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ORIGINAL RESEARCH

Effect of Statin Administration After Onset of Acute Ischemic Stroke With Large Vessel Occlusion: Insights From RESCUE-Japan Registry 2

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BACKGROUND: Statins have been associated with reduced recurrence and better functional outcomes in patients with acute ischemic stroke. However, the effect of statins in patients with acute large vessel occlusion (LVO) is not well scrutinized.

METHODS AND RESULTS: RESCUE (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism)-Japan Registry 2, a physician-initiated registry, enrolled 2420 consecutive patients with acute LVO who were admitted to 46 centers across Japan within 24 hours of onset. We compared patients with and without statin use after acute LVO onset (statin group and nonstatin group, respectively) in terms of the modified Rankin scale at 90 days. We estimated that the odds ratios for the primary outcome was modified Rankin scale and we estimated the odds ratios for a 1-scale lower modified Rankin scale adjusting for confounders. After excluding 12 patients without LVO and 9 patients without follow-up, the mean age of 2399 patients was 75.9 years; men accounted for 55% of patients. Statins were administered to 447 (19%) patients after acute LVO onset. Patients in the statin group had more atherothrombotic cerebral infarctions (34.2% versus 12.1%, $P<0.0001$), younger age (73.4 years versus 76.5 years, $P<0.0001$), and lower median National Institutes of Health Stroke Scale on admission (14 versus 17, $P<0.0001$) than the nonstatin group. The adjusted common OR of the statin group for lower modified Rankin scale was 1.29 (95% CI, 1.04–1.37; $P=0.02$). The mortality at 90 days was lower in the statin group (4.7%) than the nonstatin group (12.5%; $P<0.0001$). The adjusted OR of the statin group relative to the nonstatin group for mortality was 0.36 (95% CI, 0.21–0.62; $P=0.02$).

CONCLUSIONS: Statin administration after acute LVO onset is significantly associated with better functional outcome and mortality at 90 days.

Key Words: acute ischemic stroke ■ functional outcomes ■ large vessel occlusion ■ statins

Statins are widely recommended for the secondary prevention of atherosclerotic diseases, including cardiovascular disease and cerebrovascular diseases.[1,2] Statins for patients with acute ischemic stroke during hospitalization are also associated with better survival[3]; however, these effects were observed in patients without thrombolysis therapy.[4] In the era of thrombolysis therapy, statins failed to decrease the functional disability and mortality at 90 days in several randomized clinical trials.[5,6] However, these trials were

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CLINICAL PERSPECTIVE

What Is New?

- Previous reports on statins were associated with reduced recurrence and better functional outcomes in patients with acute ischemic stroke, but these effects were uncertain in patients with acute large vessel occlusion (LVO).
- The largest registry including 2399 patients with acute LVO showed that statin administration after the onset of acute LVO was significantly associated with better functional outcome and mortality at 90 days.

What Are the Clinical Implications?

- Although most LVOs were attributable to cardioembolism and not atherosclerosis, our study suggests that statins should be administered in patients with acute LVO as early as possible irrespective of revascularization such as recombinant tissue plasminogen activator or endovascular therapy.
- Additional clinical studies, including randomized trials, are needed to investigate other uncertainties including the dose of statins and how long they should be continued to achieve stabilized functional outcomes.

Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early CT Score
ASSORT	Administration of Statin on Acute Ischemic Stroke Patient
EVT	endovascular therapy
LVO	large vessel occlusion
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
RESCUE	Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism
rt-PA	recombinant tissue plasminogen activator
TICI	thrombolysis in cerebral infarction

underpowered to detect the statistically significant effect of statin administration on functional outcomes, while the ASSORT (Administration of Statin on Acute Ischemic Stroke Patient) trial indicated a common odds ratio (OR) of 1.19 (1/0.84) for better functional outcomes in patients with acute ischemic stroke.[6]

Endovascular therapy (EVT) and recombinant tissue plasminogen activator (rt-PA) are now widely used for patients with acute ischemic stroke caused by large vessel occlusion (LVO). These strokes are generally a more severe form of acute ischemic stroke, and their functional outcomes are considered worse. Therefore, a favorable effect of statins on clinical outcomes is needed if such treatment is to be in line with the secondary prevention of ischemic strokes. Thus, we analyzed the largest registry data of patients with acute LVO in the world,[6] and explored the effect of statin administration after onset of LVO on functional outcomes at 90 days.

METHODS

Study Design and Population

The data that support the findings of this study are available from the corresponding author on reasonable request. We analyzed the data from the RESCUE (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism)-Japan Registry 2. The methods and primary results of the RESCUE-Japan Registry 2 have been previously reported.[7] Briefly, the RESCUE-Japan Registry 2 was a prospective multicenter registry that enrolled 2420 consecutive patients with acute ischemic stroke with LVO from 46 centers across Japan between October 2014 and September 2016. The participating centers were hospitals that were capable of treating acute LVO (Table 1). The participants were 20 years or older and were hospitalized within 24 hours of stroke onset. Clinical information was collected through a review of hospital charts. Follow-up information up to 90 days was mainly collected by a review of hospital charts, and any additional information was collected by contacting patients, relatives, and referring physicians. The institutional review boards of all 46 participating centers approved the study protocol. Written informed consent from each patient was waived by the review boards in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, an opt-out method was applied to all patients to be excluded from the registry.

Study Variables

The exposure of interest of this study was administration of statins after the onset of acute LVO. Statin administration after onset was defined by any type or dose of statin administered after the onset of LVO, irrespective of the statins administered before the onset. The primary outcome was a 1-scale lower modified Rankin scale (mRS) at 90 days after the onset of acute LVO. The mRS ranged from 0 to 6, which assessed the degree of disability or dependence in daily activities, with scores ranging from 0 (no symptoms) to 6 (death), and lower mRS indicated

Table 1. Participating Centers and Investigators

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better physical function.[8] The secondary outcomes were mortality within 90 days and a good outcome defined by mRS ranging from 0 to 2 at 90 days. The assessment of mRS was conducted by an independent physician who had not treated the patient. If the mRS could not be assessed, the patients or their legally authorized representatives were contacted via telephone to estimate the mRS.

We collected data on patient characteristics, statin use, and mRS before the onset of stroke, the time from onset of symptoms to arrival at the hospital, National Institutes of Health Stroke Scale (NIHSS), laboratory values, use of rt-PA, and EVT. The diagnostic and treatment modalities were determined by the physician in charge. Acute ischemic stroke was classified as cardioembolic, atherothrombotic, cryptogenic, or other.[9] We collected data on the spread of stroke using the Alberta Stroke Program Early CT Score (ASPECTS) as assessed by diffusion-weighted imaging in magnetic resonance imaging or noncontrast computed tomography.[10,11] All ASPECTS results from either of the diagnostic modalities provided scores ranging from 0 to 10, with higher scores representing smaller early ischemic changes. ASPECTS was defined as ASPECTS on noncontrast computed tomography, ASPECTS on diffusion-weighted imaging, or diffusion-weighted imaging posterior circulation-ASPECTS. The details of ASPECTS measurements and the classification of occlusion sites in this study have been previously reported.[7] EVT consisted of any revascularization using any device approved in Japan, such as stent retrievers and/or aspiration catheters, balloon angioplasty, stenting, local fibrinolysis, piercing using guidewires and/or microcatheters, or a combination of these treatments. The degree of reperfusion of the EVT was classified by the thrombolysis in cerebral infarction (TICI) grading system.[12]

Statistical Analysis

Continuous variables were expressed as either mean and SD or median and interquartile range and compared using Student *t* test or Wilcoxon rank sum test based on their distributions. Categorical variables were presented as numbers and percentages and were compared using chi-square test.

We compared the mRS at 90 days after the onset of acute LVO between patients with and without statins after the onset of acute LVO (statin and nonstatin groups, respectively). We used the ordinal logistic regression model to estimate the common OR and its 95% CIs for the primary outcome, a 1-scale lower mRS. We also used the binary logistic regression models to estimate odds ratios (ORs) and 95% CIs for the secondary outcomes. We adjusted for age, statin use before onset, mRS (≥2 or <2) before onset, time from onset of symptoms to arrival at hospital, NIHSS, ASPECTS (≥6 or <6), site of main occlusions (anterior or posterior circulation), vessels of main occlusions (internal carotid artery and M1 segment middle cerebral artery or other arteries), cause of stroke (cardioembolic or other), rt-PA use, and EVT to estimate the adjusted ORs.[7] We constructed the multivariable ordinal regression model for the primary outcome among patients who received EVT and achieved TICI ≥2b as a sensitivity analysis.

We constructed the same multivariable ordinal logistic regression models for the primary outcome in the subgroups to estimate the adjusted common ORs for each subgroup and the interaction *P* values. The subgroups included statin use before onset, mRS before onset (≥2 or <2), NIHSS (≥16 or <16), low-density lipoprotein cholesterol (≥120 or <120 mg/dL), ASPECTS (≥6 or <6), location of main occlusions (anterior or posterior circulation), vessels of the main occlusions (internal carotid artery occlusion and M1 segment middle cerebral artery occlusion or other artery occlusion), cause of stroke (cardioembolic or noncardioembolic), use of intravenous rt-PA, and EVT.

All statistical analyses were conducted by a physician (K.U.) and study statistician (T.M.) using JMP version 14.0 or SAS version 9.4 (SAS Institute Inc). All reported *P* values were 2-tailed, and *P* values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

A total of 2399 patients were analyzed after excluding 12 patients who did not meet the eligibility criteria and 9 patients who were not followed at 90 days among the 2420 patients initially enrolled in the registry (Figure 1). The patients who were administered statins after admission were 447 (19.1%), including atorvastatin (164), rosuvastatin (152), pitavastatin (95), pravastatin (27), simvastatin (7), and fluvastatin (2). In Japan, the standard approved doses were atorvastatin 10 mg/d, rosuvastatin 5 mg/d, pitavastatin 2 mg/d, pravastatin 10 mg/d, simvastatin 5 mg/d, and fluvastatin 30 mg/d.

The statin group was significantly younger than the nonstatin group (73.4 versus 76.5 years, *P*<0.0001), but were more likely to be smokers (23.9% versus 11.7%, *P*<0.0001) and take statins before admission (43.4% versus 8.7%, *P*<0.0001). In addition, the statin group was significantly more likely to have hypertension, diabetes mellitus, and dyslipidemia (Table 2). The rate of mRS ≤1 before onset was significantly higher in the statin group (83.7% versus 76.9%, *P*=0.0013). Both NIHSS and ASPECTS on computed tomography or

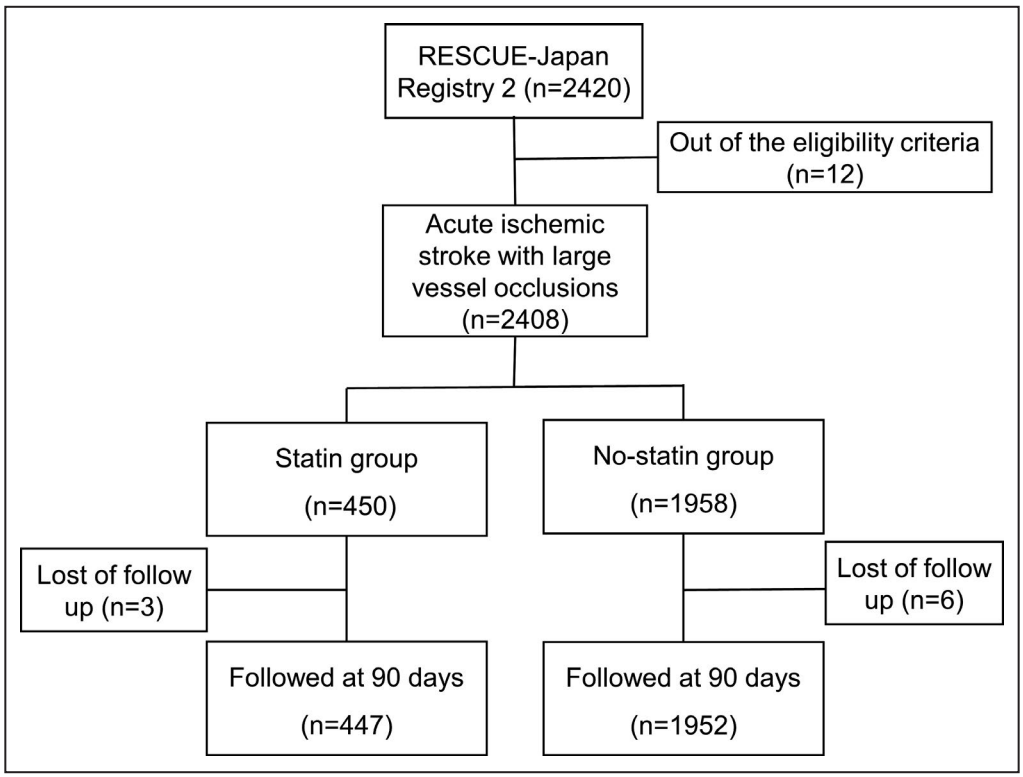


Figure 1. Study flowchart.
RESCUE indicates Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism.

magnetic resonance imaging were significantly better in the statin group than in the nonstatin group. The anterior circulation of occlusion location was infrequent in the statin group (83.0% versus 87.6%, *P*=0.011), and atherothrombotic stroke was more dominant in the statin group (34.2% versus 12.1%, *P*<0.0001).

Outcomes

The adjusted common OR of the statin group was 1.29 (95% CI, 1.04–1.37; *P*=0.02) compared with the nonstatin group (Figure 2). The mortality at 90 days was lower in the statin group (4.7%) than in the nonstatin group (12.5%) (*P*<0.0001). The adjusted OR for mortality in the statin group was 0.36 (95% CI, 0.21–0.62; *P*=0.02) (Table 3). The good outcome, defined as an mRS score of 0 to 2 at 90 days, was 45.0% in the statin group and 34.6% in the nonstatin group (*P*<0.0001). The adjusted OR of the statin group for good outcome was 1.07 (95% CI, 0.80–1.42; *P*=0.66) (Table 3). The sensitivity analysis among patients who received EVT and achieved TICI ≥2b was consistent with the primary analysis (adjusted common OR, 1.09; 95% CI, 0.81–1.47 [*P*=0.56]).

Subgroup Analysis

The subgroup analyses suggested that statin administration was generally effective in all subgroups (Figure 3). Statins were apparently effective in patients with ASPECTS ≥6, with occlusion in the anterior circulation, and with the vessels of main occlusions of the internal carotid artery or M1 segment middle cerebral artery. Moreover, statins seemed effective for patients with noncardioembolic stroke, with an adjusted OR of 1.38 (95% CI, 1.09–1.74). Statins were effective in patients without rt-PA or without EVT, with an adjusted OR of 1.65 (95% CI, 1.24–2.19) and 1.48 (95% CI, 1.06–2.05), respectively. Although these 95% CIs were not across 1, all indicate non significance were >0.05.

DISCUSSION

Based on the largest registry in real-world settings, statin administration after onset of acute LVO was significantly associated with better functional outcome and lower mortality at 90 days. The adjusted common OR of 1.29 from this registry was consistent with the point estimate of 1.19 from our previous randomized clinical trial.[6] Administration of statins after onset also reduced mortality, with an adjusted OR of 0.36. Because the effectiveness of statin administration was generally similar among the subgroups, statins were recommended for patients with acute ischemic stroke with LVO irrespective of revascularization such as rt-PA or EVT.

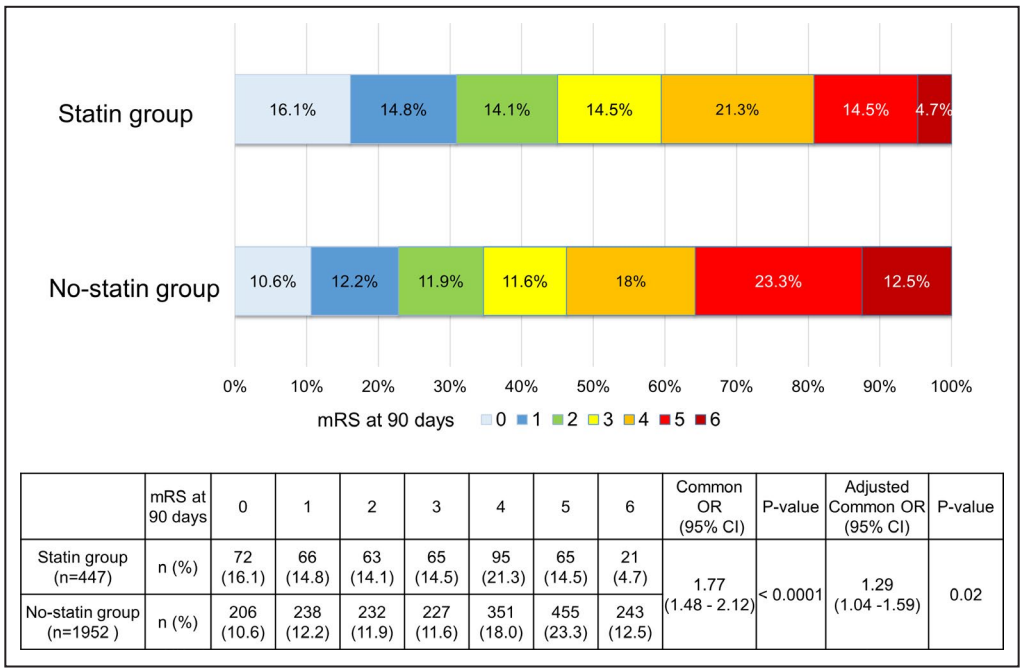
Table 2. Characteristics of Patients

Variables	Statin Group (n=447)	Nonstatin Group (n=1952)	*P* Value
Age, mean (SD), y	73.4 (11.1)	76.5 (12.1)	<0.0001
Age ≥75 y, n (%)	229 (51.2)	1210 (62.0)	<0.0001
Men, n (%)	282 (63.1)	1030 (52.8)	<0.0001
mRS before onset ≤1, n (%)	374 (83.7)	1501 (76.9)	0.001
Statin use before onset, n (%)	194 (43.4)	170 (8.7)	<0.0001
History of smoking, n (%)	107 (23.9)	228 (11.7)	<0.0001
History of hypertension, n (%)	324 (72.5)	1102 (56.5)	<0.0001
History of diabetes mellitus, n (%)	127 (28.4)	329 (16.9)	<0.0001
History of dyslipidemia, n (%)	257 (57.4)	281 (14.4)	<0.0001
History of ischemic stroke, n (%)	44 (9.8)	152 (7.8)	0.15
Systolic BP, median [IQR], mm Hg	158 [137–175] (n=439)	153 [135–172] (n=1923)	0.07
Diastolic BP, median [IQR], mm Hg	84 [73–96] (n=429)	84 [73–97] (n=1900)	0.83
Body weight, mean (SD), kg	69.7 (14.1) (n=432)	55.6 (12.3) (n=1876)	<0.0001
NIHSS on admission, median (IQR)	14 [6–20]	17 [11–23]	<0.0001
Laboratory values, mg/dL			
LDL cholesterol, mean (SD)	110.7 (32.3) (n=355)	119.0 (41.0) (n=1474)	0.0004
HDL cholesterol, mean (SD)	50.0 (14.5) (n=339)	51.5 (14.8) (n=1383)	0.11
Total cholesterol, mean (SD)	192.6 (47.3) (n=376)	182.5 (38.5) (n=1570)	<0.0001
Blood sugar, median [IQR]	127 [111–160] (n=429)	126 [109–154] (n=1880)	0.26
CRP, median [IQR]	0.18 [0.09–0.67] (n=429)	0.20 [0.09–0.90] (n=1886)	0.16
Anterior circulation occlusion, n (%)	371 (83.0)	1709 (87.6)	0.01
Location of occlusion IC or M1, n (%)	273 (61.1)	1247 (63.9)	0.27
ASPECTS ≥6, n (%)	381 (85.2)	1496 (76.6)	<0.0001
Stroke classification			
Cardioembolic, n (%)	235 (52.6)	1457 (74.8)	<0.0001
Atherothrombotic, n (%)	153 (34.2)	236 (12.1)	
Cryptogenic, n (%)	45 (10.1)	172 (8.8)	
Other*, n (%)	14 (3.1)	84 (4.3)	
Onset to door-min, median [IQR]	170 [60–400]	140 [60–340]	0.15
Intravenous thrombolysis, n (%)	171 (38.3)	782 (40.1)	0.48
Endovascular therapy, n (%)	249 (55.7)	1029 (52.7)	0.25
TICI ≥2b, n (%)	229 (92.0) (n=249)	872 (84.7) (n=1029)	0.0017

ASPECTS indicates Alberta Stroke Program Early CT Score; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; and TICI, Thrombolysis in Cerebral Infarction.

*Other: abnormality of coagulation, arterial dissection, vasculitis, or undetermined.

Several previous studies reported the association of statin administration in patients with ischemic stroke and better outcomes, including disability[6,13–15] or mortality.[3,13] Among them, the ORs of statin administration for better functional outcome in patients with acute ischemic stroke were reported to be 1.63 in an observational study[15] and 1.19 in a randomized trial.[6] These data were investigated in patients with acute ischemic stroke but they were not limited to LVO. Thus, our study is the first to attest the effectiveness of statin administration in patients with acute LVO and clearly demonstrated reduced disability at 90 days. Although ours was not a randomized clinical trial, the findings should be considered robust because of the large



	mRS at 90 days	0	1	2	3	4	5	6	Common OR (95% CI)	P-value	Adjusted Common OR (95% CI)	P-value
Statin group (n=447)	n (%)	72 (16.1)	66 (14.8)	63 (14.1)	65 (14.5)	95 (21.3)	65 (14.5)	21 (4.7)	1.77 (1.48 - 2.12)	< 0.0001	1.29 (1.04 -1.59)	0.02
No-statin group (n=1952)	n (%)	206 (10.6)	238 (12.2)	232 (11.9)	227 (11.6)	351 (18.0)	455 (23.3)	243 (12.5)				

Figure 2. Modified Rankin scale (mRS) at 90 days.
OR indicates odds ratio.

sample size, consecutive patient enrollment, and extensive multivariable adjustment.

Both cholesterol-lowering–dependent and –independent effects of statins were reported to be associated with neuroprotective effects.[16] Cholesterol-lowering–dependent effects included antiatherosclerosis, and cholesterol-lowering–independent effects included anti-inflammation, antioxidation, and modulation of nitric oxide products.[16] Immediate statin administration after ischemic stroke was reported to decrease infarct size and improve physical function in rat models.[17] Indeed, subgroups without rt-PA or EVT or with a large ischemic core had larger ORs of statin administration in our study. These patients without revascularization tended to have larger infarct sizes and thus had a relatively higher benefit from statin administration. Thus, the effects of statin administration on acute ischemic strokes should be considered mainly independent of cholesterol lowering.

Accumulation of evidence from previous randomized clinical trials and other observational studies supported the routine use of statins after the onset of acute ischemic stroke in conjunction with the current study, except for those with contraindications to statins. Although all interaction *P* values were not statistically significant in our study, statins might be more effective in patients with anterior circulation occlusions, or without receiving rt-PA or EVT. There are uncertainties regarding the use of statins for acute ischemic stroke. One of them is the influence of statins before the onset of ischemic stroke. One quasirandomized trial showed that the withdrawal of statins for the first 3 days was associated with worse functional outcomes,[13] which indicated the importance of administration just after onset rather than before onset. The ASSORT trial indicated that delayed statin administration 7 days after the onset of acute ischemic stroke was associated with worse functional outcomes than those after 24 hours, although the estimates were not statistically significant.[6] Thus, statin administration should be considered as early as possible. The administration rate of statins was 19% among patients with LVO and 39% (153/389) among those with atherothrombosis in our study. This low administration rate was common in Japan, and 53% of patients with both coronary heart disease and stroke received statins in the large registry

Table 3. Outcomes

Outcomes	Statin Group (n=447)	Nonstatin Group (n=1952)	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Mortality at 90 d, n (%)	21 (4.7)	243 (12.5)	0.35 (0.22–0.55)	<0.0001	0.36 (0.21–0.62)	0.02
mRS score 0–2 at 90 d, n (%)	201 (45.0)	676 (34.6)	1.52 (1.25–1.90)	<0.0001	1.07 (0.80–1.42)	0.66

mRS indicates modified Rankin scale.

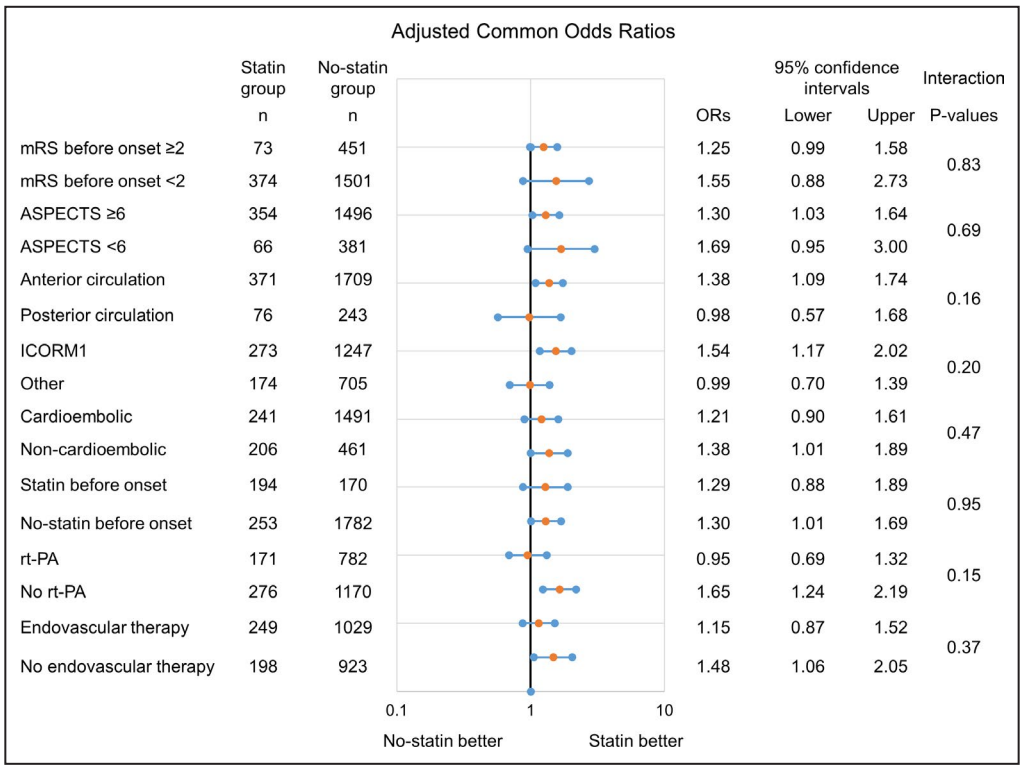


Figure 3. Subgroup analyses.
ASPECTS indicates Alberta Stroke Program Early CT Score; ICORM1, internal carotid artery occlusion OR M1 segment middle cerebral artery occlusion; mRS, modified Rankin scale; OR, odds ratio; Other, other artery occlusion; and rt-PA, recombinant tissue plasminogen activator.

study in Japan.[18] Although most LVOs were caused by cardioembolism and not atherosclerosis, the relatively low administration rate could be improved with our findings. Other uncertainties included the doses of statins and how long they should be continued to achieve stabilized functional outcomes. These uncertainties should be investigated in future studies.

Several limitations should be acknowledged when interpreting our findings. First, the study design was a registry, and, thus, the administration of statins was determined by the physician in charge. Although we extensively adjusted for clinically relevant confounders in the analyses, there were still areas of unadjustment for important factors such as those who could not take pills. Second, we measured the mRS before the onset based on the estimation from the family members, and thus some measurements of mRS might not be accurate. Therefore, we used the dichotomized mRS before onset for adjustment because mRS <2 was relatively reliable. Third, we had information on statin administration during hospitalization for stroke but did not have information on statins after discharge. Therefore, patients who started or discontinued statins after discharge were not reflected. However, such crossovers might weaken the true effect of statins if they occur equally; thus, the current findings should be considered robust. In addition, we did not follow the changes in low-density lipoprotein cholesterol after admission. Therefore, whether favorable effects of statin administration on clinical outcomes were attributable to the cholesterol-lowering effect or the effect of statins themselves was uncertain. Finally, current findings were observed in Japan, and the maximum doses of statins were nearly half of those in Western countries. Therefore, our findings should also be examined in other settings.

CONCLUSIONS

Statin administration after the onset of acute LVO was significantly associated with better functional outcome and mortality at 90 days. Statins should be administered in patients with acute ischemic stroke, including those with LVO as early as possible, until further well-designed studies have revealed otherwise.

APPENDIX

RESCUE-Japan Registry 2 Investigators

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Author contributions: Uchida and Morimoto had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Uchida, Yoshimura, Sakai, Yamagami, and Morimoto. Acquisition of data: Uchida, Yoshimura, Imamura, Ohara, Sakai, Tanaka, Yamagami, Matsumoto, and Takeuchi. Analysis and interpretation of data: Uchida, Yoshimura, Imamura, Ohara, Sakai, Tanaka, Yamagami, Matsumoto, Takeuchi, and Morimoto. Drafting of the article: Uchida and Morimoto. Critical revision of the article for important intellectual content: Yoshimura, Imamura, Ohara, Sakai, Tanaka, Yamagami, Matsumoto, and Takeuchi. Statistical analysis: Uchida and Morimoto. Funding: Yoshimura and Sakai. Administrative, technical, or material support: Yoshimura, Sakai, and Yamagami. Study supervision: Yoshimura and Sakai.

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