 (6–20)	8 (4–15)	8 (4–13)	8 (4–15)	<0.01
Stroke mechanism					<0.01
Large artery atherosclerosis	44 (15.5)	78 (40.8)	62 (33.2)	43 (21.9)	
Small vessel occlusion	1 (0.4)	14 (7.3)	8 (4.3)	10 (5.1)	
Cardioembolism	172 (60.8)	59 (30.9)	78 (41.7)	104 (53.1)	
Other determined causes	19 (6.7)	9 (4.7)	5 (2.7)	8 (4.1)	
Undetermined cause	47 (16.6)	31 (16.2)	34 (18.2)	31 (15.8)	
Vascular risk factors					
Hypertension	174 (61.5)	138 (72.3)	132 (70.6)	135 (68.9)	0.05
Diabetes	70 (24.7)	60 (31.4)	48 (25.7)	54 (27.6)	0.42
Hyperlipidemia	45 (15.9)	57 (29.8)	59 (31.6)	65 (33.2)	<0.01
Atrial fibrillation	158 (55.8)	48 (25.1)	66 (35.3)	91 (46.4)	<0.01
Regular smoking	82 (29.0)	91 (47.6)	76 (40.6)	78 (39.8)	<0.01
Pre-stroke antithrombotics	153 (54.1)	62 (32.5)	71 (38.0)	92 (46.9)	<0.01
Pre-stroke statins	51 (18.0)	42 (22.0)	47 (25.1)	60 (30.6)	0.01
Laboratory information					
White cell count (µL)	8,276±3,474	8,572±2,868	8,375±3,274	8,324±3,075	0.79
Hemoglobin (g/dL)	13.4±2.0	13.9±2.0	13.6±2.0	13.6±2.0	0.05
Initial glucose (mg/dL)	137±49	141±58	133±49	136±46	0.48
HbA1c (%)	6.0±0.9	6.2±1.2	6.2±1.1	6.3±1.1	0.07
Total cholesterol (mg/dL)	160±34	172±49	167±42	176±41	<0.01
HDL cholesterol (mg/dL)	46±13	43±11	44±11	46±11	0.04
Triglycerides (mg/dL)	99±57	116±68	111±72	109±60	0.03
LDL cholesterol (mg/dL)	95±29	106±41	101±36	108±38	<0.01
Systolic blood pressure (mmHg)	150±27	155±28	153±29	151±26	0.21
Diastolic blood pressure (mmHg)	81±16	84±18	83±20	81±18	0.22
Outcome information					
mRS score at 3 months					<0.01
0	45 (15.9)	47 (24.6)	42 (22.5)	43 (21.9)	
1	25 (8.8)	36 (18.8)	33 (17.6)	43 (21.9)	
2	36 (12.7)	27 (14.1)	34 (18.2)	23 (11.7)	
3	32 (11.3)	27 (14.1)	25 (13.4)	32 (16.3)	
4	39 (13.8)	15 (7.9)	18 (9.6)	19 (9.7)	
5	53 (18.7)	24 (12.6)	21 (11.2)	24 (12.2)	
6	53 (18.7)	15 (7.9)	14 (7.5)	12 (6.1)	
Symptomatic HT	30 (10.6)	12 (6.3)	3 (1.6)	7 (3.6)	<0.01

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HT, hemorrhage transformation.

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Supplementary Table 4. Clinical profiles by statin intensity

Variables	No statins (n=283)	Intensity of early statins		P
		Low to moderate (n=156)	High (n=418)	
Demographic information				
Age	70.4±12.9	68.7±12.3	67.8±12.5	0.02
Male sex	144 (50.9)	92 (59.0)	258 (61.7)	0.02
Premorbid mRS score=0	226 (79.9)	138 (88.5)	371 (88.8)	<0.01
Admission year, 2011–2015	158 (55.8)	99 (63.5)	335 (80.1)	<0.01
Stroke information				
NIHSS score at arrival	15 (9–20)	12 (6–18)	11 (6–17)	<0.01
Onset to treatment delay (hour)	2.8 (1.7–6.0)	2.8 (1.7–6.7)	3.0 (1.7–9.0)	0.32
Recanalization treatment				<0.01
Intravenous thrombolysis alone	71 (25.1)	67 (42.9)	142 (34.0)	
Endovascular therapy alone	88 (31.1)	46 (29.5)	148 (35.4)	
Combined	124 (43.8)	43 (27.6)	128 (30.6)	
NIHSS score after treatment	14 (6–20)	8 (4–15.25)	8 (4–14)	<0.01
Stroke mechanism				<0.01
Large artery atherosclerosis	44 (15.5)	38 (24.4)	145 (34.7)	
Small vessel occlusion	1 (0.4)	10 (6.4)	22 (5.3)	
Cardioembolism	172 (60.8)	87 (55.8)	154 (36.8)	
Other determined cause	19 (6.7)	4 (2.6)	18 (4.3)	
Undetermined cause	47 (16.6)	17 (10.9)	79 (18.9)	
Vascular risk factors				
Hypertension	174 (61.5)	107 (68.6)	298 (71.3)	0.02
Diabetes	70 (24.7)	40 (25.6)	122 (29.2)	0.39
Hyperlipidemia	45 (15.9)	58 (37.2)	123 (29.4)	<0.01
Atrial fibrillation	158 (55.8)	77 (49.4)	128 (30.6)	<0.01
Regular smoking	82 (29.0)	68 (43.6)	177 (42.3)	<0.01
Pre-stroke antithrombotics	153 (54.1)	82 (52.6)	143 (34.2)	<0.01
Pre-stroke statins	51 (18.0)	67 (42.9)	82 (19.6)	<0.01
Laboratory information				
White cell count (μL)	8,276±3,474	8,458±2,772	8,410±3,179	0.81
Hemoglobin (g/dL)	13.4±2.0	14.0±1.9	13.6±2.0	0.01
Initial glucose (mg/dL)	137±49	140±50	136±52	0.62
HbA1c (%)	6.0±0.9	6.3±1.2	6.2±1.2	0.02
Total cholesterol (mg/dL)	160±34	171±43	172±45	<0.01
HDL cholesterol (mg/dL)	46±13	45±11	44±11	0.14
Triglycerides (mg/dL)	99±57	114±73	111±64	0.02
LDL cholesterol (mg/dL)	95±29	103±39	106±38	<0.01
Systolic blood pressure (mmHg)	150±27	152±26	153±28	0.24
Diastolic blood pressure (mmHg)	81±16	80±19	83±18	0.06
Outcome information				
mRS score at 3 months				<0.01
0	45 (15.9)	38 (24.4)	94 (22.5)	
1	25 (8.8)	34 (21.8)	78 (18.7)	
2	36 (12.7)	24 (15.4)	60 (14.4)	
3	32 (11.3)	21 (13.5)	63 (15.1)	
4	39 (13.8)	14 (9.0)	38 (9.1)	
5	53 (18.7)	15 (9.6)	54 (12.9)	
6	53 (18.7)	10 (6.4)	31 (7.4)	
Symptomatic HT	30 (10.6)	7 (4.5)	15 (3.6)	<0.01

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HT, hemorrhage transformation.

Supplementary Table 5. Clinical profiles of subgroups divided by recanalization modalities

Variables	Combined IV-endovascular			Endovascular only			IV only		
	No statins (n=124)	Early statins (n=171)	P	No statins (n=88)	Early statins (n=194)	P	No statins (n=71)	Early statins (n=209)	P
Demographic information									
Age	70.6±12.6	68.8±12.4	0.22	69.5±11.9	69.0±11.5	0.71	71.2±14.4	66.4±13.1	0.02
Male sex	60 (48.4)	111 (64.9)	<0.01	49 (55.7)	114 (58.8)	0.63	35 (49.3)	125 (59.8)	0.12
Premorbid mRS score=0	106 (85.5)	149 (87.1)	0.68	65 (73.9)	169 (87.1)	0.01	55 (77.5)	191 (91.4)	<0.01
Admission year, 2011–2015	69 (55.6)	135 (78.9)	<0.01	51 (58.0)	157 (80.9)	<0.01	38 (53.5)	142 (67.9)	0.03
Stroke information									
NIHSS score at arrival	16 (12–20)	15 (10–20)	0.16	16 (10–21)	12 (6–18)	0.01	10 (5.5–17)	8 (5–12)	0.04
Onset to treatment delay (hour)	2.0 (1.4–2.9)	1.9 (1.3–2.9)	0.23	7.0 (4.6–11.6)	10.0 (6.2–14.7)	0.51	2.7 (1.8–3.2)	2.1 (1.5–3.2)	0.57
Recanalization treatment			–			–			–
Intravenous thrombolysis alone	0 (0)	0 (0)		0 (0)	0 (0)		71 (100)	209 (100)	
Endovascular therapy alone	0 (0)	0 (0)		88 (100)	194 (100)		0 (0)	0 (0)	
Combined	124 (100)	171 (100)		0 (0)	0 (0)		0 (0)	0 (0)	
NIHSS score after treatment	14 (6–20)	10 (5–16)	<0.01	17 (9–21)	10.5 (5–16)	<0.01	9 (4–17)	5 (4–11)	<0.01
Stroke mechanism			<0.01			0.01			<0.01
Large artery atherosclerosis	14 (11.3)	41 (24.0)		17 (19.3)	73 (37.6)		13 (18.3)	69 (33.0)	
Small vessel occlusion	0 (0)	0 (0)		0 (0)	0 (0)		1 (1.4)	32 (15.3)	
Cardioembolism	91 (73.4)	94 (55.0)		45 (51.1)	79 (40.7)		36 (50.7)	68 (32.5)	
Other determined cause	6 (4.8)	5 (2.9)		9 (10.2)	33 (17.0)		4 (5.6)	8 (3.8)	
Undetermined cause	13 (10.5)	31 (18.1)		17 (19.3)	33 (17.0)		17 (23.9)	32 (15.3)	
Vascular risk factors									
Hypertension	75 (60.5)	129 (75.4)	0.01	53 (60.2)	142 (73.2)	0.03	46 (64.8)	134 (64.1)	0.92
Diabetes	33 (26.6)	49 (28.7)	0.7	15 (17.0)	59 (30.4)	0.02	22 (31.0)	54 (25.8)	0.40
Hyperlipidemia	21 (16.9)	58 (33.9)	<0.01	13 (14.8)	58 (29.9)	0.01	11 (15.5)	65 (31.1)	0.01
Atrial fibrillation	82 (66.1)	85 (49.7)	<0.01	41 (46.6)	69 (35.6)	0.08	35 (49.3)	51 (24.4)	<0.01
Regular smoking	31 (25.0)	68 (39.8)	0.01	31 (35.2)	88 (45.4)	0.11	20 (28.2)	89 (42.6)	0.03
Pre-stroke antithrombotics	73 (58.9)	78 (45.6)	0.02	42 (47.7)	81 (41.8)	0.35	38 (53.5)	66 (31.6)	<0.01
Pre-stroke statins	22 (17.7)	51 (29.8)	0.02	15 (17.0)	44 (22.7)	0.28	14 (19.7)	54 (25.8)	0.30
Laboratory information									
White cell count (μL)	7,778±2,842	8,181±2,763	0.22	8,545±3,834	8,901±3,120	0.45	8,811±3,915	8,179±3,225	0.22
Hemoglobin (g/dL)	13.5±1.7	13.6±1.8	0.49	13.2±2.6	13.6±2.2	0.24	13.4±1.8	13.9±1.9	0.06
Initial glucose (mg/dL)	139±55	130±37	0.09	129±31	142±57	0.01	142±55	138±55	0.60
HbA1c (%)	6.1±0.9	6.1±0.8	0.76	5.8±0.6	6.1±1.3	<0.01	6.2±1.1	6.2±1.3	0.85
Total cholesterol (mg/dL)	163±37	165±45	0.74	154±34	169±44	<0.01	162±29	180±43	<0.01
HDL cholesterol (mg/dL)	46±14	44±11	0.12	44±12	44±12	0.68	46±12	45±11	0.53
Triglycerides (mg/dL)	94±63	108±62	0.07	103±54	109±62	0.42	103±48	118±74	0.06
LDL cholesterol (mg/dL)	98±28	99±40	0.78	90±29	104±37	<0.01	96±28	111±38	<0.01
Systolic blood pressure (mmHg)	148±28	148±25	0.92	147±27	151±26	0.26	156±26	159±29	0.39
Diastolic blood pressure (mmHg)	81±18	79±16	0.29	79±15	81±17	0.51	82±15	87±21	0.04
Outcome information									
mRS score at 3 months			<0.01			<0.01			0.18
0	20 (16.1)	44 (25.7)		8 (9.1)	31 (16.0)		17 (23.9)	57 (27.3)	
1	12 (9.7)	29 (17.0)		4 (4.5)	35 (18.0)		9 (12.7)	48 (23.0)	
2	14 (11.3)	27 (15.8)		12 (13.6)	30 (15.5)		10 (14.1)	27 (12.9)	
3	11 (8.9)	21 (12.3)		13 (14.8)	33 (17.0)		8 (11.3)	30 (14.4)	
4	18 (14.5)	11 (6.4)		15 (17.0)	23 (11.9)		6 (8.5)	18 (8.6)	
5	28 (22.6)	28 (16.4)		16 (18.2)	25 (12.9)		9 (12.7)	16 (7.7)	
6	21 (16.9)	11 (6.4)		20 (22.7)	17 (8.8)		12 (16.9)	13 (6.2)	
Symptomatic HT	14 (11.3)	5 (2.9)	<0.01	11 (12.5)	10 (5.2)	0.03	5 (7.0)	7 (3.3)	0.18

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HT, hemorrhage transformation.

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Supplementary Table 6. Clinical profiles of subgroups by stroke mechanism

Variables	LAA			CE			Non-LAA/CE		
	No statins (n=44)	Early statins (n=183)	P	No statins (n=172)	Early statins (n=241)	P	No statins (n=67)	Early statins (n=150)	P
Demographic information									
Age	67.6±11.4	66.8±11.7	0.67	73.0±11.8	71.2±10.5	0.10	65.7±14.8	64.4±14.7	0.56
Male sex	29 (65.9)	130 (71.0)	0.51	83 (48.3)	123 (51.0)	0.58	32 (47.8)	97 (64.7)	0.02
Premorbid mRS score=0	35 (79.5)	169 (92.3)	0.01	140 (81.4)	205 (85.1)	0.32	51 (76.1)	135 (90.0)	0.01
Admission year, 2011–2015	15 (34.1)	127 (69.4)	<0.01	107 (62.2)	188 (78.0)	<0.01	36 (53.7)	119 (79.3)	<0.01
Stroke information									
NIHSS score at arrival	11 (6.75–19.25)	10 (5–15)	0.05	16 (10.75–20)	15 (9–20)	0.13	14 (6–19)	9 (5–15)	<0.01
Onset to treatment delay (hour)	3.6 (2.4–11.3)	3.8 (1.9–11.2)	0.31	2.6 (1.7–5.3)	2.6 (1.7–8.1)	0.01	2.7 (1.7–5.5)	2.5 (1.4–5.5)	0.33
Recanalization treatment			0.37			0.02			0.10
Intravenous thrombolysis alone	13 (29.5)	69 (37.7)		36 (20.9)	68 (28.2)		22 (32.8)	72 (48.0)	
Endovascular therapy alone	17 (38.6)	73 (39.9)		45 (26.2)	79 (32.8)		26 (38.8)	42 (28.0)	
Combined	14 (31.8)	41 (22.4)		91 (52.9)	94 (39.0)		19 (28.4)	36 (24.0)	
NIHSS score after treatment	11 (6–19)	6 (4–13)	0.01	15 (6–21)	11 (5–17)	<0.01	14 (4.5–19.5)	6 (4–11)	<0.01
Stroke mechanism			–			–			<0.01
Large artery atherosclerosis	44 (100)	183 (100)		0 (0)	0 (0)		0 (0)	0 (0)	
Small vessel occlusion	0 (0)	0 (0)		0 (0)	0 (0)		1 (1.5)	32 (21.3)	
Cardioembolism	0 (0)	0 (0)		172 (100)	241 (100)		0 (0)	0 (0)	
Other determined cause	0 (0)	0 (0)		0 (0)	0 (0)		19 (28.4)	22 (14.7)	
Undetermined cause	0 (0)	0 (0)		0 (0)	0 (0)		47 (70.1)	96 (64.0)	
Vascular risk factors									
Hypertension	30 (68.2)	131 (71.6)	0.66	106 (61.6)	176 (73.0)	0.02	38 (56.7)	98 (65.3)	0.23
Diabetes	13 (29.5)	56 (30.6)	0.89	42 (24.4)	71 (29.5)	0.26	15 (22.4)	35 (23.3)	0.88
Hyperlipidemia	8 (18.2)	52 (28.4)	0.17	26 (15.1)	81 (33.6)	<0.01	11 (16.4)	48 (32.0)	0.02
Atrial fibrillation	1 (2.3)	0 (0)	0.04	147 (85.5)	194 (80.5)	0.19	10 (14.9)	11 (7.3)	0.08
Regular smoking	19 (43.2)	99 (54.1)	0.19	39 (22.7)	77 (32.0)	0.04	24 (35.8)	69 (46.0)	0.16
Pre-stroke antithrombotics	17 (38.6)	59 (32.2)	0.42	108 (62.8)	129 (53.5)	0.06	28 (41.8)	37 (24.7)	0.01
Pre-stroke statins	10 (22.7)	40 (21.9)	0.90	31 (18.0)	76 (31.5)	<0.01	10 (14.9)	33 (22.0)	0.23
Laboratory information									
White cell count (μL)	9,058±3,568	8,932±3,288	0.83	7,752±2,948	7,976±2,949	0.45	9,105±4,350	8,521±2,902	0.32
Hemoglobin (g/dL)	14.2±1.7	14.0±2.0	0.56	13.5±1.9	13.5±1.9	0.73	12.5±2.3	13.7±2.2	<0.01
Initial glucose (mg/dL)	145±51	146±62	0.85	134±44	132±45	0.64	140±59	134±45	0.47
HbA1c (%)	6.1±0.8	6.4±1.4	0.11	6.0±0.9	6.2±1.0	0.08	5.9±1.1	6.1±1.0	0.36
Total cholesterol (mg/dL)	180±35	172±43	0.17	155±31	168±44	<0.01	161±37	178±46	0.01
HDL cholesterol (mg/dL)	48±16	43±11	0.10	47±12	45±12	0.21	42±12	44±10	0.18
Triglycerides (mg/dL)	117±56	118±74	0.88	88±41	101±59	0.01	116±80	121±67	0.67
LDL cholesterol (mg/dL)	109±29	105±37	0.37	91±27	103±37	<0.01	96±29	110±42	0.01
Systolic blood pressure (mmHg)	148±27	156±28	0.11	151±27	151±24	0.79	147±26	153±31	0.10
Diastolic blood pressure (mmHg)	82±15	83±18	0.67	81±18	81±19	0.83	80±13	84±18	0.11
Outcome information									
mRS score at 3 months			0.03			0.06			<0.01
0	4 (9.1)	38 (20.8)		29 (16.9)	55 (22.8)		12 (17.9)	39 (26.0)	
1	4 (9.1)	43 (23.5)		17 (9.9)	35 (14.5)		4 (6.0)	34 (22.7)	
2	7 (15.9)	29 (15.8)		23 (13.4)	30 (12.4)		6 (9.0)	28 (18.7)	
3	7 (15.9)	29 (15.8)		17 (9.9)	34 (14.1)		8 (11.9)	21 (14.0)	
4	7 (15.9)	17 (9.3)		25 (14.5)	27 (11.2)		7 (10.4)	8 (5.3)	
5	9 (20.5)	20 (10.9)		32 (18.6)	40 (16.6)		12 (17.9)	9 (6.0)	
6	6 (13.6)	10 (5.5)		29 (16.9)	20 (8.3)		18 (26.9)	11 (7.3)	
Symptomatic HT	6 (13.6)	5 (2.7)	<0.01	18 (10.5)	12 (5.0)	0.03	6 (9.0)	5 (3.3)	0.08

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
LAA, large artery atherosclerosis; CE, cardioembolism; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HT, hemorrhage transformation.

Supplementary Table 7. Clinical profiles of subgroups by pre-stroke statin use

Variables	Pre-stroke statin use: yes			Pre-stroke statin use: no		
	No statins (n=51)	Early statins (n=149)	P	No statins (n=232)	Early statins (n=425)	P
Demographic information						
Age	73.1±9.3	70.9±10.4	0.15	69.9±13.5	67.0±12.9	0.01
Male sex	25 (49.0)	86 (57.7)	0.28	119 (51.3)	264 (62.1)	0.01
Premorbid mRS score=0	41 (80.4)	122 (81.9)	0.81	185 (79.7)	387 (91.1)	<0.01
Admission year, 2011–2015	32 (62.7)	117 (78.5)	0.03	126 (54.3)	317 (74.6)	<0.01
Stroke information						
NIHSS score at arrival	15 (8–19)	12 (6–18)	0.21	15 (9–20)	11 (6–17)	<0.01
Onset to treatment delay (hour)	3.2 (1.8–6.4)	2.8 (1.6–7.9)	0.92	2.7 (1.7–5.8)	2.9 (1.7–8.8)	0.06
Recanalization treatment			0.43			<0.01
Intravenous thrombolysis alone	14 (27.5)	54 (36.2)		57 (24.6)	155 (36.5)	
Endovascular therapy alone	15 (29.4)	44 (29.5)		73 (31.5)	150 (35.3)	
Combined	22 (43.1)	51 (34.2)		102 (44.0)	120 (28.2)	
NIHSS score after treatment	15 (6.5–18.5)	9 (4–16)	0.01	14 (5.75–20)	8 (4–14)	<0.01
Stroke mechanism			0.45			<0.01
Large artery atherosclerosis	10 (19.6)	40 (26.8)		34 (14.7)	143 (33.6)	
Small vessel occlusion	0 (0)	6 (4.0)		1 (0.4)	26 (6.1)	
Cardioembolism	31 (60.8)	76 (51.0)		141 (60.8)	165 (38.8)	
Other determined cause	2 (3.9)	4 (2.7)		17 (7.3)	18 (4.2)	
Undetermined cause	8 (15.7)	23 (15.4)		39 (16.8)	73 (17.2)	
Vascular risk factors						
Hypertension	43 (84.3)	125 (83.9)	0.94	131 (56.5)	280 (65.9)	0.02
Diabetes	15 (29.4)	66 (44.3)	0.06	55 (23.7)	96 (22.6)	0.75
Hyperlipidemia	34 (66.7)	131 (87.9)	<0.01	11 (4.7)	50 (11.8)	<0.01
Atrial fibrillation	25 (49.0)	66 (44.3)	0.56	133 (57.3)	139 (32.7)	<0.01
Regular smoking	12 (23.5)	56 (37.6)	0.07	70 (30.2)	189 (44.5)	<0.01
Pre-stroke antithrombotics	40 (78.4)	108 (72.5)	0.40	113 (48.7)	117 (27.5)	<0.01
Pre-stroke statins	51 (100)	149 (100)	–	0 (0)	0 (0)	–
Laboratory information						
White cell count (μL)	8,038±2,564	8,004±2,940	0.94	8,328±3,646	8,570±3,107	0.39
Hemoglobin (g/dL)	13.3±2.1	13.4±1.8	0.83	13.4±2.0	13.8±2.1	0.01
Initial glucose (mg/dL)	141±55	141±51	0.96	136±48	135±52	0.89
HbA1c (%)	6.2±1.3	6.5±1.2	0.28	6.0±0.8	6.1±1.1	0.03
Total cholesterol (mg/dL)	157±32	152±41	0.40	161±35	179±43	<0.01
HDL cholesterol (mg/dL)	46±12	44±10	0.26	45±13	44±11	0.28
Triglycerides (mg/dL)	101±54	104±53	0.71	99±57	115±70	<0.01
LDL cholesterol (mg/dL)	90±29	87±37	0.51	96±28	111±37	<0.01
Systolic blood pressure (mmHg)	157±24	152±27	0.22	148±28	153±28	0.02
Diastolic blood pressure (mmHg)	81±14	80±16	0.94	81±17	83±19	0.11
Outcome information						
mRS score at 3 months			<0.01			<0.01
0	6 (11.8)	45 (30.2)		39 (16.8)	87 (20.5)	
1	3 (5.9)	23 (15.4)		22 (9.5)	89 (20.9)	
2	7 (13.7)	19 (12.8)		29 (12.5)	65 (15.3)	
3	5 (9.8)	17 (11.4)		27 (11.6)	67 (15.8)	
4	13 (25.5)	12 (8.1)		26 (11.2)	40 (9.4)	
5	9 (17.6)	19 (12.8)		44 (19.0)	50 (11.8)	
6	8 (15.7)	14 (9.4)		45 (19.4)	27 (6.4)	
Symptomatic HT	9 (17.6)	4 (2.7)	<0.01	21 (9.1)	18 (4.2)	0.01

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HT, hemorrhage transformation.

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Supplementary Table 8. Full models of multivariable analyses

Variables	Adjusted OR (95% CI)	P
All patients: mRS shift at 3 months*		
Early statins	1.52 (1.13–2.03)	0.01
Age (per 1-year increase)	0.96 (0.95–0.97)	<0.01
Male sex	0.77 (0.56–1.05)	0.10
Premorbid mRS score = 0	1.68 (1.15–2.46)	0.01
NIHSS score at arrival (per 1-point increase)	1.03 (1.00–1.06)	0.03
Onset to treatment delay (per 1-hour increase)	1.00 (0.99–1.01)	0.82
Recanalization treatment		
Intravenous thrombolysis alone	Referent	-
Endovascular therapy alone	0.86 (0.62–1.21)	0.40
Combined	1.02 (0.74–1.42)	0.89
NIHSS score after treatment (per 1-point increase)	0.82 (0.79–0.84)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	-
Small vessel occlusion	0.91 (0.46–1.80)	0.78
Cardioembolism	1.52 (0.97–2.39)	0.07
Other determined cause	0.33 (0.17–0.65)	<0.01
Undetermined cause	1.01 (0.68–1.49)	0.97
Hypertension	1.26 (0.95–1.68)	0.11
Hyperlipidemia	0.98 (0.67–1.45)	0.93
Atrial fibrillation	0.87 (0.57–1.32)	0.51
Regular smoking	1.41 (1.03.192)	0.03
Pre-stroke antithrombotics	0.90 (0.67–1.20)	0.47
Pre-stroke statins	1.16 (0.76–1.76)	0.49
Hemoglobin (per 1 g/dL increase)	1.06 (0.98–1.14)	0.14
HbA1c (per 1% increase)	0.87 (0.77–0.97)	0.02
Triglycerides (per 1 mg/dL increase)	1.001 (0.999–1.003)	0.54
LDL cholesterol (per 1 mg/dL increase)	0.995 (0.991–0.998)	0.01
All patients: mRS 0–1 at 3 months†		
Early statins	1.66 (1.09–2.52)	0.02
Age	0.64 (0.52–0.80)	<0.01
Male sex	0.75 (0.47–1.19)	0.22
Premorbid mRS score=0	1.88 (1.01–3.49)	0.047
NIHSS score at arrival (per 1-point increase)	1.02 (0.98–1.06)	0.35
Onset to treatment delay (per 1-hour increase)	0.988 (0.971–1.005)	0.16
Recanalization treatment		
Intravenous thrombolysis alone	Referent	
Endovascular therapy alone	0.64 (0.40–1.02)	0.06
Combined	0.87 (0.55–1.38)	0.56
NIHSS score after treatment (per 1-point increase)	0.82 (0.78–0.85)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	
Small vessel occlusion	0.62 (0.26–1.50)	0.29
Cardioembolism	1.54 (0.82–2.92)	0.18
Other determined cause	0.78 (0.31–1.96)	0.60
Undetermined cause	1.01 (0.59–1.72)	0.98
Hypertension	1.10 (0.73–1.64)	0.65
Hyperlipidemia	1.50 (0.85–2.65)	0.16
Atrial fibrillation	1.01 (0.56–1.84)	0.96
Regular smoking	1.98 (1.27–3.08)	<0.01

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Pre-stroke antithrombotics	0.84 (0.55–1.27)	0.40
Pre-stroke statins	0.96 (0.51–1.78)	0.89
Hemoglobin (per 1 g/dL increase)	1.03 (0.93–1.14)	0.54
HbA1c (per 1% increase)	0.86 (0.72–1.02)	0.08
Triglycerides	1.02 (0.85–1.21)	0.87
LDL cholesterol	0.77 (0.64–0.92)	<0.01
All patients: symptomatic HT		
Early statins	0.44 (0.24–0.83)	0.01
Age (per 1-year increase)	1.00 (0.98–1.03)	0.89
Male sex	1.27 (0.69–2.35)	0.44
Premorbid mRS score=0	1.13 (0.51–2.52)	0.76
NIHSS score at arrival (per 1-point increase)	0.93 (0.89–0.99)	0.01
Onset to treatment delay (per 1-hour increase)	1.00 (0.98–1.03)	0.87
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	1.27 (0.56–2.90)	0.57
Combined	1.17 (0.53–2.61)	0.69
NIHSS score after treatment (per 1-point increase)	1.13 (1.07–1.18)	<0.01
Exposure (time of statin administration)-response analysis: mRS shift at 3 months[‡]		
Statin time: <12 hours	1.70 (1.17–2.46)	0.01
Statin time: 12–24 hours	1.48 (1.03–2.12)	0.03
Statin time: 24–72 hours	1.43 (1.001–2.03)	0.049
Age (per 1-year increase)	0.96 (0.95–0.97)	<0.01
Male sex	0.77 (0.56–1.05)	0.10
Premorbid mRS score=0	1.69 (1.16–2.47)	0.01
NIHSS score at arrival (per 1-point increase)	1.03 (1.002–1.06)	0.03
Onset to treatment delay (per 1-hour increase)	1.00 (0.99–1.01)	0.81
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	0.84 (0.60–1.18)	0.32
Combined	1.01 (0.73–1.41)	0.95
NIHSS score after treatment (per 1-point increase)	0.82 (0.80–0.84)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	
Small vessel occlusion	0.89 (0.45–1.76)	0.73
Cardioembolism	1.53 (0.98–2.41)	0.06
Other determined cause	0.33 (0.17–0.66)	<0.01
Undetermined cause	1.01 (0.68–1.49)	0.96
Hypertension	1.26 (0.95–1.67)	0.12
Hyperlipidemia	0.98 (0.66–1.44)	0.91
Atrial fibrillation	0.88 (0.58–1.34)	0.55
Regular smoking	1.41 (1.03–1.92)	0.03
Pre-stroke antithrombotics	0.91 (0.68–1.21)	0.51
Pre-stroke statins	1.17 (0.77–1.78)	0.47
Hemoglobin (per 1 g/dL increase)	1.06 (0.98–1.14)	0.16
HbA1c (per 1% increase)	0.87 (0.77–0.97)	0.02
Triglycerides (per 1 mg/dL increase)	1.001 (0.999–1.003)	0.53
LDL cholesterol (per 1 mg/dL increase)	0.995 (0.991–0.998)	0.01

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Exposure (time of statin administration)-response analysis: mRS 0–1 at 3 months[†]		
Statin time: <12 hours	1.91 (1.13–3.24)	0.02
Statin time: 12–24 hours	1.39 (0.84–2.32)	0.20
Statin time: 24–72 hours	1.74 (1.06–2.86)	0.03
Age	0.64 (0.51–0.79)	<0.01
Male sex	0.74 (0.47–1.18)	0.21
Premorbid mRS score=0	1.88 (1.01–3.50)	0.045
NIHSS score at arrival (per 1-point increase)	1.02 (0.98–1.06)	0.38
Onset to treatment delay (per 1-hour increase)	0.99 (0.97–1.01)	0.17
Recanalization treatment		
Intravenous thrombolysis alone	Referent	
Endovascular therapy alone	0.62 (0.39–1.01)	0.053
Combined	0.86 (0.55–1.36)	0.52
NIHSS score after treatment (per 1-point increase)	0.82 (0.78–0.85)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	
Small vessel occlusion	0.59 (0.24–1.44)	0.25
Cardioembolism	1.53 (0.81–2.90)	0.19
Other determined cause	0.75 (0.30–1.89)	0.55
Undetermined cause	1.00 (0.59–1.72)	0.99
Hypertension	1.10 (0.73–1.64)	0.65
Hyperlipidemia	1.51 (0.85–2.65)	0.16
Atrial fibrillation	1.02 (0.56–1.86)	0.94
Regular smoking	1.97 (1.26–3.06)	<0.01
Pre-stroke antithrombotics	0.84 (0.55–1.27)	0.40
Pre-stroke statins	0.95 (0.51–1.79)	0.89
Hemoglobin (per 1 g/dL increase)	1.03 (0.93–1.14)	0.55
HbA1c (per 1% increase)	0.86 (0.72–1.02)	0.08
Triglycerides	1.01 (0.85–1.21)	0.88
LDL cholesterol	0.76 (0.63–0.91)	<0.01
Exposure (time of statin administration)-response analysis: symptomatic HT		
Statin time: <12 hours	0.73 (0.34–1.57)	0.42
Statin time: 12–24 hours	0.19 (0.05–0.64)	0.01
Statin time: 24–72 hours	0.42 (0.18–1.02)	0.06
Age (per 1-year increase)	1.00 (0.98–1.03)	0.93
Male sex	1.26 (0.68–2.33)	0.47
Premorbid mRS score=0	1.13 (0.50–2.52)	0.77
NIHSS score at arrival (per 1-point increase)	0.94 (0.89–0.99)	0.02
Onset to treatment delay (per 1-hour increase)	1.00 (0.98–1.03)	0.84
Recanalization treatment		
Intravenous thrombolysis alone	Referent	
Endovascular therapy alone	1.16 (0.51–2.68)	0.72
Combined	1.17 (0.53–2.61)	0.70
NIHSS score after treatment (per 1-point increase)	1.12 (1.07–1.18)	<0.01
Exposure (statin intensity)-response analysis: mRS shift at 3 months[§]		
Statins: low to moderate intensity	1.78 (1.22–2.60)	<0.01
Statins: high intensity	1.40 (1.02–1.93)	0.04
Age (per 1-year increase)	0.96 (0.95–0.97)	<0.01

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Male sex	0.77 (0.56–1.06)	0.11
Premorbid mRS score=0	1.69 (1.15–2.46)	0.01
NIHSS score at arrival (per 1-point increase)	1.03 (1.003–1.06)	0.03
Onset to treatment delay (per 1-hour increase)	1.00 (0.99–1.01)	0.79
Recanalization treatment		
Intravenous thrombolysis alone	Referent	
Endovascular therapy alone	0.88 (0.63–1.23)	0.45
Combined	1.04 (0.75–1.45)	0.81
NIHSS score after treatment (per 1-point increase)	0.82 (0.79–0.84)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	
Small vessel occlusion	0.91 (0.46–1.80)	0.78
Cardioembolism	1.50 (0.96–2.36)	0.08
Other determined cause	0.32 (0.16–0.64)	<0.01
Undetermined cause	1.01 (0.68–1.48)	0.98
Hypertension	1.28 (0.96–1.70)	0.09
Hyperlipidemia	1.01 (0.68–1.50)	0.96
Atrial fibrillation	0.85 (0.56–1.29)	0.45
Regular smoking	1.39 (1.02–1.91)	0.04
Pre-stroke antithrombotics	0.90 (0.67–1.19)	0.45
Pre-stroke statins	1.09 (0.71–1.67)	0.71
Hemoglobin (per 1 g/dL increase)	1.06 (0.98–1.14)	0.15
HbA1c (per 1% increase)	0.87 (0.77–0.97)	0.02
Triglycerides (per 1 mg/dL increase)	1.001 (0.999–1.002)	0.60
LDL cholesterol (per 1 mg/dL increase)	0.995 (0.991–0.998)	0.01
Exposure (statin intensity)-response analysis: mRS 0–1 at 3 months[†]		
Statins: low to moderate intensity	2.04 (1.20–3.47)	0.01
Statins: high intensity	1.51 (0.97–2.35)	0.07
Age	0.64 (0.51–0.79)	<0.01
Male sex	0.76 (0.48–1.21)	0.25
Premorbid mRS score=0	1.90 (1.02–3.54)	0.04
NIHSS score at arrival (per 1-point increase)	1.02 (0.98–1.06)	0.37
Onset to treatment delay (per 1-hour increase)	0.99 (0.97–1.005)	0.16
Recanalization treatment		
Intravenous thrombolysis alone	Referent	
Endovascular therapy alone	0.65 (0.41–1.04)	0.07
Combined	0.89 (0.57–1.41)	0.62
NIHSS score after treatment (per 1-point increase)	0.82 (0.78–0.85)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	
Small vessel occlusion	0.61 (0.25–1.48)	0.28
Cardioembolism	1.51 (0.80–2.86)	0.21
Other determined cause	0.76 (0.30–1.91)	0.56
Undetermined cause	1.01 (0.59–1.72)	0.97
Hypertension	1.12 (0.75–1.68)	0.58
Hyperlipidemia	1.56 (0.89–2.76)	0.12
Atrial fibrillation	0.99 (0.54–1.79)	0.97
Regular smoking	1.96 (1.26–3.05)	<0.01
Pre-stroke antithrombotics	0.83 (0.55–1.25)	0.37

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Pre-stroke statins	0.88 (0.46–1.66)	0.69
Hemoglobin (per 1 g/dL increase)	1.03 (0.93–1.14)	0.62
HbA1c (per 1% increase)	0.86 (0.72–1.02)	0.08
Triglycerides	1.01 (0.85–1.20)	0.92
LDL cholesterol	0.76 (0.64–0.92)	<0.01
Exposure (statin intensity)-response analysis: symptomatic HT		
Statins: low to moderate intensity	0.49 (0.20–1.19)	0.12
Statins: high intensity	0.42 (0.21–0.85)	0.02
Age (per 1-year increase)	1.00 (0.98–1.03)	0.90
Male sex	1.27 (0.69–2.34)	0.44
Premorbid mRS score=0	1.13 (0.51–2.52)	0.77
NIHSS score at arrival (per 1-point increase)	0.93 (0.89–0.99)	0.01
Onset to treatment delay (per 1-hour increase)	1.00 (0.98–1.03)	0.87
Recanalization treatment		
Intravenous thrombolysis alone	Referent	
Endovascular therapy alone	1.28 (0.56–2.93)	0.56
Combined	1.18 (0.53–2.63)	0.68
NIHSS score after treatment (per 1-point increase)	1.13 (1.07–1.18)	<0.01
Subgroup (combined IV-endovascular treatment): mRS shift at 3 months[‖]		
Early statins	1.88 (1.18–3.00)	0.01
Age (per 1-year increase)	0.96 (0.94–0.98)	<0.01
Male sex	0.41 (0.24–0.72)	<0.01
Premorbid mRS score=0	1.05 (0.55–2.04)	0.88
NIHSS score at arrival (per 1-point increase)	1.06 (1.01–1.11)	0.01
Onset to treatment delay (per 1-hour increase)	1.02 (0.98–1.06)	0.42
NIHSS score after treatment (per 1-point increase)	0.80 (0.77–0.84)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	–
Cardioembolism	3.27 (1.34–8.01)	0.01
Other determined cause	0.45 (0.12–1.67)	0.23
Undetermined cause	1.89 (0.88–4.05)	0.10
Hypertension	1.40 (0.82–2.39)	0.22
Hyperlipidemia	0.83 (0.41–1.68)	0.61
Atrial fibrillation	0.79 (0.37–1.69)	0.54
Regular smoking	2.00 (1.15–3.45)	0.01
Pre-stroke antithrombotics	0.77 (0.47–1.27)	0.30
Pre-stroke statins	1.25 (0.59–2.63)	0.56
Hemoglobin (per 1 g/dL increase)	1.19 (1.02–1.39)	0.03
HbA1c (per 1% increase)	0.85 (0.66–1.10)	0.22
Triglycerides (per 1 mg/dL increase)	1.003 (0.999–1.007)	0.12
LDL cholesterol (per 1 mg/dL increase)	0.995 (0.988–1.001)	0.12
Subgroup (combined IV-endovascular treatment): mRS 0–1 at 3 months[†]		
Early statins	2.28 (1.05–4.94)	0.04
Age	0.72 (0.47–1.09)	0.12
Male sex	0.18 (0.07–0.47)	<0.01
Premorbid mRS score=0	1.19 (0.39–3.63)	0.76
NIHSS score at arrival (per 1-point increase)	1.03 (0.97–1.09)	0.40
Onset to treatment delay (per 1-hour increase)	1.04 (0.97–1.11)	0.24
NIHSS score after treatment (per 1-point increase)	0.77 (0.72–0.83)	<0.01

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Stroke mechanism		
Large artery atherosclerosis	Referent	–
Cardioembolism	7.02 (1.49–32.95)	0.01
Other determined cause	3.02 (0.52–17.46)	0.22
Undetermined cause	3.94 (1.19–13.04)	0.02
Hypertension	0.82 (0.35–1.91)	0.64
Hyperlipidemia	2.52 (0.69–9.24)	0.16
Atrial fibrillation	1.00 (0.28–3.58)	0.995
Regular smoking	3.75 (1.61–8.78)	<0.01
Pre-stroke antithrombotics	0.59 (0.26–1.37)	0.22
Pre-stroke statins	0.60 (0.14–2.50)	0.48
Hemoglobin (per 1 g/dL increase)	1.35 (1.05–1.74)	0.02
HbA1c (per 1% increase)	0.91 (0.61–1.36)	0.65
Triglycerides	1.61 (1.04–2.51)	0.03
LDL cholesterol	0.63 (0.44–0.90)	0.01
Subgroup (combined IV-endovascular treatment): symptomatic HT		
Early statins	0.29 (0.09–0.87)	0.03
Age (per 1-year increase)	1.01 (0.96–1.06)	0.68
Male sex	1.70 (0.58–4.98)	0.33
Premorbid mRS score=0	1.56 (0.31–7.79)	0.59
NIHSS score at arrival (per 1-point increase)	0.96 (0.87–1.05)	0.39
Onset to treatment delay (per 1-hour increase)	1.03 (0.98–1.09)	0.27
NIHSS score after treatment (per 1-point increase)	1.12 (1.04–1.21)	<0.01
Subgroup (endovascular only): mRS shift at 3 months¶		
Early statins	1.48 (0.86–2.54)	0.16
Age (per 1-year increase)	0.96 (0.94–0.99)	<0.01
Male sex	0.83 (0.47–1.47)	0.52
Premorbid mRS score=0	2.62 (1.41–4.90)	<0.01
NIHSS score at arrival (per 1-point increase)	1.02 (0.98–1.07)	0.31
Onset to treatment delay (per 1-hour increase)	1.01 (0.99–1.02)	0.45
NIHSS score after treatment (per 1-point increase)	0.82 (0.78–0.86)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	–
Cardioembolism	0.92 (0.41–2.07)	0.84
Other determined cause	0.21 (0.06–0.73)	0.01
Undetermined cause	0.69 (0.35–1.36)	0.28
Hypertension	1.03 (0.62–1.72)	0.90
Hyperlipidemia	1.46 (0.75–2.85)	0.27
Atrial fibrillation	0.76 (0.35–1.66)	0.49
Regular smoking	1.03 (0.58–1.82)	0.91
Pre-stroke antithrombotics	1.02 (0.60–1.71)	0.95
Pre-stroke statins	1.07 (0.51–2.24)	0.87
Hemoglobin (per 1 g/dL increase)	1.11 (0.98–1.26)	0.10
HbA1c (per 1% increase)	0.82 (0.66–1.02)	0.08
Triglycerides (per 1 mg/dL increase)	1.001 (0.997–1.004)	0.77
LDL cholesterol (per 1 mg/dL increase)	0.996 (0.989–1.003)	0.25
Subgroup (endovascular only): mRS 0–1 at 3 months‡		
Early statins	1.92 (0.80–4.59)	0.14
Age	0.63 (0.41–0.95)	0.03

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Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Male sex	0.85 (0.33–2.17)	0.73
Premorbid mRS score=0	3.14 (0.84–11.74)	0.09
NIHSS score at arrival (per 1-point increase)	0.99 (0.92–1.06)	0.71
Onset to treatment delay (per 1-hour increase)	0.98 (0.96–1.01)	0.19
NIHSS score after treatment (per 1-point increase)	0.84 (0.77–0.90)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	-
Cardioembolism	0.83 (0.24–2.89)	0.77
Other determined cause	0.46 (0.08–2.71)	0.39
Undetermined cause	0.45 (0.17–1.19)	0.11
Hypertension	0.96 (0.43–2.14)	0.92
Hyperlipidemia	1.57 (0.57–4.35)	0.39
Atrial fibrillation	1.00 (0.29–3.40)	0.997
Regular smoking	1.34 (0.55–3.27)	0.52
Pre-stroke antithrombotics	1.15 (0.51–2.60)	0.74
Pre-stroke statins	1.42 (0.44–4.59)	0.56
Hemoglobin (per 1 g/dL increase)	1.02 (0.85–1.23)	0.81
HbA1c (per 1% increase)	1.08 (0.78–1.49)	0.63
Triglycerides	1.02 (0.74–1.40)	0.90
LDL cholesterol	0.83 (0.58–1.18)	0.29
Subgroup (endovascular only): symptomatic HT		
Early statins	0.44 (0.16–1.19)	0.11
Age (per 1-year increase)	0.97 (0.93–1.01)	0.14
Male sex	0.62 (0.23–1.67)	0.35
Premorbid mRS score=0	1.78 (0.46–6.83)	0.40
NIHSS score at arrival (per 1-point increase)	0.92 (0.84–0.99)	0.03
Onset to treatment delay (per 1-hour increase)	1.00 (0.97–1.03)	0.86
NIHSS score after treatment (per 1-point increase)	1.13 (1.04–1.22)	<0.01
Subgroup (intravenous only): mRS shift at 3 months**		
Early statins	1.17 (0.67–2.04)	0.57
Age (per 1-year increase)	0.95 (0.93–0.97)	<0.01
Male sex	1.44 (0.81–2.54)	0.21
Premorbid mRS score=0	2.42 (1.10–5.31)	0.03
NIHSS score at arrival (per 1-point increase)	1.01 (0.96–1.07)	0.66
Onset to treatment delay (per 1-hour increase)	0.986 (0.968–1.004)	0.13
NIHSS score after treatment (per 1-point increase)	0.82 (0.77–0.87)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	-
Small vessel occlusion	0.99 (0.47–2.09)	0.97
Cardioembolism	1.76 (0.83–3.69)	0.14
Other determined cause	0.61 (0.18–2.02)	0.42
Undetermined cause	1.07 (0.53–2.13)	0.86
Hypertension	1.58 (0.98–2.56)	0.06
Hyperlipidemia	0.92 (0.46–1.84)	0.82
Atrial fibrillation	0.97 (0.48–2.00)	0.94
Regular smoking	1.16 (0.65–2.10)	0.61
Pre-stroke antithrombotics	0.90 (0.52–1.56)	0.71
Pre-stroke statins	1.03 (0.47–2.24)	0.94
Hemoglobin (per 1 g/dL increase)	0.92 (0.81–1.05)	0.23

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
HbA1c (per 1% increase)	0.88 (0.73–1.04)	0.14
Triglycerides (per 1 mg/dL increase)	0.999 (0.996–1.003)	0.69
LDL cholesterol (per 1 mg/dL increase)	0.992 (0.985–0.999)	0.03
Subgroup (intravenous only): mRS 0–1 at 3 months[†]		
Early statins	1.20 (0.56–2.54)	0.64
Age	0.53 (0.36–0.78)	<0.01
Male sex	1.61 (0.76–3.41)	0.21
Premorbid mRS score=0	2.53 (0.83–7.72)	0.10
NIHSS score at arrival (per 1-point increase)	1.05 (0.97–1.15)	0.24
Onset to treatment delay (per 1-hour increase)	0.97 (0.94–1.01)	0.13
NIHSS score after treatment (per 1-point increase)	0.81 (0.74–0.89)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	-
Small vessel occlusion	0.70 (0.26–1.89)	0.49
Cardioembolism	1.84 (0.67–5.09)	0.24
Other determined cause	0.81 (0.16–4.15)	0.80
Undetermined cause	1.22 (0.49–3.03)	0.66
Hypertension	1.45 (0.76–2.79)	0.26
Hyperlipidemia	1.41 (0.53–3.75)	0.49
Atrial fibrillation	0.68 (0.26–1.79)	0.43
Regular smoking	1.25 (0.59–2.64)	0.56
Pre-stroke antithrombotics	0.74 (0.35–1.56)	0.43
Pre-stroke statins	0.86 (0.29–2.55)	0.78
Hemoglobin (per 1 g/dL increase)	0.93 (0.78–1.10)	0.41
HbA1c (per 1% increase)	0.70 (0.53–0.93)	0.01
Triglycerides	0.90 (0.66–1.24)	0.52
LDL cholesterol	0.71 (0.50–1.00)	0.05
Subgroup (intravenous only): symptomatic HT		
Early statins	0.85 (0.18–3.87)	0.83
Age (per 1-year increase)	1.05 (0.98–1.12)	0.14
Male sex	4.02 (0.84–19.16)	0.08
Premorbid mRS score=0	0.53 (0.09–3.02)	0.47
NIHSS score at arrival (per 1-point increase)	0.91 (0.79–1.05)	0.18
Onset to treatment delay (per 1-hour increase)	0.66 (0.38–1.16)	0.15
NIHSS score after treatment (per 1-point increase)	1.20 (1.05–1.36)	0.01
Subgroup (large artery atherosclerosis): mRS shift at 3 months[††,‡‡]		
Early statins	2.02 (1.07–3.82)	0.03
Age (per 1-year increase)	0.96 (0.94–0.99)	<0.01
Male sex	1.27 (0.66–2.43)	0.48
Premorbid mRS score=0	1.65 (0.70–3.90)	0.25
NIHSS score at arrival (per 1-point increase)	1.03 (0.98–1.08)	0.26
Onset to treatment delay (per 1-hour increase)	1.01 (0.99–1.03)	0.28
Recanalization treatment		
Intravenous thrombolysis alone	Referent	-
Endovascular therapy alone	1.07 (0.58–1.99)	0.83
Combined	0.76 (0.39–1.49)	0.43
NIHSS score after treatment (per 1-point increase)	0.82 (0.78–0.87)	<0.01
Hypertension	1.53 (0.86–2.73)	0.15
Hyperlipidemia	0.80 (0.41–1.55)	0.51

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Regular smoking	1.17 (0.64–2.14)	0.61
Pre-stroke antithrombotics	0.64 (0.35–1.17)	0.15
Pre-stroke statins	0.92 (0.43–1.97)	0.84
Hemoglobin (per 1 g/dL increase)	1.03 (0.89–1.18)	0.72
HbA1c (per 1% increase)	0.87 (0.72–1.05)	0.15
Triglycerides (per 1 mg/dL increase)	1.001 (0.997–1.005)	0.61
LDL cholesterol (per 1 mg/dL increase)	0.994 (0.987–1.001)	0.07
Subgroup (large artery atherosclerosis): mRS 0–1 at 3 month[†,††]		
Early statins	2.39 (0.90–6.40)	0.08
Age	0.67 (0.45–1.02)	0.06
Male sex	1.56 (0.59–4.10)	0.37
Premorbid mRS score=0	1.43 (0.35–5.85)	0.62
NIHSS score at arrival (per 1-point increase)	1.06 (0.97–1.14)	0.19
Onset to treatment delay (per 1-hour increase)	0.99 (0.96–1.02)	0.52
Recanalization treatment		
Intravenous thrombolysis alone	Referent	-
Endovascular therapy alone	1.05 (0.44–2.49)	0.91
Combined	0.38 (0.15–0.98)	0.05
NIHSS score after treatment (per 1-point increase)	0.81 (0.74–0.89)	<0.01
Hypertension	0.84 (0.38–1.87)	0.67
Hyperlipidemia	1.48 (0.54–4.10)	0.45
Regular smoking	1.38 (0.61–3.14)	0.44
Pre-stroke antithrombotics	0.84 (0.36–1.95)	0.68
Pre-stroke statins	0.90 (0.28–2.88)	0.86
Hemoglobin (per 1 g/dL increase)	1.14 (0.94–1.38)	0.17
HbA1c (per 1% increase)	0.82 (0.60–1.11)	0.20
Triglycerides	0.95 (0.68–1.33)	0.75
LDL cholesterol	0.74 (0.52–1.05)	0.09
Subgroup (large artery atherosclerosis): symptomatic HT		
Early statins	0.19 (0.04–0.96)	0.04
Age (per 1-year increase)	1.33 (0.56–3.18)	0.52
Male sex	0.79 (0.17–3.59)	0.76
Premorbid mRS score=0	1.25 (0.15–10.16)	0.83
NIHSS score at arrival (per 1-point increase)	0.93 (0.83–1.05)	0.26
Onset to treatment delay (per 1-hour increase)	1.01 (0.98–1.04)	0.44
Recanalization treatment		
Intravenous thrombolysis alone	Referent	-
Endovascular therapy alone	1.01 (0.17–5.96)	0.99
Combined	1.04 (0.14–7.60)	0.97
NIHSS score after treatment (per 1-point increase)	1.11 (0.99–1.25)	0.08
Subgroup (cardioembolism): mRS shift at 3 months[§§]		
Early statins	1.28 (0.87–1.88)	0.22
Age (per 1-year increase)	0.95 (0.93–0.97)	<0.01
Male sex	0.71 (0.46–1.10)	0.13
Premorbid mRS score=0	1.66 (1.01–2.74)	0.05
NIHSS score at arrival (per 1-point increase)	1.01 (0.98–1.05)	0.45
Onset to treatment delay (per 1-hour increase)	1.00 (0.97–1.03)	0.88
Recanalization treatment		
Intravenous thrombolysis alone	Referent	-

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Endovascular therapy alone	0.76 (0.44–1.30)	0.31
Combined	1.04 (0.65–1.66)	0.88
NIHSS score after treatment (per 1-point increase)	0.82 (0.79–0.85)	<0.01
Hypertension	1.28 (0.84–1.94)	0.25
Hyperlipidemia	1.04 (0.58–1.85)	0.90
Atrial fibrillation	1.08 (0.66–1.79)	0.75
Regular smoking	1.26 (0.80–2.00)	0.32
Pre-stroke antithrombotics	0.83 (0.56–1.23)	0.35
Pre-stroke statins	1.28 (0.70–2.32)	0.42
Hemoglobin (per 1 g/dL increase)	0.99 (0.88–1.10)	0.79
HbA1c (per 1% increase)	0.82 (0.67–1.00)	0.05
Triglycerides (per 1 mg/dL increase)	1.003 (0.999–1.006)	0.13
LDL cholesterol (per 1 mg/dL increase)	0.993 (0.988–0.999)	0.02
Subgroup (cardioembolism): mRS 0–1 at 3 months[†]		
Early statins	1.32 (0.74–2.37)	0.35
Age	0.66 (0.47–0.91)	0.01
Male sex	0.62 (0.32–1.20)	0.16
Premorbid mRS score=0	1.76 (0.72–4.34)	0.22
NIHSS score at arrival (per 1-point increase)	0.99 (0.94–1.04)	0.69
Onset to treatment delay (per 1-hour increase)	0.99 (0.95–1.03)	0.52
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	0.60 (0.27–1.30)	0.19
Combined	1.14 (0.58–2.21)	0.71
NIHSS score after treatment (per 1-point increase)	0.82 (0.77–0.87)	<0.01
Hypertension	1.22 (0.64–2.31)	0.55
Hyperlipidemia	1.20 (0.48–2.97)	0.70
Atrial fibrillation	1.19 (0.57–2.45)	0.64
Regular smoking	1.81 (0.92–3.56)	0.08
Pre-stroke antithrombotics	0.70 (0.38–1.27)	0.24
Pre-stroke statins	1.06 (0.41–2.76)	0.90
Hemoglobin (per 1 g/dL increase)	0.95 (0.80–1.12)	0.54
HbA1c (per 1% increase)	0.97 (0.73–1.30)	0.86
Triglycerides	1.23 (0.93–1.64)	0.15
LDL cholesterol	0.68 (0.50–0.91)	0.01
Subgroup (cardioembolism): symptomatic HT		
Early statins	0.60 (0.26–1.38)	0.23
Age (per 1-year increase)	0.98 (0.94–1.01)	0.21
Male sex	1.09 (0.49–2.44)	0.83
Premorbid mRS score=0	1.19 (0.40–3.47)	0.76
NIHSS score at arrival (per 1-point increase)	0.91 (0.84–0.98)	0.02
Onset to treatment delay (per 1-hour increase)	0.97 (0.89–1.06)	0.53
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	1.69 (0.49–5.82)	0.41
Combined	1.11 (0.38–3.21)	0.85
NIHSS score after treatment (per 1-point increase)	1.15 (1.07–1.23)	<0.01
Subgroup (other stroke mechanisms): mRS shift at 3 months[‖]		
Early statins	1.89 (1.02–3.53)	0.04

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Age (per 1-year increase)	0.97 (0.95–0.99)	0.01
Male sex	0.46 (0.23–0.94)	0.03
Premorbid mRS score=0	1.84 (0.80–4.23)	0.15
NIHSS score at arrival (per 1-point increase)	1.06 (0.997–1.12)	0.06
Onset to treatment delay (per 1-hour increase)	0.99 (0.97–1.01)	0.19
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	0.82 (0.42–1.58)	0.55
Combined	0.99 (0.50–1.95)	0.98
NIHSS score after treatment (per 1-point increase)	0.80 (0.75–0.85)	<0.01
Hypertension	1.19 (0.67–2.12)	0.55
Hyperlipidemia	0.70 (0.28–1.77)	0.45
Atrial fibrillation	0.82 (0.34–1.99)	0.66
Regular smoking	2.19 (1.10–4.36)	0.03
Pre-stroke antithrombotics	1.33 (0.71–2.49)	0.37
Pre-stroke statins	2.36 (0.79–7.07)	0.12
Hemoglobin (per 1 g/dL increase)	1.25 (1.08–1.44)	<0.01
HbA1c (per 1% increase)	0.83 (0.66–1.06)	0.14
Triglycerides (per 1 mg/dL increase)	1.000 (0.996–1.003)	0.84
LDL cholesterol (per 1 mg/dL increase)	0.999 (0.991–1.006)	0.73
Subgroup (other stroke mechanisms): mRS 0–1 at 3 months[†]		
Early statins	1.93 (0.78–4.79)	0.15
Age	0.59 (0.39–0.89)	0.01
Male sex	0.45 (0.15–1.29)	0.14
Premorbid mRS score=0	2.07 (0.60–7.14)	0.25
NIHSS score at arrival (per 1-point increase)	1.05 (0.97–1.14)	0.23
Onset to treatment delay (per 1-hour increase)	0.98 (0.95–1.01)	0.29
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	0.50 (0.19–1.31)	0.16
Combined	1.14 (0.43–3.03)	0.79
NIHSS score after treatment (per 1-point increase)	0.78 (0.70–0.86)	<0.01
Hypertension	1.57 (0.69–3.54)	0.28
Hyperlipidemia	1.66 (0.48–5.80)	0.43
Atrial fibrillation	1.20 (0.32–4.49)	0.79
Regular smoking	4.14 (1.47–11.64)	0.01
Pre-stroke antithrombotics	0.92 (0.36–2.35)	0.87
Pre-stroke statins	1.47 (0.33–6.56)	0.62
Hemoglobin (per 1 g/dL increase)	1.03 (0.84–1.27)	0.74
HbA1c (per 1% increase)	0.69 (0.47–1.02)	0.06
Triglycerides	0.98 (0.69–1.39)	0.91
LDL cholesterol	0.96 (0.65–1.43)	0.86
Subgroup (other stroke mechanisms): symptomatic HT		
Early statins	0.49 (0.12–1.99)	0.32
Age (per 1-year increase)	1.02 (0.97–1.08)	0.43
Male sex	3.19 (0.68–14.93)	0.14
Premorbid mRS score=0	0.94 (0.15–5.86)	0.95
NIHSS score at arrival (per 1-point increase)	0.94 (0.83–1.07)	0.36
Onset to treatment delay (per 1-hour increase)	0.98 (0.89–1.08)	0.72

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	1.00 (0.16–6.35)	1.00
Combined	1.34 (0.24–7.59)	0.74
NIHSS score after treatment (per 1-point increase)	1.13 (1.01–1.27)	0.03
Subgroup (pre-stroke statins: yes): mRS shift at 3 months¶¶		
Early statins	1.58 (0.84–2.99)	0.16
Age (per 1-year increase)	0.96 (0.92–0.99)	0.01
Male sex	0.91 (0.45–1.84)	0.78
Premorbid mRS score=0	2.85 (1.35–5.99)	0.01
NIHSS score at arrival (per 1-point increase)	1.01 (0.95–1.07)	0.82
Onset to treatment delay (per 1-hour increase)	1.00 (0.98–1.03)	0.77
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	1.37 (0.65–2.91)	0.40
Combined	1.30 (0.64–2.66)	0.47
NIHSS score after treatment (per 1-point increase)	0.80 (0.75–0.85)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	
Small vessel occlusion	4.00 (0.54–29.51)	0.17
Cardioembolism	2.32 (0.85–6.33)	0.10
Other determined cause	0.41 (0.06–2.82)	0.36
Undetermined cause	1.89 (0.78–4.61)	0.16
Hypertension	1.54 (0.73–3.23)	0.26
Hyperlipidemia	0.71 (0.27–1.87)	0.49
Atrial fibrillation	0.92 (0.37–2.26)	0.85
Regular smoking	0.90 (0.45–1.83)	0.78
Pre-stroke antithrombotics	1.61 (0.84–3.06)	0.15
Hemoglobin (per 1 g/dL increase)	1.15 (0.97–1.38)	0.11
HbA1c (per 1% increase)	1.21 (0.91–1.60)	0.19
Triglycerides (per 1 mg/dL increase)	1.00 (0.99–1.01)	0.81
LDL cholesterol (per 1 mg/dL increase)	0.993 (0.984–1.001)	0.09
Subgroup (pre-stroke statins: yes): mRS 0–1 at 3 months†		
Early statins	2.63 (0.94–7.38)	0.07
Age	0.60 (0.36–1.00)	0.0499
Male sex	0.62 (0.21–1.82)	0.38
Premorbid mRS score=0	2.34 (0.68–8.09)	0.18
NIHSS score at arrival (per 1-point increase)	0.98 (0.91–1.07)	0.67
Onset to treatment delay (per 1-hour increase)	0.99 (0.96–1.03)	0.61
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	1.71 (0.58–5.06)	0.33
Combined	1.31 (0.47–3.68)	0.60
NIHSS score after treatment (per 1-point increase)	0.82 (0.75–0.90)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	–
Small vessel occlusion	6.66 (0.43–103.28)	0.17
Cardioembolism	1.38 (0.32–5.97)	0.67
Other determined cause	0.62 (0.04–10.76)	0.74

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Undetermined cause	0.92 (0.25–3.36)	0.90
Hypertension	1.84 (0.57–5.89)	0.30
Hyperlipidemia	1.71 (0.37–7.95)	0.49
Atrial fibrillation	1.18 (0.31–4.55)	0.81
Regular smoking	1.14 (0.41–3.12)	0.80
Pre-stroke antithrombotics	2.04 (0.74–5.60)	0.17
Hemoglobin (per 1 g/dL increase)	1.09 (0.84–1.43)	0.50
HbA1c (per 1% increase)	1.27 (0.85–1.88)	0.24
Triglycerides	1.06 (0.69–1.63)	0.79
LDL cholesterol	0.60 (0.39–0.94)	0.02
Subgroup (pre-stroke statins: yes): symptomatic HT		
Early statins	0.16 (0.04–0.60)	0.01
Age (per 1-year increase)	0.99 (0.92–1.07)	0.87
Male sex	2.31 (0.57–9.39)	0.24
Premorbid mRS score=0	0.73 (0.16–3.33)	0.68
NIHSS score at arrival (per 1-point increase)	0.99 (0.86–1.14)	0.92
Onset to treatment delay (per 1-hour increase)	1.04 (0.996–1.08)	0.08
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	0.17 (0.02–1.79)	0.14
Combined	1.30 (0.28–6.09)	0.74
NIHSS score after treatment (per 1-point increase)	1.10 (0.97–1.24)	0.13
Subgroup (pre-stroke statins: no): mRS shift at 3 months***		
Early statins	1.43 (1.03–1.98)	0.03
Age (per 1-year increase)	0.96 (0.95–0.97)	<0.01
Male sex	0.73 (0.51–1.04)	0.08
Premorbid mRS score=0	1.39 (0.88–2.18)	0.16
NIHSS score at arrival (per 1-point increase)	1.03 (1.004–1.06)	0.03
Onset to treatment delay (per 1-hour increase)	1.00 (0.99–1.01)	0.90
Recanalization treatment		
Intravenous thrombolysis alone	Referent	
Endovascular therapy alone	0.77 (0.52–1.13)	0.18
Combined	0.98 (0.67–1.43)	0.91
NIHSS score after treatment (per 1-point increase)	0.82 (0.79–0.84)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	
Small vessel occlusion	0.70 (0.33–1.46)	0.34
Cardioembolism	1.45 (0.87–2.43)	0.16
Other determined cause	0.25 (0.12–0.53)	<0.01
Undetermined cause	0.84 (0.54–1.31)	0.44
Hypertension	1.28 (0.93–1.75)	0.13
Hyperlipidemia	0.70 (0.42–1.15)	0.16
Atrial fibrillation	0.78 (0.48–1.26)	0.31
Regular smoking	1.68 (1.17–2.40)	<0.01
Pre-stroke antithrombotics	0.81 (0.59–1.12)	0.20
Hemoglobin (per 1 g/dL increase)	1.04 (0.96–1.13)	0.35
HbA1c (per 1% increase)	0.77 (0.67–0.89)	<0.01
Triglycerides (per 1 mg/dL increase)	1.001 (0.999–1.003)	0.55
LDL cholesterol (per 1 mg/dL increase)	0.998 (0.994–1.003)	0.46

Supplementary Table 8. Continued

Variables	Adjusted OR (95% CI)	P
Subgroup (pre-stroke statins: no): mRS 0–1 at 3 months[†]		
Early statins	1.36 (0.84–2.20)	0.22
Age	0.66 (0.51–0.84)	<0.01
Male sex	0.77 (0.45–1.32)	0.35
Premorbid mRS score=0	1.81 (0.82–4.00)	0.14
NIHSS score at arrival (per 1-point increase)	1.02 (0.98–1.07)	0.31
Onset to treatment delay (per 1-hour increase)	0.98 (0.96–1.01)	0.16
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	0.53 (0.31–0.93)	0.03
Combined	0.80 (0.47–1.35)	0.40
NIHSS score after treatment (per 1-point increase)	0.81 (0.77–0.85)	<0.01
Stroke mechanism		
Large artery atherosclerosis	Referent	–
Small vessel occlusion	0.38 (0.14–1.02)	0.05
Cardioembolism	1.61 (0.75–3.47)	0.22
Other determined cause	0.67 (0.24–1.86)	0.44
Undetermined cause	0.92 (0.49–1.72)	0.78
Hypertension	1.06 (0.68–1.66)	0.79
Hyperlipidemia	0.98 (0.48–2.03)	0.96
Atrial fibrillation	0.95 (0.46–1.95)	0.89
Regular smoking	2.44 (1.46–4.10)	<0.01
Pre-stroke antithrombotics	0.68 (0.42–1.10)	0.12
Hemoglobin (per 1 g/dL increase)	1.03 (0.92–1.16)	0.61
HbA1c (per 1% increase)	0.75 (0.60–0.93)	0.01
Triglycerides	0.98 (0.80–1.21)	0.88
LDL cholesterol	0.93 (0.75–1.16)	0.54
Subgroup (pre-stroke statins: no): symptomatic HT		
Early statins	0.16 (0.04–0.60)	0.01
Age (per 1-year increase)	0.99 (0.92–1.07)	0.87
Male sex	2.31 (0.57–9.39)	0.24
Premorbid mRS score=0	0.73 (0.16–3.33)	0.68
NIHSS score at arrival (per 1-point increase)	0.99 (0.86–1.14)	0.92
Onset to treatment delay (per 1-hour increase)	1.04 (0.996–1.08)	0.08
Recanalization treatment		
Intravenous thrombolysis alone	Referent	–
Endovascular therapy alone	0.17 (0.02–1.79)	0.14
Combined	1.30 (0.28–6.09)	0.74
NIHSS score after treatment (per 1-point increase)	1.10 (0.97–1.24)	0.13

OR, odds ratio; CI, Contidence interval; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; LDL, low-density lipoprotein; IV, intravenous; HT, hemorrhage transformation.
*Likelihood ratio test of non-proportional odds for early statins: P=0.16; [†]Age, triglycerides, and LDL cholesterol were standardized for the mixed model; [‡]Likelihood ratio test of non-proportional odds for early statins: P=0.76; [§]Likelihood ratio test of non-proportional odds for early statins: P=0.55; [‖]Likelihood ratio test of non-proportional odds for early statins: P=0.58; [¶]Likelihood ratio test of non-proportional odds for early statins: P=0.67; [**]Likelihood ratio test of non-proportional odds for early statins: P=0.80; [††]Atrial fibrillation was excluded from the model due to its singularity; [‡‡]Likelihood ratio test of non-proportional odds for early statins: P=0.95; [§§]Likelihood ratio test of non-proportional odds for early statins: P=0.77; [‖‖]Likelihood ratio test of non-proportional odds for early statins: P=0.33; [¶¶]Likelihood ratio test of non-proportional odds for early statins: P=0.24; [***]Likelihood ratio test of non-proportional odds for early statins: P=0.04.