Original Research

Low-dose statin pretreatment improves function and prognosis of recurrent ischemic stroke patients

Chaohua Cui* (iD) **, Shuju Dong*, Ning Chen, Jiajia Bao and Li He**

Abstract

Background: Statins are effective in improving the prognosis of stroke patients. In clinical practice, low-dose statins are often administered to stroke patients in Asian countries but their effects on the prognosis of recurrent ischemic stroke patients are still unclear.
Methods: Data of consecutive recurrent ischemic stroke patients were prospectively collected. The National Institutes of Health Stroke Scale (NIHSS) of admission and discharge and the modified Rankin scale (mRs) of 90 days after stroke onset were adopted to evaluate primary outcomes. Secondary outcomes included the subgroup analysis.
Results: Among 219 patients (mean age 65.41 ± 11.58 years), 150 (68.5%) were male. The low-dose statin group had a higher percentage of milder stroke at admission ($p < 0.001$) and discharge ($p < 0.001$), and favorable functional outcome at 90 days ($p < 0.001$). Univariable regression analysis showed that the use of low-dose statins was inversely associated with higher discharge NIHSS [odds ratio (OR) = 0.36, $p = 0.009$] and higher mRs at 90 days (OR = 0.230, $p < 0.001$). Multivariable logistic regression analysis revealed that low-dose statins also had a significantly inverse association with higher mRs at 90 days (OR = 0.098, $p = 0.049$). According to subgroup analysis, a significant effect was found in the good-persistency subgroup (NIHSS score at discharge: OR = 0.051, $p = 0.004$; mRs score at 3 months: OR = 0.053, $p = 0.005$), but not in the poor-persistency subgroup.
Conclusion: Low-dose statin pretreatment alleviated stroke severity and improved functional outcomes of recurrent stroke patients.

Keywords: low-dose statins, prognosis, recurrent ischemic stroke, severity

Introduction

Stroke is the second most prevalent illness that causes death and disability globally.[1] Statins can effectively lower the occurrence and recurrence risk of stroke,[2,3] and statin pretreatment is related to better neurological function and prognosis in patients with acute ischemic stroke.[4,5]

Previous studies were mostly conducted in western countries and whether evidence could be applied to Asian patients remains uncertain. In western countries, high-dose statins are usually prescribed and recommended in guidelines,[6] whereas in Asian countries, low-dose statins are mostly used in clinic practice. Statins can lower low-density lipoprotein (LDL-C) values and their efficacy is dose dependent;[3] however, it is uncertain whether the effects of low-dose statins are comparable with those of high-dose statins.

At present, low-dose statins are used for the prevention of stroke. The MEGA study revealed that low-dose pravastatin is nonsignificantly related to the incidence of stroke among Japanese.[7] The J-STARS study indicated that low-dose pravastatin reduced the recurrence of atherothrombotic

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stroke in Japanese patients.[8] Our previous retrospective study showed that stroke patients pretreated with low-dose statin in western China had better functional outcomes and prognosis for primary prevention.[9] However, the retrospective study design could not contain data on all risk factors, which may cause bias for statistical results. Further, the study did not include recurrent stroke patients. Therefore, whether low-dose statins exert effects on the functional outcomes of recurrent ischemic stroke patients is uncertain.

The present study investigated the relationship between low-dose statin pretreatment and prognosis for recurrent ischemic stroke patients, and explored whether different risk factors could affect the effects of statins in Asian patients with recurrent stroke.

Methods

Participants
The study was a prospective observational cohort. We consecutively recruited patients of recurrent acute ischemic stroke in the Neurology Department of West China Hospital, Sichuan University. The patients were enrolled from 1 November 2018 to 31 May 2019, and followed up from 1 February 2019 to 31 August 2019. All patients receiving low-dose statin pretreatment were assigned to the statin group. The other eligible patients were assigned to the control group. We estimated the number of participants based on a previous article,[4] which indicated that 180 participants were needed to prove a significant difference. Considering the 10% loss to follow-up, we initially recruited more than 200 patients.

The inclusion criteria were: (1) aged more than 18 years; (2) recurrent stroke [modified Rankin scale (mRs) < 2 before onset]; (3) having received conventional medicine therapy after admission; (4) the statin group: taking low-dose statins for more than 1 month; the control group: no statin use; (5) diagnosis of stroke in accordance with World Health Organization diagnostic criteria with evidence of neuroimage including magnetic resonance imaging or computed tomography.

The exclusion criteria were: (1) unavailable details of statin use; (2) time between admission and onset of more than 7 days; (3) strokes associated with trauma or surgery; (4) having taken other lipid-lowering drugs; (5) having received a

thrombolysis or endovascular treatment; (6) having intracerebral hemorrhage, subarachnoid hemorrhage, coagulopathy, cancer, cardiac failure, severe hepatic or renal dysfunction; and (7) having a history of drug or alcohol abuse.

The study was performed in accordance with the Declaration of Helsinki and the ethical standards of the institutional or national research committee. The study was approved by the Ethics Committee of West China Hospital, Sichuan University with approval number 2019(319). The study did not need consent to participate given the observational nature of the study.

Data collection
Baseline data were collected from electronic clinical records and the structured questionnaires were filled in by patients or their relatives at the patients' admission to the hospital. The data included age, sex, height, weight, systolic pressure, diastolic pressure, history of smoking and drinking, history of diseases such as stroke, hypertension, diabetes, hyperlipidemia, coronary artery disease and atrial fibrillation, and the history of using antiplatelet, antihypertensive, antidiabetics or insulin and anticoagulants drugs. Types of stroke, types of statin, time and persistency of statin use were also collected. We recorded laboratory data including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood glucose, platelet, glutamic-pyruvic transaminase (ALT), creatinine (Cr) and international normalized ratio (INR) at the time of hospital admission.

Definition of risk factors
The definition of vascular risk factor was in accordance with American Heart Association/American Stroke Association 2018 guideline for ischemic stroke.[6] TOAST criteria were adopted for the subtypes of stroke, including large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology.[10] Low-dose statins were defined as atorvastatin 10 mg per day, simvastatin 20 mg per day, or rosuvastatin 5 mg per day. An mRs score of 0–1 was defined as a favorable functional outcome (FFO) and 2–6 as an unfavorable functional outcome. A National Institutes of Health Stroke Scale (NIHSS) score of 0–4 was defined as a milder stroke. Statin use

of more than 6 months previously was defined as a long time. Previous statin use of more than 80% was defined as a good persistency.[11]

Follow-up and outcomes

The primary outcome was the NIHSS score at admission and discharge and an mRs score at 90 days after stroke onset. The secondary outcome was a compound indicator, including the recurrence of stroke, vascular deaths and deaths of all causes. We collected the NIHSS scores at admission and discharge *via* face-to-face interviews. The mRs scores at 90 days after stroke onset were collected *via* telephone or mail. All the adverse events in 90 days from stroke onset were collected *via* telephone or mail. The neurologists who processed the data were unaware of the patient's grouping. All events and outcomes were determined by two experienced neurologists blinded to the patients' condition and grouping.

Statistical analysis

To describe the baseline characteristics, the continuous variables were expressed as mean and standard deviation (SD), and the discrete variables were expressed as frequencies. To compare the difference between the statin group and the control group, a Student's t test was conducted for continuous data following the normal distribution. A nonparametric test (Mann–Whitney U test) was conducted for the continuous data that did not follow a normal distribution. A Chi-square test was conducted for categorized and ranked data. Statistical significance was set at $p < 0.05$.

To analyze the outcome events, we compared the statin group and the control group using a Chi-square test. We analyzed the effects of risk factors on the outcome events using logistic regression methods. First, the relationship between all risk factors and primary outcome was analyzed using univariable logistic regression methods. The eligible factors of multivariable logistic regression included: (1) p values of univariable logistic regression <0.1; and (2) factors with clinical significance. Then we analyzed eligible data using multivariable logistic regression methods. We calculated the value of odds ratios (ORs), 95% confidence intervals (CIs) and p values using logistic regression methods.

In the subgroup analysis, strokes were subdivided as noncardioembolic or cardioembolic. The time of statin use was subdivided as a long or short time, as previously defined. The persistency of statin use was subdivided as good or poor, as previously defined. The effects of the subgroup risk factors on the outcomes were analyzed using univariable logistic regression methods. SPSS 23.0 for Windows was used to process the data.

Results

Patients

The study included 219 eligible patients (114 in the statin group and 105 in the control group), whose baseline data were analyzed. As 11 patients (9 in the statin group and 2 in the control group) were lost in the follow-up, the outcome data of 208 patients (105 in the statin group and 103 in the control group) were acquired. Among the 219 patients (mean age 65.41 ± 11.58 years), 150 (68.5%) were male. The number of cardioembolic patients was 25 (statin group, 12; control group, 13; Table 1). The types of statins included simvastatin ($n = 11$), atorvastatin ($n = 83$), and rosuvastatin ($n = 20$).

Comparing the baseline data of the two groups, the statin group had a higher percentage of coronary heart disease, and antiplatelet and hypertension drug use. Meanwhile, the statin group had a lower percentage of anticoagulation drug use, and lower INR, blood glucose, TC and LDL-C values at admission. No significant difference in other baseline data was found between the two groups (Table 1).

Primary outcome

In the Chi-square test, we found that the statin group had lower admission ($p < 0.001$) and discharge ($p = 0.001$) NIHSS and mRs scores at 90 days ($p < 0.001$) than the control group, and that the differences were statistically significant (Table 2). We also found that the statin group had a higher percentage of milder strokes at discharge ($p = 0.008$) and FFO ($p < 0.001$) at 90 days than the control group, and that the differences were statistically significant (Table 2).

In the univariate logistic regression analysis, we found older age (OR = 1.056, $p = 0.001$), female

Table 1. Baseline characteristics.

Variables	Statins group (*n* = 114)	Control group (*n* = 105)	*P* value*
Age, years, mean (SD)	66.00 (12.31)	64.77 (10.75)	0.434
Male, %	77 (67.5)	73 (69.5)	0.753
Length of stay, days, mean (SD)	6.83 (1.96)	7.12 (2.13)	0.562
BMI, mean (SD)	24.30 (3.09)	24.45 (3.72)	0.759
Systolic blood pressure mmHg, Med (IQR)	138 (129–152)	141 (129–155)	0.342
Diastolic blood pressure mmHg, Med (IQR)	84 (75–92)	82 (70–91)	0.264
Smoking, %	61 (53.5)	45 (42.9)	0.115
Hypertension, %	82 (71.9)	69 (65.7)	0.321
Diabetes mellitus, %	35 (30.7)	28 (26.7)	0.510
Coronary heart disease, %	25 (21.9)	9 (8.6)	0.006
Atrial fibrillation, %	12 (10.5)	13 (12.4)	0.666
Antiplatelet drug, %	103 (90.4)	7 (6.7)	<0.001
Antihypertensive, %	79 (69.3)	54 (51.4)	0.007
Hypoglycemic, %	32 (28.1)	23 (21.9)	0.293
Anticoagulation, %	2 (1.8)	11 (10.5)	0.006
Platelet, mmol/l, mean (SD)	178.27 (49.20)	192.95 (63.83)	0.061
INR, mean (SD)	0.97 (0.11)	1.02 (0.23)	0.029
ALT, mmol/l, mean (SD)	30.66 (31.07)	23.84 (17.95)	0.066
Creatinine, mmol/l, mean (SD)	87.86 (71.39)	79.70 (25.51)	0.397
Glucose, mmol/l, mean (SD)	6.76 (2.97)	7.55 (3.71)	0.017
Triglyceride, mmol/l, mean (SD)	1.41 (0.81)	1.55 (0.96)	0.405
Total cholesterol, mmol/l, mean (SD)	3.68 (0.95)	4.12 (1.06)	0.001
HDL-C, mmol/l, mean (SD)	1.28 (0.36)	1.24 (0.35)	0.480
LDL-C, mmol/l, mean (SD)	1.95 (0.81)	2.37 (0.88)	<0.001
Cardioembolic, %	12 (10.5)	13 (12.4)	0.720

*P value was calculated by Student's *t* test, Chi-square test, or Mann–Whitney *U* test as appropriate.
ALT, glutamic-pyruvic transaminase; BMI, body mass index; HDL-C high-density lipoprotein cholesterol; INR, international normalized ratio; IQR, interquartile range; LDL-C, low-density lipoprotein; Mean, mean value; Med, median value; SD, standard deviation.

Table 2. Admission, discharge NIHSS score and mRs score at 90 days.

Variables	Statin group (n1 = 114, n2 = 105)	Control group (n = 105, n2 = 103)	P value*
Admission NIHSS score, Med (IQR)	1 (0–3)	2 (1–4)	<0.001
Admission NIHSS score 0–4, %	98 (86.0)	81 (77.1)	0.091
Discharge NIHSS score, Med (IQR)	1 (0–2)	1 (0–3)	0.001
Discharge NIHSS score 0–4, %	103 (90.4)	81 (77.1)	0.008
mRs score at 90 days, Med (IQR)	0 (0–1)	1 (0–2)	<0.001
FFO at 90 days, %	93 (88.6)	66 (64.2)	<0.001

*p values were calculated by Mann–Whitney U test and Chi-square test.
IQR, interquartile range; FFO, favorable functional outcome (mRs=0–1); mRs, modified Rankin scale; n1, number of patients at admission and discharge; n2, number of patients at 90 days; NIHSS National Institutes of Health Stroke Scale.

(OR = 2.053, p = 0.045), higher blood glucose value (OR = 1.141, p = 0.005) and cardioembolic stroke (OR = 7.723, p < 0.001) were related to a higher NIHSS score (>4) at admission (Table 3). We also found the use of low-dose statins (OR = 0.36, p = 0.009) were inversely associated with a higher NIHSS score (>4) at discharge. In addition, higher NIHSS at admission (OR = 2.096, p < 0.001), older age (OR = 1.048, p = 0.008), female (OR = 2.397, p = 0.020), higher blood glucose value (OR = 1.117, p = 0.019) and cardioembolic stroke (OR = 6.499, p < 0.001) were related to a higher NIHSS score (>4) at discharge (Table 3). The use of low-dose statins (OR = 0.230, p < 0.001), use of antiplatelet drugs (OR = 0.365, p = 0.004) and smoking (OR = 0.433, p = 0.015) were inversely associated with higher mRs (>1) at 90 days. Higher NIHSS at admission (OR = 1.944, p < 0.001), older age (OR = 1.041, p = 0.009), female (OR = 2.386, p = 0.010), higher blood glucose values (OR = 1.170, p = 0.001), higher TC values (OR = 1.389, p = 0.033), higher LDL-C values (OR = 1.614, p = 0.009), and cardioembolic stroke (OR = 6.338, p < 0.001) were significantly related to higher mRs (>1) at 90 days (Table 3). The other factors were not significantly related to the NIHSS score at admission or discharge or the mRs score at 90 days.

In the multivariable logistic regression analysis, after adjusting the risk factors respectively, we found that older age (OR = 1.045, p = 0.021), higher blood glucose values (OR = 1.144, p = 0.007) and cardioembolic stroke (OR = 4.815, p = 0.001) were still related to a higher NIHSS score (>4) at admission. The higher admission NIHSS (OR = 2.134, p < 0.001) was related to a higher NIHSS score (>4) at discharge. The use of low-dose statins (OR = 0.098, p = 0.049) was inversely associated with a higher mRs score (>1) at 90 days. The higher admission NIHSS (OR = 1.909, p < 0.001) was related to a higher mRs score (>1) at 90 days. The other factors were not significantly related to NIHSS score at admission or discharge or the mRs score at 90 days (Table 4).

Secondary outcome
In the 3-month follow-up, the statin group had two death events (1.8%, one vascular death and one death of other causes) and one recurrent event (0.9%), while the control group had three death events (2.9%, two vascular deaths and one deaths of other causes) and two recurrent events (1.9%). The Chi-square test revealed the statin group had lower death and recurrent rates than the control group, but the differences were not significant (p = 0.171 and p = 0.617, respectively; Table 5).

In the subgroup analysis, we only performed analysis for the NIHSS score at discharge and mRs score at 90 days because using low-dose statins was not significantly related to admission NIHSS score. We found that the use of statins only significantly affected the noncardioembolic patients (NIHSS score at discharge: OR = 0.157, p = 0.001; mRs score at 90 days: OR = 0.090, p < 0.001) rather than the cardioembolic patients (NIHSS score at discharge: p = 0.324; mRs score at 90 days: p = 0.515). A significant effect

Table 3. Univariable regression analysis outcome (1).

Variables	Admission stroke severity (NIHSS score >4)		Discharge stroke severity (NIHSS score >4)	
	OR (95% CI)	*p* value*	OR (95% CI)	*p* value*
Age	1.056 (1.022–1.092)	0.001	1.048 (1.012–1.084)	0.008
Female	2.053 (1.017–4.145)	0.045	2.397 (1.148–5.007)	0.020
Statins	0.551 (0.274–1.107)	0.095	0.36 (0.167–0.779)	0.009
NIHSS of admission	–	–	2.096 (1.675–2.623)	<0.001
Blood glucose	1.141 (1.042–1.251)	0.005	1.117 (1.018–1.225)	0.019
Cardioembolic	7.723 (3.156–18.898)	<0.001	6.499 (2.629–16.064)	<0.001

Univariable regression analysis outcome (2).

Variables	Outcome at 90 days (mRs ⩾2)	
	OR (95% CI)	*p* value*
Age	1.041 (1.010–1.072)	0.009
Female	2.386 (1.232–4.623)	0.010
Statins	0.230 (0.112–0.475)	<0.001
Antiplatelet drug	0.365 (0.184–0.723)	0.004
Admission NIHSS	1.944 (1.589–2.379)	<0.001
Total cholesterol	1.389 (1.027–1.879)	0.033
LDL-C	1.614 (1.130–2.306)	0.009
Smoking	0.433 (0.221–0.849)	0.015
Blood glucose	1.170 (1.065–1.287)	0.001
Cardioembolic	6.338 (2.617–15.348)	<0.001

*p values were calculated by univariate logistic regression.
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; mRs, modified Rankin scale; NIHSS National Institutes of Health Stroke Scale; OR, odds ratio.

(OR = 0.360, p = 0.018) was only found in the atorvastatin subgroup rather than the other statin subgroups (p = 0.121) for NIHSS score at discharge. But for mRs at 90 days, a significant effect was found in the atorvastatin subgroup (OR = 0.240, p = 0.001) as well as the other subgroups (OR = 0.204, p = 0.013). As for the time of statin use, a significant effect was found in both the long-time subgroup (NIHSS score at discharge: OR = 0.497, p = 0.040; mRs score at 90 days: OR = 0.315, p = 0.004) and the short-time subgroup (NIHSS score at discharge: OR = 0.102, p = 0.029; mRs score at 90 days:

OR = 0.059, p = 0.006). A significant effect was found in the good-persistency subgroup (NIHSS score at discharge: OR = 0.110, p < 0.001; mRs score at 90 days: OR = 0.064, p < 0.001), but not in the poor-persistency subgroup (NIHSS score at discharge: p = 0.084; mRs score at 90 days: p = 0.347; Figures 1 and 2).

Discussions

This study aimed to explore the relationship between low-dose statin pretreatment and the function and prognosis of Chinese patients with

Table 4. Multivariable regression analysis outcome (1).

Variables	Admission stroke severity (NIHSS score >4)		Discharge stroke severity (NIHSS score >4)	
	OR (95% CI)	*p* value *	OR (95% CI)	*p* value*
Age	1.045 (1.007–1.086)	0.021	0.987 (0.928–1.050)	0.675
Female	1.787 (0.811–3.936)	0.150	1.167 (0.266–5.111)	0.838
Statins	0.487 (0.221–1.073)	0.074	0.228 (0.046–1.054)	0.058
NIHSS of admission	–	–	2.134 (1.653–2.754)	<0.001
Blood glucose	1.144 (1.038–1.262)	0.007	1.034 (0.905–1.182)	0.621
Cardioembolic	4.815 (1.830–12.667)	0.001	1.604 (0.278–9.261)	0.597

Multivariable regression analysis outcome (2).

Variables	Outcome at 90 days (mRs ⩾2)	
	OR (95% CI)	*p* value *
Age	1.019 (0.971–1.070)	0.441
Female	2.048 (0.464–9.044)	0.344
Statins	0.098 (0.010–0.988)	0.049
Antiplatelet drug	1.318 (0.152–11.415)	0.802
Admission NIHSS	1.909 (1.515–2.405)	<0.001
Total cholesterol	0.457 (0.090–2.315)	0.344
LDL-C	4.510 (0.592–34.339)	0.146
Smoking	1.044 (0.250–4.366)	0.953
Blood glucose	1.084 (0.953–1.233)	0.220
Cardioembolic	2.341 (0.496–11.040)	0.282

*p values were calculated by multivariable logistic regression.
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; mRs, modified Rankin scale; NIHSS National Institutes of Health Stroke Scale; OR, odds ratio.

Table 5. Death and recurrent stroke outcome.

Variables	Statins (*n* = 103)	Control (*n* = 105)	*p* value*
Death *n* (%)	2 (1.8)	3 (2.9)	0.171
Recurrent *n* (%)	1 (0.9)	2 (1.9)	0.617

*p values were calculated by Chi-square test.

recurrent ischemic stroke. We found that patients pretreated with low-dose statins had a lower NIHSS score at admission and discharge and a lower mRs score at 90 days after stroke onset. Low-dose statin pretreatment was related to a milder stroke at discharge and more FFO at
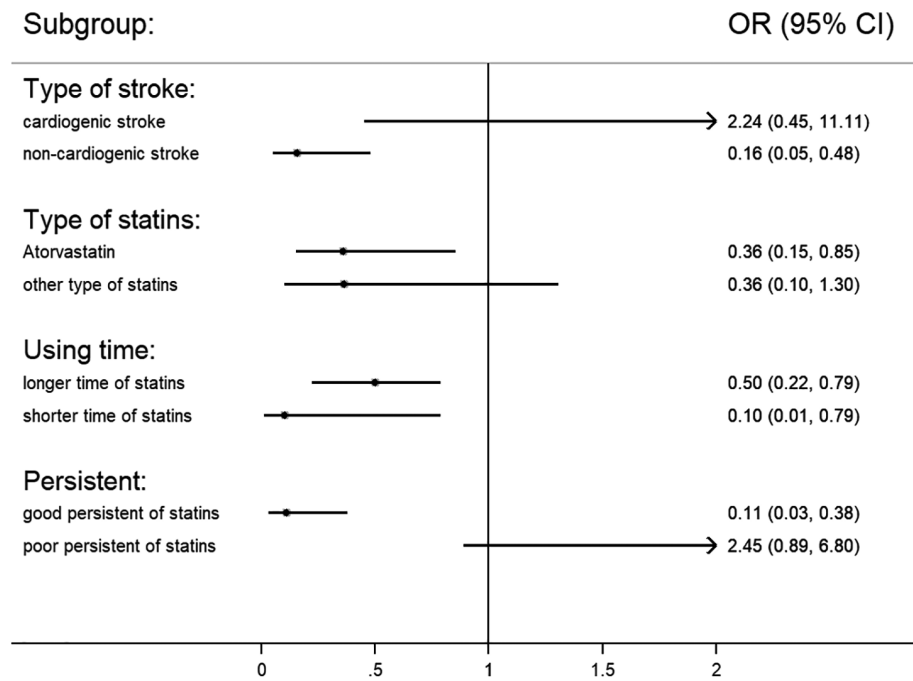
Low dose statins and NIHSS at discharge

Subgroup:		OR (95% CI)
Type of stroke:		
cardiogenic stroke		2.24 (0.45, 11.11)
non-cardiogenic stroke		0.16 (0.05, 0.48)
Type of statins:		
Atorvastatin		0.36 (0.15, 0.85)
other type of statins		0.36 (0.10, 1.30)
Using time:		
longer time of statins		0.50 (0.22, 0.79)
shorter time of statins		0.10 (0.01, 0.79)
Persistent:		
good persistent of statins		0.11 (0.03, 0.38)
poor persistent of statins		2.45 (0.89, 6.80)

Figure 1. Subgroup logistic regression analysis outcome: low-dose statins and NIHSS score at discharge. NIHSS, National Institutes of Health Stroke Scale.

low dose statins and mRs score at 90 days

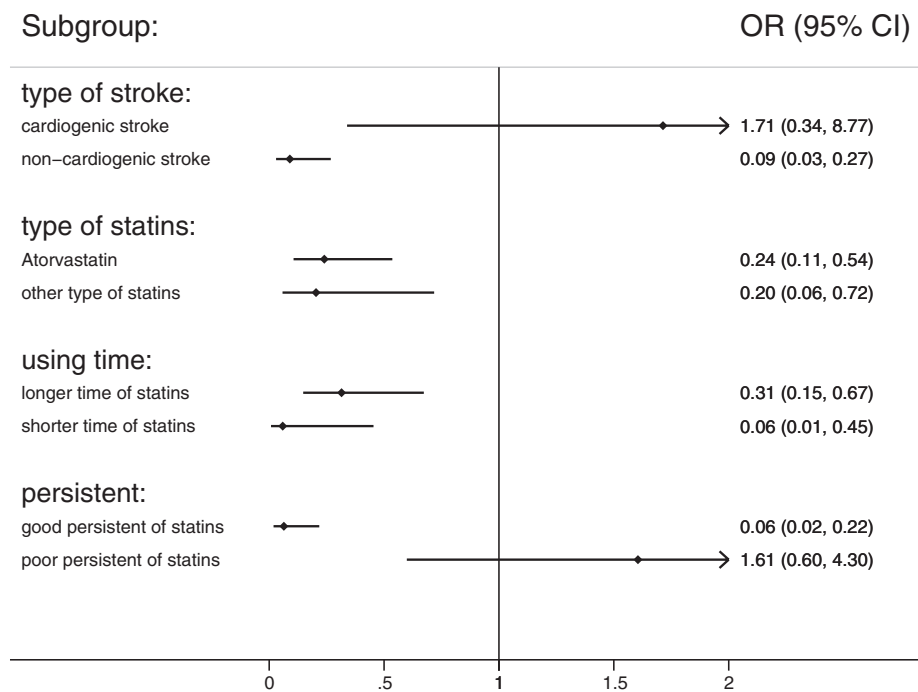| Subgroup:		OR (95% CI)
type of stroke:		
cardiogenic stroke		1.71 (0.34, 8.77)
non–cardiogenic stroke		0.09 (0.03, 0.27)
type of statins:		
Atorvastatin		0.24 (0.11, 0.54)
other type of statins		0.20 (0.06, 0.72)
using time:		
longer time of statins		0.31 (0.15, 0.67)
shorter time of statins		0.06 (0.01, 0.45)
persistent:		
good persistent of statins		0.06 (0.02, 0.22)
poor persistent of statins		1.61 (0.60, 4.30)

Figure 2. Subgroup logistic regression analysis outcome: low-dose statins and mRs score at 90 days. mRs, modified Rankin scale.

90 days. The low-dose statin group had nonsignificantly fewer deaths and recurrent stroke events. Low-dose statins exerted a significant effect on noncardioembolic patients rather than cardioembolic patients. The time or type of statin use made no difference in patients. Meanwhile, low-dose statins did not exert a significant effect on patients with poor persistency.

High-dose statins have been proven to lower LDL-C,[3] therefore, the dose of statins could be an influencing factor for patients with ischemic stroke. However, some studies have found that the dose of statins did not produce a significant difference in patients with stroke.[12,13] We found that low-dose statin group had lower LDL-C and TC values than the control group, although the value of LDL-C did not reach the recommended level.[6] The low-dose statin group had a milder neurological defect and a better functional outcome than the control group. In the logistic regression analysis, we found that low-dose statin use related to lower NIHSS scores at discharge and lower mRs score at 90 days. After adjusting risk factors, the effect of low-dose statins on mRs scores at 90 days still exhibited a statistical significance, suggesting that low-dose statins had a statistically stable power. The results in the present study are consistent with our previous study about low-dose statins in the primary prevention for patients with stroke.[9] Our findings are also in accordance with the studies by Tsivgoulis and Martí-Fàbregas, in which they found that patients using a conventional dose of statins had a higher percentage of favorable functional outcomes 1 month after stroke onset (mRs score ≤1) and a lower NIHSS score at admission.[4,5] The results of the present study indicate that pretreatment of low-dose statins could improve the outcome and prognosis of recurrent ischemic stroke in Asian patients.

We found females had a worse outcome than males. Female patients had a higher NIHSS score at admission. After adjusting the NIHSS score at admission, the effect of low-dose statins on females did not show a significant difference. The results are consistent with our previous study[9] and a meta-analysis.[14] Interestingly, we found that smoking was a protecting factor for FFO at 3 months in the univariate regression analysis. But the effect did not show a significant difference after adjustment for sex and NIHSS score at admission. Because patients who smoked were mainly men, this result can be explained by the male patients' lower NIHSS score at admission.

We found a lower incidences of death and recurrent stroke in the statin group than the control group, although the difference was not statistically significant. Our findings are consistent with previous studies. Hassan's study indicated that using a conventional dose of statins reduced the mortality of patients with ischemic stroke.[15] The J-STARS study also found that low-dose statins decreased the incidence of recurrent stroke in Japanese patients with ischemic stroke, which was consistent with our results.[8] The SPARCL study had a similar conclusion regarding the use of a conventional dose of statins.[3] Our results did not reveal a statistically significant difference, which might be attributed to the small event number and the short follow-up. A study with a longer follow-up is needed to confirm our results in the future.

In subgroup analysis, statins only had a significant effect on noncardioembolic patients, which might be explained by the different pathogenesis.[16] The types and the time of statin use could influence the effect of low-dose statins.[16–18] In the analysis regarding the relationship between different types of statins and severity of stroke, only atorvastatin exerted a significant effect on patients, which could be attributed to the different effects of different types of statins.[17] Another possible explanation is that other types of statin were less used in patients in this study, leading to a lower statistical power. Our study showed that the time of statin use was not related the function and outcome of patients with ischemic stroke. This result is not consistent with a meta-analysis, in which the time of statin use had a significant impact on cardiovascular diseases.[18] We believe that this difference can be explained by the difference between cardiovascular and cerebrovascular diseases. The persistency of statin use made a significant difference in stroke patients. Good persistency had a significant correlation with better function and outcome of patients with ischemic stroke, which was in accordance with the results of Chen's study in patients from Taiwan.[11] The patients with good persistency for statins often have a good persistency for antiplatelet or antihypertensive drugs, so the joint benefit of drugs can enhance the efficacy of statins.

The strength of our study is that the data were collected prospectively, so we could reduce biases and adjust confounding factors to get more accurate results. In addition, analyses of different risk factor subgroups were conducted.

One limitation of our study is that we did not compare the effect of different statin doses, which needs further exploration. Another limitation is that we only conducted a 3-month follow-up, which might have prevented us from finding more events. A study with a longer follow-up is needed. Also, the present study might have a selection bias because we excluded patients on thrombolysis or endovascular treatment for the adjustment of confounding factors. Further research should be conducted to investigate the relationship between low-dose statins and thrombolysis or endovascular treatment.

In conclusion, we found a relationship between low-dose statin pretreatment and favorable functional outcomes for patients with recurrent ischemic stroke. The patients with persistent statin use had a milder stroke and better functional outcomes than patients with discontinuous statin use.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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