Original Article

Low-to-moderate dose statins improve the functional outcome of acute ischemic stroke with conventional medication treatment

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Background: Low-to-moderate dose statins (LMDSs) are more commonly used among Asian acute ischemic stroke (AIS) patients in clinical practice. However, the correlation between the LMDS use and prognosis has not been evaluated in AIS patients with conventional medication treatment alone. This study aimed to investigate the influence of LMDS on the prognosis of AIS patients and how prognosis and potential prognostic factors interact with different statin doses.

Methods: This retrospective cohort study included AIS patients who were admitted within 7 days after symptom onset and received conventional medication treatment alone from November 2019 to November 2020 in the Neurology, Department of West China Hospital, Sichuan University. From a total of 782 initial patients, a final cohort of 327 patients was included in the study. These patients were divided into three groups based on statin doses: non-statin (48 patients), LMDS (152 patients), and high-dose statin (HDS) (127 patients). The follow-up period was 3 months after the onset of stroke and the primary outcome was defined as a modified Rankin scale (mRS) score of 0 to 2 at 3 months, secondary outcomes were hemorrhagic transformation (HT) and death within 3 months. Stratified analysis was also conducted to test the robustness of the relationship between the use of different statin doses and functional outcomes in various subgroups.

Results: Compared with non-statin therapy, both LMDS therapy and HDS therapy were associated with good functional outcomes [odds ratio (OR) =3.68, 95% confidence interval (CI): 1.13–12.01, P=0.0309; OR =3.45, 95% CI: 1.06–11.26, P=0.0402, respectively] and a lower risk of HT (OR =0.30, 95% CI: 0.11–0.86, P=0.0253; OR =0.36, 95% CI: 0.13–0.99, P=0.0488, respectively). However, there was no significant difference in all-cause death within 3 months among the three groups (OR =0.84, 95% CI: 0.29–2.46, P=0.7468; OR =0.76, 95% CI: 0.26–2.22, P=0.6104). Additionally, no significant differences were observed between LMDS therapy and HDS therapy regarding good functional outcomes at 3 months (OR =0.94, 95% CI: 0.50–1.77, P=0.8411) and the occurrence of HT (OR =1.19, 95% CI: 0.47–3.02, P=0.7093). The results of the relationship between different statin doses and 3-month good functional outcome were consistent after interaction tests.

Conclusions: Our findings provide evidence for the benefit and safety of LMDS therapy in AIS patients with medication treatment alone. LMDS therapy is associated with favorable impacts on 3-month functional outcomes and a reduced risk of HT compared to non-statin therapy. There were no significant differences in achieving 3-month good functional outcome, the risk of HT or death within 3 months were observed between LMDS and HDS therapy in our study. Further studies with prospective design and larger sample sizes are necessary to validate our results.

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Introduction

Acute ischemic stroke (AIS) is the second leading cause of disability and death worldwide (1,2). Despite advances and developments in reperfusion treatments for AIS, the years of life lived with disability (YLDs) from AIS remains high (2). However, only approximately 20% of AIS patients are able to undergo hyperacute reperfusion therapies, such as intravenous thrombolysis (IVT) and endovascular treatment (EVT), due to the narrow therapeutic time window and limited medical resources (3-7). Hence, most of the patients with AIS received conventional medication treatment alone in the real world (5-7).

Statins are one of the most vital medications in both primary and secondary prevention of arteriosclerotic cardiovascular disease (ASCVD), owing to their pleiotropic effects, including the attenuation of adverse cardiovascular events, anti-inflammatory effects, and enhancement of endothelial function (8). Since Asians are more responsive to the lipid-lowering effects of statins than non-Asians which may be attributed to the differences in dosage effects, drug metabolism, body size, and dietary habits, low-to-moderate dose statins (LMDSs) are more commonly prescribed among ASCVD patients in daily clinical practice, particularly in Asia (9-14). Evidence has demonstrated that the efficacy of LMDS for cardiovascular disease (CVD) patients in Asia, such as GOALLS study, STATT study, and RAEL-CAD study (9,13-15). Similarly, in regards to AIS, our previous studies have indicated that AIS patients after reperfusion therapies treated with a low-dose statin (LDS) in west China had a better prognosis compared with non-statin (16-18). However, the correlation between LMDS use and prognosis has not been evaluated in AIS patients with conventional medication treatment alone.

Therefore, we performed the retrospective cohort study to evaluate the effect of different statin doses on the prognosis of AIS patients with conventional medication treatment alone. Furthermore, how prognosis and potential prognostic factors interact with different statin doses was also explored in this cohort. We present this article in accordance with the STROBE reporting checklist (19) (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-77/rc).

Highlight box

Key findings

- LMDS therapy is associated with favorable effects on 3-month functional outcomes and a reduced risk of HT compared to non-statin therapy in AIS patients with conservative medication therapy alone.

What is known and what is new?

- LMDS therapy after AIS onset was beneficial for the prognosis of AIS patients receiving conservative medication therapy alone, compared to non-statin therapy. However, our study did not find significant differences between LMDS and HDS therapy.
- Our findings provide evidence for the benefit and safety of LMDS therapy in AIS patients receiving conservative medication therapy alone.

What is the implication, and what should change now?

- These findings suggest that the benefits of LMDS and HDS therapy appear to be similar in AIS patients receiving conservative medication therapy alone. Further studies with larger sample sizes and prospective study designs are needed to validate our results.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of West China Hospital, Sichuan University [No. 2019(319)], and the need for obtaining patient informed consent was waived since all data were retrospectively collected and individual information was not disclosed.

Study design and patient population

We performed a retrospective cohort study. Consecutive patients with AIS were screened and selected from our AIS

registry program of in the Neurology, Department of West China Hospital, Sichuan University. The diagnosis of AIS was made according to World Health Organization stroke diagnostic criteria with neuroimaging evidence, including magnetic resonance imaging or computed tomography. From November 2019 to November 2020, a total of 782 AIS patients were prescreened for enrollment. Patients were selected if they met all of the following criteria: (I) aged 18 years or older; (II) admitted to the hospital within 7 days of stroke onset; (III) received conventional medication treatment alone without reperfusion therapies such as IVT or EVT; and (IV) had baseline laboratory investigations. The exclusion criteria were as follows: (I) modified Rankin scale (mRS) score was ≥2 before onset; (II) infection within 2 weeks prior to AIS onset; (III) recent major trauma or surgery, hematological diseases, coagulopathy, cancer, cardiac failure, severe hepatic or renal dysfunction, a history of drug or alcohol abuse; (IV) received other lipid-lowering drugs; and (V) unavailable details of statin use or incomplete data. Finally, 327 patients fulfilled the inclusion criteria and were included in the study (*Figure 1*).

Data collection and definitions

For each patient, we recorded demographics, vascular risk factors, admission baseline National Institutes of Health Stroke Scale (NIHSS) score, and medication treatment before and after AIS onset. Stroke subtype was evaluated by Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (20). We defined hemorrhagic transformation (HT) as any degree of hyperdensity within the area of low attenuation in follow-up CT scans within 7 days of admission. The classification of HT was based on the European Cooperative Acute Stroke Study (ECASS) criteria, which divide HT into four subtypes (21). Statin treatment after admission was defined by any type or dosage of statin administered after the onset of AIS, regardless of whether they had received statins before AIS onset (22). The exposed group was defined as patients who received statin treatment after admission, while the control group was composed of patients who did not receive statin treatment after stroke onset. For the exposed group, the high-dose statin (HDS) was defined as atorvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin >20 mg per day, and rosuvastatin at a dose >10 mg per day (23). LMDS was defined as atorvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin ≤20 mg per day, and rosuvastatin ≤10 mg per day (24). Stroke severity was assessed with the NIHSS score on admission, with scores of 0 to 4 referring to a milder stroke, 5 to 15 referring to a moderate stroke, and 16 to 40 referring to a severe stroke, as previously described (16). Body mass index (BMI) thresholds were as follows (25): <18.5 kg/m^2 for underweight, 18.5 to 22.9 kg/m^2 for normal weight, 23.0 to 27.4 kg/m^2 for overweight, 27.5 to 32.4 kg/m^2 for obese, or ≥32.5 kg/m^2 for severely obese. We used the terms 'elderly' to encompass those patients aged 65–79 years, and 'very old' to encompass those patients aged ≥80 years, as previously described (26).

All patients had blood samples obtained within 24 hours after admission in accordance with the standard institutional guidelines. Complete blood counts, serum lipids, and serum glucose were recorded.

Follow-up and outcomes

The mRS at 3 months was assessed through a face-to-face interview or via telephone follow-up with the patients, their relatives, or their general practitioners by a certified neurologist who was blinded to the clinical information. The follow-up period was 3 months after the onset of stroke, with a window period of 7 days. A good functional outcome was defined as a mRS score of 0 to 2 at 3 months. A favorable functional outcome was defined as a mRS score of 0 to 1 at 3 months. Additional outcomes included the occurrence of HT after AIS at 3 months, as well as the incidence of all-cause death within 3 months from AIS onset.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software (version 22; IBM Corp, Armonk, NY, USA), and the statistical package R (The R Foundation; https://www.r-project.org; version 4.2.0).

We described categorical and ordinal variables as frequencies and percentages, respectively, and quantitative continuous variables as the mean ± standard deviation (SD) or median [interquartile range (IQR)]. For between-group comparisons of demographics and clinical variables, one-way analysis of variance (ANOVA) was used for normally distributed measurement data. Subsequently, we employed both univariate and multivariate logistic regression to explore which variables were possibly associated with the functional outcomes. Variables with P values less than or equal to 0.1 in the univariate regression were included in a further multivariate logistic analysis. The odds ratio (OR)

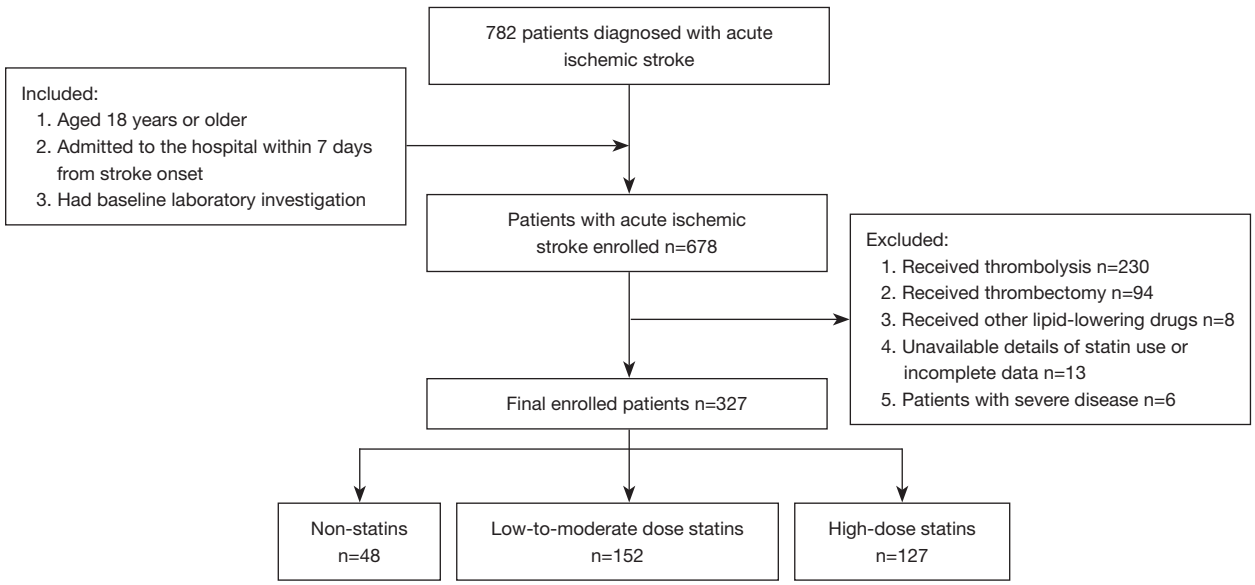

Figure 1 Flowchart of patient enrollment.

with 95% confidence interval (CI) was estimated to evaluate the effects.

Stratified analysis was also conducted to test the relationship between statin use and functional outcomes in various subgroups (age, gender, BMI, stroke subtype, stroke severity, pretreatment with statins, anticoagulant treatment after admission, smoking status, and HT).

Furthermore, we conducted interaction tests to evaluate the heterogeneity in the effect of different statin doses on the 3-month good functional outcome across all subgroup risk factors. The potential interactions between the effects of statins and the various subgroups on the primary outcome were explored using multivariate logistic regression. Each statin group by subgroup interaction was assessed by examining the change in log likelihood when including the interaction term into a logistic regression model that incorporated the different statin doses, subgroup main effects, and major adjustment variables. The statistical significance of the interactions was assessed by the likelihood ratio test. For factors with more than two levels, the test aimed to examine the null hypothesis that all levels shared the same underlying ORs, compared to the alternative hypothesis of a linear trend in ORs (if the levels were ordered) or simply the inequality of ORs (if the levels were not ordered).

In all statistical analyses, a two-sided P value of less than 0.05 was considered statistically significant.

Results

Clinical demographics

For the 782 patients in the register study, 327 patients (male: 181; female: 146) were enrolled in our final cohort (*Figure 1*). The mean age of the patient cohort was 68.98±14.26 years and the average BMI was 23.71± 3.60 kg/m^2. The median baseline NIHSS score and onset to admission time were 9 [4–16] and 281 [155–544] min, respectively. Almost half of the patients (48.93%) had a good functional outcome (mRS 0–2 at 3 months) and 117 of 327 patients (35.78%) died within 3 months. The overall risks of HT and death in the present study were 11.62% and 18.35%, respectively. The demographic data, clinical characteristics, laboratory index, and outcomes are described in *Table 1*.

Of the total patients, 279 patients (85.32%) received statin therapy after AIS onset. The patients were stratified into 3 groups according to different statin doses (non-statin use, LMDS, HDS). There were 48 patients in the non-statin group, 152 patients in the LMDS group, and 127 patients in the HDS group. Patients treated with LMDS and HDS had lower baseline NIHSS scores, higher proportion of patients with AF, higher proportion of antiplatelet treatment after admission, and better 3-month functional outcomes compared with patients who did not

Table 1 Baseline characteristics of the study population and study outcomes

Parameters	Total (n=327)	Non-statin (n=48)	Statin therapy		P value
			LMDS (n=152)	HDS (n=127)	
Demographic characteristics					
Age (years)	68.98±14.26	65.96±17.81	71.12±13.38	67.57±13.51	0.088
Gender					0.083
Female	146 (44.65)	23 (47.92)	76 (50.00)	47 (37.01)	
Male	181 (55.35)	25 (52.08)	76 (50.00)	80 (62.99)	
Blood pressure (mmHg)					
SBP	147.14±25.15	138.98±23.76	146.45±24.21	151.05±26.13	0.050
DBP	86.17±16.70	82.19±12.20	85.86±16.36	88.06±18.32	0.154
BMI (kg/m^2)	23.71±3.60	24.09±4.54	23.54±3.70	23.74±3.18	0.851
Preexisting conditions					
Hypertension	180 (55.05)	22 (45.83)	93 (61.18)	65 (51.18)	0.094
Diabetes mellitus	51 (15.60)	7 (14.58)	28 (18.42)	16 (12.60)	0.401
AF	94 (28.75)	17 (35.42)	53 (34.87)	24 (18.90)	0.007*
Coronary heart disease	42 (12.84)	3 (6.25)	24 (15.79)	15 (11.81)	0.206
Dyslipidemia	10 (3.06)	0 (0.00)	5 (3.29)	5 (3.94)	0.392
History of stroke	65 (19.88)	12 (25.00)	36 (23.68)	17 (13.39)	0.063
Current smoking	116 (35.47)	13 (27.08)	55 (36.18)	48 (37.80)	0.405
Medication treatment before onset					
Antiplatelets	33 (10.09)	7 (14.58)	17 (11.18)	9 (7.09)	0.282
Anticoagulants	32 (9.79)	11 (22.92)	16 (10.53)	5 (3.97)	<0.001*
Statins	25 (7.65)	7 (14.58)	14 (9.21)	4 (3.15)	0.024*
Antihypertensive	112 (34.25)	14 (29.17)	62 (40.79)	36 (28.35)	0.067
Hypoglycemic	31 (9.48)	2 (4.17)	23 (15.13)	6 (4.72)	0.005*
Clinical variables					
Baseline NIHSS	9 [4–16]	16 [12–22]	8 [3–14]	8 [3–15]	<0.001*
TOAST					<0.001*
LAO	112 (34.25)	12 (25.00)	43 (28.29)	57 (44.88)	
CE	143 (43.73)	26 (54.17)	72 (47.37)	45 (35.43)	
SAO	26 (7.95)	0 (0.00)	22 (14.47)	4 (3.15)	
OE	10 (3.06)	2 (4.17)	1 (0.66)	7 (5.51)	
UE	36 (11.01)	8 (16.67)	14 (9.21)	14 (11.02)	
Onset to admission time (min)	281 [155–544]	240 [152–320]	276 [134–557]	300 [180–642]	0.080

Table 1 (*continued*)

Table 1 (*continued*)

Parameters	Total (n=327)	Non-statin (n=48)	Statin therapy		P value
			LMDS (n=152)	HDS (n=127)	
Laboratory parameters					
RBC	5.76±24.08	4.32±0.70	4.40±0.65	7.93±38.56	0.119
Platelet ($\times10^9$/L)	168.2±64.2	159.88±70.98	169.32±64.01	159.83±56.37	0.576
INR	1.12±1.44	1.16±0.36	1.22±2.10	0.99±0.14	<0.001*
TG (mmol/L)	2.09±10.06	1.21±0.83	1.58±1.49	3.01±16.01	0.026*
TC (mmol/L)	6.11±26.88	4.06±1.32	4.28±1.14	9.07±43.06	0.152
LDL (mmol/L)	2.42±0.94	2.23±1.19	2.47±0.90	2.44±0.89	0.050
HDL (mmol/L)	1.40±0.61	1.45±0.60	1.41±0.70	1.37±0.49	0.717
Albumin (g/L)	40.37±8.99	41.04±7.77	40.11±7.52	40.43±10.89	0.050
Serum glucose (mmol/L)	8.39±5.16	7.97±3.63	8.43±5.49	8.51±5.26	0.945
Medication treatment after admission					
Antiplatelets	247 (75.54)	14 (29.17)	125 (82.24)	108 (85.04)	<0.001*
Anticoagulants	64 (19.57)	11 (22.92)	30 (19.74)	23 (18.11)	0.773
Antihypertensive	145 (44.34)	21 (43.75)	68 (44.74)	56 (44.09)	0.990
Hypoglycemic	54 (16.51)	6 (12.50)	28 (18.42)	20 (15.75)	0.602
Outcomes					
Good functional outcome (mRS 0–2 at 3 months)	160 (48.93)	9 (18.75)	81 (53.29)	70 (55.12)	<0.001*
Favorable functional outcome (mRS 0–1 at 3 months)	117 (35.78)	6 (12.50)	60 (39.47)	51 (40.16)	0.001*
HT	38 (11.62)	15 (31.25)	11 (7.24)	12 (9.45)	<0.001*
Death within 3 months	60 (18.35)	17 (35.42)	26 (17.11)	17 (13.39)	0.003*

Data are presented as mean ± SD, n (%), or median [IQR]. *, P<0.05. LMDS, low-to-moderate dose statin; HDS, high-dose statin; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; AF, atrial fibrillation; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAO, large atherosclerosis occlusion; CE, cardioembolic; SAO, small-artery occlusion; OE, other etiology; UE, undetermined etiology; RBC, red blood cell; INR, international normalized ratio; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; mRS, modified Rankin scale; HT, hemorrhagic transformation; SD, standard deviation; IQR, interquartile range.

receive statin therapy, whereas no differences were found in age, gender, baseline blood pressure, or BMI level (*Table 1*).

Independent influencing factors for functional outcome

Good functional outcome (mRS 0–2) occurred in 160 (48.93%) patients during follow-up. In the univariable logistic regression analysis, age (OR =0.96, 95% CI: 0.94–0.98, P<0.0001), gender (OR =2.82, 95% CI: 1.79–4.43, P<0.0001), history of atrial fibrillation (AF) (OR =0.35, 95% CI: 0.21–0.58, P<0.0001), history of coronary artery disease (CAD) (OR =0.48, 95% CI: 0.24–0.94, P=0.0330), current smoking (OR =1.94; 95% CI: 1.22–3.07, P=0.0049), baseline NIHSS (OR =0.81, 95% CI: 0.77–0.85, P<0.0001), cardioembolic (CE) stroke subtype (OR =0.34, 95% CI: 0.20–0.57, P<0.0001), antiplatelet use after admission (OR =2.13, 95% CI: 1.26–3.60, P=0.0046), statin use after admission (OR =5.11, 95% CI: 2.39–10.95, P<0.0001),

and HT (OR =0.16, 95% CI: 0.07–0.41, P<0.0001) were significantly associated with good functional outcome. After adjusting for potential confounders (model 1: age, gender, TOAST, onset to admission time, history of AF, history of CAD, current smoking, baseline NIHSS; model 2: model 1 adding to statin therapy after admission, antiplatelet therapy after admission, HT), the multivariate logistic regression analysis showed that prior antiplatelet treatment (OR =3.09, 95% CI: 1.09–8.72, P=0.0333), anticoagulant treatment after admission (OR =2.68, 95% CI: 1.14–6.32, P=0.0241), and statin treatment after admission (OR =3.56, 95% CI: 1.14–11.12, P=0.0287) were positively associated with good functional outcome. In contrast, age (OR =0.96, 95% CI: 0.93–0.98, P=0.0006), baseline NIHSS (OR =0.82, 95% CI: 0.78–0.87, P<0.0001), baseline low-density lipoprotein (LDL) (OR =0.68, 95% CI: 0.49–0.96, P=0.0268) and HT (OR =0.26, 95% CI: 0.08–0.84, P=0.0243) were negatively associated with good functional outcome. After dividing patients into three groups of different statin doses (the non-statin group, the LMDS group, and the HDS group), both the LMDS group (OR =3.68, 95% CI: 1.13–12.01, P=0.0309) and the HDS group (OR =3.45, 95% CI: 1.06–11.26, P=0.0402) were independently associated with good functional outcome, compared with the non-statin group (*Table 2*). Additionally, we encoded LMDS as a dummy variable to allow for a comparison with the HDS group and found that the HDS group had a reduced likelihood of achieving favorable functional outcomes at 3-month when compared to the LMDS group. However, this difference was not statistically significant (OR =0.94, 95% CI: 0.50–1.77, P=0.8411) (Table S1).

Interaction of statin doses and good functional outcome

Further stratified analysis and interaction tests were used to investigate the potential impact of different statin doses on good functional outcome between various subgroups (*Figure 2*). The proportion of good functional outcome at 3 months in patients with LMDS after admission was 35.53% for females *vs.* 71.05% for males, compared with HDS was 46.81% for females and 60.00% for males, P=0.0707 for interaction. In patients with large atherosclerosis occlusion (LAO), 65.12% of patients had good functional outcome with LMDS, and 66.67% had good functional outcome with HDS. In patients with CE, 34.72% had good functional outcome at 3 months with LMDS therapy, whereas 42.22% were in the HDS group.

After adjusting for potential confounders, there were no significant interactions between statin dose and 3-month good functional outcome between various subgroups (age classes, gender, BMI level, stroke severity, stroke subtypes, HT, smoking status, prior antiplatelet treatment, anticoagulants treatment after admission) at the P<0.05 level. The results of the relationship between different statin doses and good functional outcome were consistent after the interaction test, showing that our results for different statin doses were stable.

Correlation between secondary outcomes and statin therapy

As *Table 1* shown, the secondary outcomes were different among the non-statin group, the LMDS group, and the HDS group. There was a 31.25% risk of HT in those patients without statin treatment, whereas there was a 7.24% and 9.45% risk of HT in the LMDS and HDS, respectively, at 3 months (P<0.001). Meanwhile, the all-course mortality was higher in the non-statin group (35.42%) than in the LMDS group (17.11%) and HDS group (13.39%), P=0.003 (*Table 1*). After adjusting for potential confounders, we found that LMDS therapy and HDS therapy at admission were related to a reduced risk of HT (OR =0.30, 95% CI: 0.11–0.86, P=0.0253; OR =0.36, 95% CI: 0.13–0.99, P=0.0488, respectively) (*Table 3*). After encoding LMDS as a dummy variable, it was observed that the likelihood of HT occurrence was comparatively higher in the HDS group than the LMDS group. However, this difference did not reach statistical significance (OR =1.19, 95% CI: 0.47–3.02, P=0.7093) (Table S1). We did not find any significant relationship between statin therapy at admission and death within 3 months in multivariate logistic regression analysis (*Table 3*).

Discussion

In this retrospective cohort study, we aimed to investigate the correlation between LMDS treatment and the prognosis of AIS with medication treatment alone. Our results suggested that statin therapy after AIS onset was beneficial for the prognosis of AIS patients, and the benefits of LMDS and HDS therapy appear to be similar in AIS patients receiving conservative medication therapy. The relationship between different statin doses and good functional outcome were consistent across various subgroups in interaction tests.

Statins are first-line drugs worldwide for decreasing ASCVD events in both primary and secondary prevention.

Table 2 Univariate and multivariate regression analysis of influencing factors for good functional outcome (mRS 0–2) at 3 months

Good functional outcome (mRS 0–2) at 3 months	N=160	Univariate regression, OR (95% CI), P value	Multivariate regression, OR (95% CI), P value	
			Model 1	Model 2
Demographic characteristics				
Age (years)	65.03±14.83	0.96 (0.94, 0.98), <0.0001*	0.96 (0.94, 0.99), 0.0016*	0.96 (0.93, 0.98), 0.0006*
Male	109 (68.12)	2.82 (1.79, 4.43), <0.0001*	1.76 (0.86, 3.63), 0.1227	1.90 (0.90, 4.04), 0.0945
Baseline blood pressure (mmHg)				
SBP	148.50±25.26	1.00 (1.00, 1.01), 0.3377	1.00 (0.99, 1.01), 0.7820	1.00 (0.99, 1.01), 0.7297
DBP	87.19±15.57	1.01 (0.99, 1.02), 0.2841	1.00 (0.98, 1.02), 0.8208	1.00 (0.98, 1.01), 0.6503
BMI (kg/m^2)	23.86±3.05	1.02 (0.95, 1.10), 0.5105	0.94 (0.86, 1.04), 0.2403	0.94 (0.85, 1.04), 0.2433
Preexisting conditions				
Hypertension	82 (51.25)	0.74 (0.48, 1.15), 0.1772	0.89 (0.49, 1.62), 0.7096	0.82 (0.44, 1.50), 0.5129
Diabetes mellitus	20 (12.50)	0.63 (0.34, 1.15), 0.1331	0.73 (0.33, 1.58), 0.4212	0.68 (0.31, 1.50), 0.3364
AF	29 (18.13)	0.35 (0.21, 0.58), <0.0001*	0.83 (0.36, 1.91), 0.6557	0.82 (0.34, 1.97), 0.6603
Coronary heart disease	14 (8.75)	0.48 (0.24, 0.94), 0.0330*	1.27 (0.50, 3.21), 0.6135	1.04 (0.42, 2.62), 0.9274
Dyslipidemia	5 (3.13)	1.05 (0.30, 3.68), 0.9452	0.34 (0.07, 1.70), 0.1905	0.34 (0.07, 1.75), 0.1971
History of stroke	27 (16.88)	0.69 (0.40, 1.19), 0.1843	0.89 (0.43, 1.85), 0.7600	0.82 (0.39, 1.73), 0.6098
Current smoking	69 (43.13)	1.94 (1.22, 3.07), 0.0049*	0.83 (0.39, 1.74), 0.6198	0.69 (0.32, 1.49), 0.3432
Medication treatment before onset				
Antiplatelets	19 (11.88)	1.47 (0.71, 3.05), 0.2969	3.08 (1.10, 8.64), 0.0327*	3.09 (1.09, 8.72), 0.0333*
Anticoagulants	15 (9.38)	0.91 (0.44, 1.88), 0.7928	1.17 (0.42, 3.30), 0.7613	1.45 (0.45, 4.65), 0.5344
Statins	14 (8.75)	1.36 (0.60, 3.09), 0.4632	2.85 (0.90, 9.03), 0.0745	3.22 (0.99, 10.52), 0.0530
Antihypertensive	49 (30.63)	0.73 (0.46, 1.15), 0.1768	0.75 (0.41, 1.38), 0.3529	0.72 (0.39, 1.35), 0.3101
Hypoglycemic	14 (8.75)	0.85 (0.40, 1.78), 0.6594	0.68 (0.26, 1.74), 0.4173	0.63 (0.24, 1.66), 0.3509
Clinical variables				
Baseline NIHSS	14.0 [9.0–19.8]	0.81 (0.77, 0.85), <0.0001*	0.81(0.77,0.85), <0.0001*	0.82 (0.78, 0.87), <0.0001*
TOAST				
LAO	67 (41.88)	–	–	–
CE	48 (30.00)	0.34 (0.20, 0.57), <0.0001*	1.00 (0.44, 2.26), 0.9924	1.06 (0.44, 2.56), 0.9029
SAO	19 (11.88)	1.82 (0.71, 4.69), 0.2131	0.97 (0.32, 2.95), 0.9618	0.89 (0.29, 2.69), 0.8327
OE	7 (4.38)	1.57 (0.38, 6.38), 0.5306	0.66 (0.08, 5.64), 0.7055	0.82 (0.08, 8.13), 0.8635
UE	19 (11.88)	0.75 (0.35, 1.60), 0.4569	0.55 (0.21, 1.45), 0.2271	0.55 (0.20, 1.50), 0.2435
Onset to admission time (min)	240.0 [150.0–357.5]	1.00 (1.00, 1.00), 0.0587	1.00 (1.00, 1.00), 0.4974	1.00 (1.00, 1.00), 0.3300

Table 2 (*continued*)

Table 2 (*continued*)

Good functional outcome (mRS 0–2) at 3 months	N=160	Univariate regression, OR (95% CI), P value	Multivariate regression, OR (95% CI), P value	
			Model 1	Model 2
Laboratory parameters				
RBC	4.54±0.65	0.99 (0.97, 1.02), 0.5385	0.77 (0.48, 1.25), 0.2943	0.72 (0.43, 1.18), 0.1894
Platelet ($\times10^9$/L)	169.97±64.98	1.00 (1.00, 1.01), 0.1049	1.00 (0.99, 1.00), 0.4709	1.00 (0.99, 1.00), 0.2751
INR	1.02±0.18	0.36 (0.11, 1.15), 0.0848	0.51 (0.11, 2.36), 0.3885	0.60 (0.09, 3.90), 0.5897
TG (mmol/L)	1.58±1.22	0.99 (0.94, 1.03), 0.4934	0.95 (0.75, 1.20), 0.6547	0.93 (0.70, 1.24), 0.6144
TC (mmol/L)	4.91±6.93	1.00 (0.98, 1.01), 0.4964	0.99 (0.98, 1.00), 0.1869	0.99 (0.98, 1.01), 0.3582
LDL (mmol/L)	2.44±0.87	1.03 (0.81, 1.31), 0.8115	0.72 (0.52, 1.00), 0.0474*	0.68 (0.49, 0.96), 0.0268*
HDL (mmol/L)	1.35±0.66	0.74 (0.49, 1.12), 0.1562	0.95 (0.59, 1.53), 0.8370	0.98 (0.60, 1.59), 0.9260
Albumin (g/L)	41.19±7.74	1.02 (1.00, 1.05), 0.1119	1.02 (0.99, 1.05), 0.2252	1.02 (0.98, 1.05), 0.3138
Serum glucose (mmol/L)	8.66±6.44	1.02 (0.98, 1.07), 0.3759	1.05 (0.98, 1.13), 0.1450	1.04 (0.97, 1.12), 0.2680
Medication treatment after admission				
Antiplatelets	132 (82.50)	2.13 (1.26, 3.60), 0.0046*	1.28 (0.63, 2.60), 0.4995	0.79 (0.35, 1.77), 0.5733
Anticoagulants	38 (23.75)	1.69 (0.97, 2.94), 0.0639	2.72 (1.20, 6.19), 0.0168*	2.68 (1.14, 6.32), 0.0241*
Statins	151 (94.38)	5.11 (2.39, 10.95), <0.0001*	3.35 (1.21, 9.26), 0.0196*	3.56 (1.14, 11.12), 0.0287*
Statin dose				
Non-statin	9 (5.63)	–	–	–
LMDS	81 (50.63)	4.94 (2.24, 10.91), <0.0001*	3.53 (1.22,10.26), 0.0203*	3.68 (1.13, 12.01), 0.0309*
HDS	70 (43.75)	5.32 (2.38, 11.90), <0.0001*	3.18 (1.10,9.23), 0.0329*	3.45 (1.06, 11.26), 0.0402*
Antihypertensive	73 (45.63)	1.11 (0.72, 1.71), 0.6478	1.59 (0.88, 2.88), 0.1242	1.76 (0.95, 3.28), 0.0726
Hypoglycemic	23 (14.38)	0.74 (0.41, 1.33), 0.3090	0.72 (0.33, 1.58), 0.4131	0.69 (0.31, 1.54), 0.3599
HT	6 (3.75)	0.16 (0.07, 0.41), <0.0001*	0.26 (0.08, 0.79), 0.0176*	0.26 (0.08, 0.84), 0.0243*

Model 1 adjusted for age, gender, stroke subtypes, history of AF, history of CAD, smoking status, baseline NIHSS; model 2 adjusted for model 1 adding HT, antiplatelets treatment after admission, statins treatment after admission. *, P<0.05. mRS, modified Rankin scale; OR, odd ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; AF, atrial fibrillation; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAO, large atherosclerosis occlusion; CE, cardioembolic; SAO, small-artery occlusion; OE, other etiology; UE, undetermined etiology; RBC, red blood cell; INR, international normalized ratio; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LMDS, low-to-moderate dose statin; HDS, high-dose statin; HT, hemorrhagic transformation; CAD, coronary artery disease.

There were differences in clinical practice for statin therapy intensity and dose for cardiovascular disease prevention. The American College of Cardiology/American Heart Association 2013 guideline (2013 ACC/AHA guideline) has recommended using high- and moderate-intensity statins. However, since there is a racial difference in the plasma LDL cholesterol (LDL-C) reduction response and the risk of statin toxicity (Asian have higher blood statin levels) between Asians and Caucasians, LMDS is commonly prescribed among Chinese AIS patients except for those patients with a very high risk of ASCVD (13,27,28). Therefore, whether LMDS therapy has similar beneficial effects on AIS patients with HDS therapy deserves further attention. Notably, our previous studies have demonstrated that LDS could improve functional outcomes in AIS patients treated with thrombolysis and thrombectomy (16,17). In the present study, we provided the available evidence of the benefit of LMDS in Chinese AIS patients

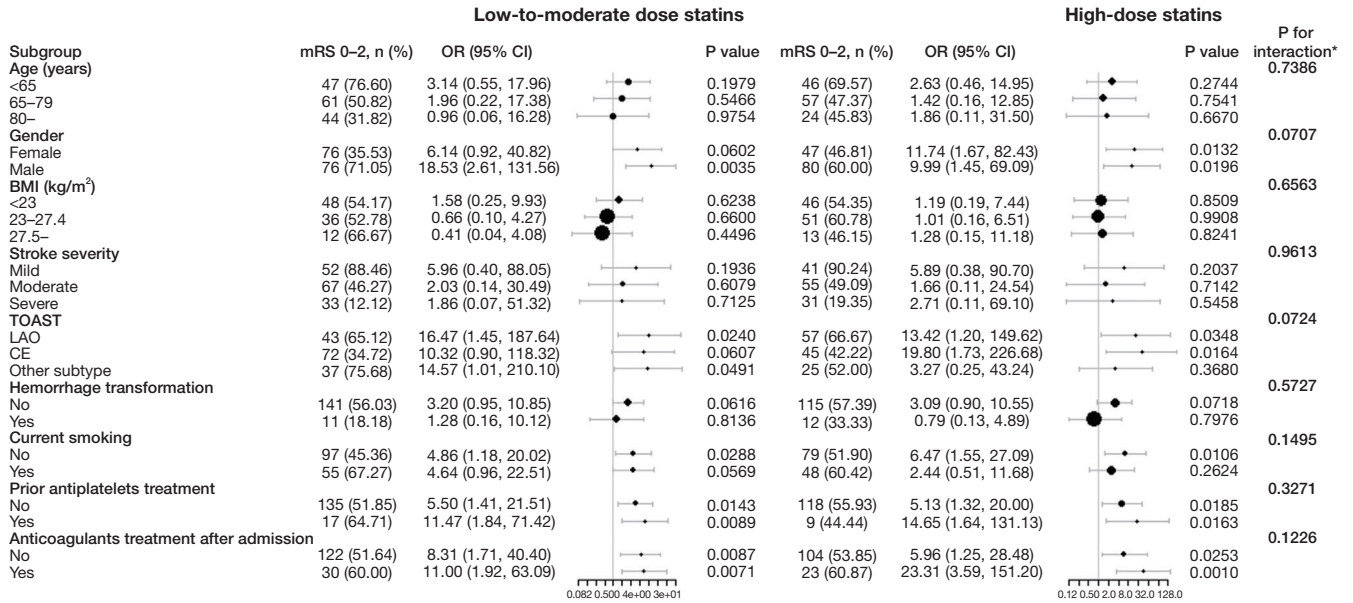

Figure 2 Interaction tests for the association between LMDS or HDS and functional outcome at 3 months. *, adjusted for age, gender, stroke subtypes, history of AF, history of CAD, smoking status, baseline NIHSS, HT, antiplatelet treatment after admission, statins treatment after admission. mRS, modified Rankin scale; OR, odd ratio; CI, confidence interval; BMI, body mass index; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAO, large atherosclerosis occlusion; CE, cardioembolic; LMDS, low-to-moderate dose statin; HDS, high-dose statin; AF, atrial fibrillation; CAD, coronary artery disease; NIHSS, National Institutes of Health Stroke Scale; HT, hemorrhagic transformation.

who did not receive reperfusion therapies. In other words, this finding may be helpful to guide clinical strategies.

Interestingly, we found that there likely was a greater benefit of LMDS therapy than HDS therapy (OR =3.68 and 3.45, respectively) when comparing with non-statin group. However, after encoding LMDS as a dummy variable in a multivariable regression analysis for comparison with HDS, the effect in 3-month good functional outcome between LMDS and HDS therapy was not statistically significant (OR =0.94, P=0.8411). These findings suggest that the benefits of LMDS and HDS therapy appear to be similar in AIS patients receiving conservative medication therapy. And the higher OR value in the LMDS group could be explained by the following reason. Firstly, as previously reported, Asians had nearly greater plasma exposure to statins than Caucasians (27). Due to the increased sensitivity of Asians to statins, previous studies have found that lower statin doses could achieve the lowering-LDL-C treatment targets than non-Asians (9,11). Additionally, it has been shown that lipid levels are also related to stroke outcomes, with lower lipid levels predicting a better prognosis (29). Secondly, HT, as a complication of AIS, has a negative impact on the prognosis of AIS patients (30). And a lower incidence of HT was found in LMDS group than in the HDS group in our cohort. Thirdly, the HDS group had a higher percentage (24.4%) of severe stroke (NIHSS >15), which was more likely to have worse functional outcomes, compared with the LMDS group (21.7%). Lastly, a prior literature reported a lower rate of adherence in the HDS group in stable CAD patients than in the LDS group, thereby possibly nullifying some of the effect of HDS relative to LDS therapy (13). This could partly explain the lower proportion of favorable outcomes at 3 months in the HDS group observed in our study. Moreover, based on recently updated lipid management guidelines from China (31), LDL levels remain the predominant target for lipid intervention. Nevertheless, obtaining comprehensive information regarding to the adherence to statin therapy and the attainment of lipid-lowering targets among patients in real clinical practice, particularly in retrospective studies, can be challenging. Given the urgency of lipid management, prospective cohort studies are necessary to investigate the effect of different statin dosages on lipid-lowering efficacy and adherence to statin therapy in future studies.

Table 3 Multivariate logistic regression analysis results of secondary outcome

Characteristics	HT		Death	
	OR (95% CI)	P value†	OR (95% CI)	P value‡
Age	1.00 (0.97, 1.03)	0.9133	1.04 (1.01, 1.08)	0.0150*
Male	1.75 (0.69, 4.43)	0.2394	0.78 (0.32, 1.88)	0.5775
Statins dose				
Non-statin	–	–	–	–
LMDS	0.30 (0.11, 0.86)	0.0253*	0.84 (0.29, 2.46)	0.7468
HDS	0.36 (0.13, 0.99)	0.0488*	0.76 (0.26, 2.22)	0.6104
Baseline NIHSS	1.07 (1.02, 1.13)	0.0065*	1.09 (1.04, 1.14)	0.0005*
TOAST				
LAO	–	–	–	–
CE	1.27 (0.48, 3.37)	0.6371	1.75 (0.64, 4.84)	0.2787
SAO	0.00 (0.00, Inf)	0.9895	0.97 (0.17, 5.55)	0.9683
OE	1.87 (0.26, 13.66)	0.5365	0.00 (0.00, Inf)	0.9895
UE	0.53 (0.12, 2.46)	0.4192	1.15 (0.32, 4.15)	0.8282
Current smoking	0.20 (0.06, 0.68)	0.0102*	0.62 (0.23, 1.66)	0.3428

†, adjusted for age, sex, stroke subtypes, smoking status, baseline NIHSS, statins treatment after admission, antihypertensive treatment after admission, antiplatelets treatment after admission; ‡, adjusted for age, sex, stroke subtypes, smoking status, baseline NIHSS, history of AF, history of CAD, HT, statins treatment after admission, antiplatelets treatment after admission; *, P<0.05. HT, hemorrhagic transformation; OR, odd ratio; CI, confidence interval; LMDS, low-to-moderate dose statin; HDS, high-dose statin; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAO, large atherosclerosis occlusion; CE, cardioembolic; SAO, small-artery occlusion; OE, other etiology; UE, undetermined etiology; AF, atrial fibrillation; CAD, coronary artery disease.

Concerning safety, we found that the incidence of death did not differ among different statin dose groups. Moreover, statin use after admission was associated with a lower risk of HT and there was no significant difference in the risk of HT occurrence between LMDS and HDS therapy. This finding of HT was in agreement with previous literatures, which might be explained by the anti-inflammatory effects of statins (32-34). Our result adds to the evidence that statin therapy seems safe in AIS patients (35,36). Furthermore, the role of statins in HT patients may depend on individual patient conditions.

Besides, in accordance with previous studies, we also observed that prior antiplatelet treatment was positively associated with functional outcome at 3 months (37), whereas the older age (38), more severe stroke (higher baseline NIHSS score) (39), and higher baseline LDL level were risk factors for functional outcome at 3 months in those patients with conservative medication treatment (40,41). In particular, we observed that patients treated with anticoagulant after admission were prone to having a good functional outcome at 3 months, which was inconsistent with prior studies (42,43). One explanation for this might be a higher proportion of CE stroke in our study, which could introduce a bias towards overestimating the role of anticoagulant in the current study owing to that anticoagulation may be more effective in CE stroke than in atherosclerosis stroke (44). However, there are still uncertainties in anticoagulant management in AIS patients, and our results of anticoagulant should be considered carefully (45).

Several limitations of this study need to be acknowledged (46). First, the retrospective design and the limitation of sample size might make the results at risk of bias, hence the results should be interpreted cautiously. Second, this study enrolled AIS patients who did not receive reperfusion therapy; thus, the results of our research cannot be generalized to

all patients with AIS. Third, since the occurrence of HT was 11.62% in our study, we did not perform the subgroup analysis according to ECASS for the purpose of ensuring the power of the test. Finally, due to the absence of data regarding the incidence of statin side effects and adherence to statin therapy at follow-up (47), our evaluation of potential differences in these outcomes between the LMDS group and the HDS group was impeded.

Conclusions

In conclusion, our findings provide evidence for the benefit and safety of LMDS therapy in AIS patients with medication treatment alone compared to the non-statin group, whereas no significant differences between LMDS and HDS therapy in terms of clinical outcomes. Nevertheless, further studies with larger sample sizes and prospective study designs are warranted to validate our results and comprehensively evaluate the benefits and potential risks of LMDS therapy in this AIS patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-77/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-77/dss

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-77/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-77/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of West China Hospital, Sichuan University [No. 2019(319)] and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Ordinal logistic regression analysis of different statin dose for 3-month good functional outcome (mRS 0–2) and HT

Statin dosage	3-month good functional outcome		HT	
	OR (95% CI)	P value[†]	OR (95% CI)	P value[‡]
Non-statin				
LMDS	3.68 (1.13, 12.01)	0.0309*	0.30 (0.11, 0.86)	0.0253*
HDS	3.45 (1.06, 11.26)	0.0402*	0.36 (0.13, 0.99)	0.0488*
LMDS				
Non-statin	0.27 (0.08, 0.89)	0.0309*	3.29 (1.16, 9.36)	0.0253*
HDS	0.94 (0.50, 1.77)	0.8411	1.19 (0.47, 3.02)	0.7093

[†], adjusted for model 1 adding HT, antiplatelets treatment after admission, statins treatment after admission; [‡], adjusted for age, sex, stroke subtypes, smoking status, baseline NIHSS, statins treatment after admission, antihypertensive treatment after admission, antiplatelets treatment after admission; *, P<0.05. mRS, modified Rankin scale; HT, hemorrhagic transformation; OR, odd ratio; CI, confidence interval; LMDS, low-to-moderate dose statin; HDS, high-dose statin.

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