Title Page

1. Full title: Inpatient Statin Use Is Associated with Decreased Mortality of Acute Stroke Patients with Very Low Low-density Lipoprotein Cholesterol

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- 5. Running title:** Statin Decreased Mortality of Stroke Patients with Very Low
LDL-C

ABSTRACT

Objective— To investigate the potential benefits of inpatient statin therapy on mortality of acute stroke patients with very low admission low-density lipoprotein cholesterol (LDL-C) level (< 1.81 mmol/L).

Methods—The acute stroke patients with admission LDL-C level < 1.81 mmol/L were enrolled from the China National Stroke Registry. The patients were divided into statin group and non-statin group during hospitalization. The association between statin therapy and mortality of participants in 1 year was analyzed by multivariable binary logistic regression models.

Results—A total of 1018 patients were enrolled, the cumulative mortality rate was 10.1% at 3 months, 13.1% at 6 months, and 15.9 % at 1 year. The all-cause mortality rate in statin group was significantly lower than non-statin group (3.6% versus 13.7% at 3 months, $P<0.001$; 6.2% versus 16.9% at 6 months, $P<0.001$; 8.4% versus 20% at 1 year, $P<0.001$). The logistic analyses showed that statin therapy during hospitalization was independently associated with decreased mortality at 3 months (odds ratio [OR], 0.35; 95% confidence interval [CI], 0.18-0.67), at 6 months (OR, 0.42; 95% CI, 0.25-0.73) and at 1 year (OR, 0.47; 95% CI, 0.29-0.76).

Conclusions— Statin use during hospitalization could decrease mortality of acute ischemic stroke patients with very low admission LDL-C.

Introduction

Statins, a 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors, which are recommended for primary and secondary prevention of ischemic cerebrovascular disease, have potential pleiotropic effects on stroke. It was reported that statin use before or after stroke onset can improve clinical outcome [1-5] and decrease mortality [6-8] of ischemic stroke in many cohort studies. Meanwhile it would take an unfavorable outcome after ischemic stroke with discontinuation of statins.[9]Although the AHA/ASA guidelines[10] for the early management of patients with acute ischemic stroke mentioned statins as possible neuroprotective agents, it is very necessary to evaluate the neuroprotective effects of statins in real world studies before good-quality randomized controlled trials are established.

Some studies[11, 12]had showed that statin use after stroke could improve the outcome of ischemic stroke after adjusted with low-density lipoprotein cholesterol (LDL-C), and some observational studies about acute coronary syndromes showed that patients with very low LDL-C levels in hospitalization receiving statin therapy had less mortality than those without statin treatment.[13-15] However it is not clear whether statins could take an advantage to stroke patients with very low LDL-C level (< 1.81 mmol/L) at admission as these patients have less possibility to receive statin treatment. Therefore, it is worthwhile to speculate whether statin treatment has any clinical effect on the outcome of ischemic stroke with very low LDL-C levels. In this study, we assessed the effect of statin therapy during hospitalization on the outcome of acute ischemic stroke patients with very low LDL-C levels from the China

National Stroke Registry (CNSR).[16]

Materials and Methods

Data source

The CNSR is a nationwide prospective hospital-based registry, recruiting consecutive acute stroke patients data from 137 hospitals from September 2007 to August 2008 in 27 provinces and 4 municipalities (including Hong Kong SAR) in China. CNSR is an observational cohort study without any intervention. The aims of the CNSR were evaluating demography, risk factors, clinical characteristics, treatment, prevention status survey, and prognosis of acute stroke. The detailed design information of the CNSR registry has been published previously.[16, 17]

All physicians received the unified training, recorded all information of enrolled stroke patients on the well-designed Case Report Forms (CRFs) including demographics, vascular risk factors, clinical features, laboratory examinations, diagnosis, treatment, secondary prevention and outcome. All enrolled patients were followed-up by trained research personnel at Beijing Tiantan Hospital by telephone interview.

Ethics Statement

This research was approved by the central Institutional Review Board at BeijingTiantanHospital. The informed consent form was signed by all patients or their legally authorized representative.

Study population

Ischemic stroke was diagnosed based on World Health Organization (WHO) criteria with brain CT or MRI evidence.[18] The inclusion criteria of this study were: (1) age was over 18 years old, (2) ischemic stroke onset within 14 days, (3) no statin use before stroke onset and (4) fasting LDL-C levels $<1.81\text{mmol/L}$ within 24 hours after admission. We excluded patients diagnosed with hemorrhagic stroke, transient ischemic attack(TIA, based on WHO TIA diagnostic criteria[18]) and those with unclear clinical information or a life expectancy of less than 1 year because of severe disorders such as cancer and hepatic disease. The cohort groups were established based on whether patients took statins regularly by prescription before discharge, patients who took statins regularly by prescription before discharge were assigned to the statin use group irrespective of type or dosage, and patients who did not receive a statin during hospitalization were assigned to the non-statin use group.

Detailed baseline data were registered prospectively in the paper CRFs. Information on demography and vascular risk factors including age, sex, body mass index (weight divided by the square of the height) current or previous smoking, moderate or heavy alcohol consumption (≥ 2 standard volume of alcohol consumption per day), history of hypertension, diabetes mellitus (DM), coronary heart disease (CHD), atrial fibrillation(AF), TIA and stroke history was obtained from patients' self-reports with medical record or treatment data. The severity of stroke was evaluated by the National Institutes of Health Stroke Scale (NIHSS) [19] at admission. Based on clinical and neuroimaging data, stroke etiological subtypes were classified according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria.

[20] Medications during hospitalization included regular use of antithrombotic, antihypertensive, antidiabetic drugs and statins by prescription before discharge. Antithrombotic medication included antiplatelet and anticoagulation drugs used during hospitalization; Antihypertensive medication included any treatment of venous or oral antihypertensive drugs. Antidiabetic medication included insulin or oral hypoglycemic drugs. Fasting lipid profiles level, including LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol and triglycerides, were tested at the next morning after admission. All-cause death was recorded at 3 month, 6 month and 1 year on telephone interview.

Statistical analysis

Continuous variables are presented as the mean $\pm$ SD or median and interquartile ranges, and categorical variables are presented as numbers and percentages. The demographic data and clinical manifestations of the groups were compared using the Chi-square test for categorical variables and an unpaired Student t test or Mann-Whitney rank sum test for continuous variables. Multivariate logistic regression analyses were used to calculate the adjusted odds ratios (OR) with 95% confidence intervals (CI). To test the independent benefits of inpatient statin therapy on mortality of acute stroke patients with LDL-C level less than 1.81mmol/L, multivariable logistic regression models were constructed, adjusting for potential confounders including age, sex, NIHSS score at admission, vascular risk factors and medications during hospitalized. Statistical significance was achieved at $P < 0.05$. All data were analyzed by SAS statistical software, Version 9.1.3 (SAS Institute Inc).

Results

Patient flow

From September 2007 to August 2008, a total of 22,216 hospitalized acute stroke patients within 14 days after onset were recruited, in which 12,415 (55.9%) were diagnosed with acute ischemic stroke. A total of 1018 patients were enrolled in this study after 318 patients were excluded due to statin use before index stroke, 9,999 excluded due to LDL-C level $\geq 1.81\text{mmol/L}$, and 80 excluded due to loss to 1-year follow-up. (Figure 1)

Baseline characteristics

The average age of the patients was 65.3 ± 12.9 years old, 331(32.5%) were female, and 359(35.3%) received statin therapy during hospitalization. There were 330 patients (32.4%) who had stroke history, most of them (308, 93.3%) was ischemic stroke. The baseline demographic information, risk factors, clinical manifestations and medical therapy are listed in Table 1. The serum level of triglycerides was higher in the patients with statin therapy during hospitalization than those without statin therapy, and there was no difference in other lipid profiles between the two groups. Patients in the statin use group were more likely to have concomitant hypertension, and to be prescribed antithrombotic, antihypertensive, and antidiabetic medications. The patients in the non-statin group had a higher NIHSS score than the statin group. The patients with large-artery atherosclerosis subtype were more likely to receive statins.

Outcome of patients

Death occurred in 103 patients (10.1%) at 3 month, 133 (13.1%) at 6 month, and 162 (15.9%) at 1 year. The mortality of the statin group and non-statin group was 3.6% versus 13.7% ($P<0.001$) at 3 month, 6.2% versus 16.9% ($P<0.001$) at 6 month, 8.4% versus 20% ($P<0.001$) at 1 year, respectively. (Figure 2)

The analyses showed that statin therapy during hospitalization could decrease mortality at 3 months (OR, 0.35; 95% CI, 0.18-0.67), at 6 months (OR, 0.42; 95% CI, 0.25-0.73), and at 1 year (OR, 0.47; 95% CI, 0.29-0.76) after adjusting confounding variables, such as demographic data, vascular risk factors, stroke severity, and other in-hospital medications. The other medication that could decrease mortality was antithrombotic therapy. Additionally, factors such as age, history of AF and severity at admission were significantly related to the 3-month, 6-month and 1-year mortality.

Discussion

About one-third of stroke patients with LDL-C level less than 1.81mmol/L received statin therapy during hospitalization in this study. We found that statin therapy for acute ischemic stroke patients with very low LDL-C level could improve poststroke survival in both short and long period.

Our finding was consistent with results of other researches. It has been revealed that in-hospital initiation of lower lipid therapy was associated with a better clinical outcome in patients with ischemic stroke or transient ischemic attack.[12] In a

meta-analysis including 113,148 subjects (27 studies), statin therapy at stroke onset was associated with improved functional independence and survival poststroke.[21] And a study of 12,689 patients found that statin used early in stroke hospitalization was strongly associated with improved poststroke survival, and statin withdrawal in the hospital was associated with worsened survival.[8] Another observational study showed that statin use within 72 hours after IV thrombolysis may positively influence short- and long-term outcome.[22]

However it is not clear about the relationship between clinical outcomes of ischemic stroke and low cholesterol level,[23-27] some research suggested an association between low cholesterol level and increased risk of hemorrhagic stroke[26, 27]as well as poor clinical outcome.[28]Data from the SPARCL (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial [29]showed that ischemic patients who received the high-dose statin had higher incidence of hemorrhagic stroke. Thus, the ischemic stroke patients were less likely to receive statins due to those data. To our knowledge, this is the only research focusing on statin therapy on ischemic stroke patients with low LDL-C level. In a 104 patients observational research found that lower admission LDL-C level with statin treatment are associated with greater risk of symptomatic hemorrhagic transformation after recanalization therapy for ischemic stroke.[30]Different from our study, they did not analyze the clinical outcomes of stroke in a long time, and they only focused on recanalization therapy for ischemic stroke and TIA.

Some experimental[31]and clinical studies had confirmed that statins have

pleiotropic effect on stroke. In a first-ever non-lacunar ischemic stroke study showed that statin treatment during acute phase could increase circulating endothelial progenitor cells by nitric oxide related mechanisms after acute ischemic stroke.[32] A prospective case control study including 120 acute ischemic patients and 80 control cases showed that statin therapy reduced plasma Ox-LDL level after stroke.[33]

This present research has some limitations. First, this research was not primarily designed to evaluate associations between statin use in acute stroke patients with very low LDL-C levels and clinical outcomes, so our results should be confirmed by the specially designed trial. Secondly, patients were enrolled in 14 days after stroke onset in this research, there was no regular statin initiation time. Thirdly, we didn't consider the compliance of statin treatment, which might affect the clinical outcome. Fourthly, some patients with severe comorbidities were not enrolled, and some patients without follow-up information were excluded, which might lead to bias too. Furthermore, the LDL-C level, liver and renal function, and the death reasons after statin therapy at discharge and regular follow-up time were not recorded, thus the side effects of statins were not evaluated in this study, especially some studies have shown that statins use were associated with the increment of hemorrhagic stroke recurrence. Last, without record of the causes of death in this study, it is hard to tell whether the statin use increased the risk of symptomatic hemorrhage and then led to the increased mortality.

Conclusion

Our research shows that statin use in early stage could decrease mortality of acute

ischemic stroke patients with very low low-density lipoprotein cholesterol.

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Figure 1 Flow of participants selection. CNSR: the China National Stroke Registry

Table 1 Baseline Characteristics and Mortality of the Patients According to Statin

Use			
Variable	Non-Statins(n=659)	Statin(n=359)	p-value
Age, mean±SD, years	65.0±13.8	65.6±12.1	0.80
Gender (Female), n (%)	219(33.2%)	112(31.2%)	0.51
BMI(kg/m ²), median (IQR)	23.7(21.3, 26.0)	23.9(21.6, 26.0)	0.31
History of DM, n (%)	121(18.4%)	71(19.8%)	0.60
History of Hypertension, n (%)	373(56.7%)	230(64.1%)	<0.02
History of CHD, n (%)	87(13.2%)	47(13.1%)	0.96
History of AF, n (%)	95(14.4%)	38(10.6%)	0.08
History of TIA, n (%)	19(2.9%)	15(4.2%)	0.27
Smoking, n (%)	294(44.6%)	151(42.1%)	0.43
Alcohol, n (%)	71(10.8%)	34(9.5%)	0.51
NIHSS, median (IQR)	5(2, 11)	4(2, 9)	0.01
History of Stroke	215(32.6%)	115(32%)	0.85
Pre-IS	200(30.4%)	108(30%)	0.93
Pre-ICH	15(2.3%)	7(1.9%)	0.73
Lipid profile(mmol/L)			
LDL-C	1.41±0.36	1.39±0.36	0.16
HDL-C	1.21±0.52	1.17±0.47	0.22
TG	1.64±1.67	1.99±2.02	0.008

TC	3.48±1.05	3.66±1.21	0.21
Stroke etiological subtypes, n (%)			
Large-artery atherosclerosis	236(35.8%)	176(49.0%)	<0.001
Cardioembolism	121(18.4%)	59(16.4%)	
Small-artery occlusion	55(8.4%)	23(6.4%)	
Other determined etiology	12(1.8%)	6(1.7%)	
Undetermined etiology	235(36.7%)	95(26.5%)	
Medications in-hospital			
Antithrombotic, n (%)	574(87.1%)	337(93.9%)	<0.001
Antihypertension, n (%)	236(35.8%)	181(50.4%)	<0.001
Antidiabetic, n (%)	115(17.5%)	86(24.0%)	<0.001

BMI: body mass index; DM: diabetes mellitus; CHD: coronary arterial disease; AF: atrial fibrillation; TIA: transient ischemic attack; Smoking: current or previous smoking; Alcohol: moderate or heavy alcohol consumption; NIHSS: the National Institutes of Health Stroke Scale evaluated at admission; IQR : indicates interquartile range; Pre-IS: previous ischemic stroke; Pre-ICH: previous intracranial hemorrhage; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

Figure 2 Mortality of patients at 3 month, 6 month and 1 year.

Table 2 Predictors of All-cause Mortality at 3 Month, 6 Month and 1 Year

Variables	3M DEATH	6M DEATH	12M DEATH
Age	1.04 (1.02-1.07)	1.05(1.03-1.08)	1.06(1.04-1.08)
History of AF	2.95(1.65-5.25)	2.9(1.68-5.02)	2.4 (1.43-4.06)
NIHSS	1.09(1.06-1.12)	1.1(1.07-1.13)	1.1(1.08-1.13)
Antithrombotic,	0.36(0.20-0.66)	0.44(0.24-0.78)	0.4(0.23-0.7)
Statin	0.35(0.18-0.67)	0.42(0.25-0.73)	0.47(0.29-0.76)

AF: atrial fibrillation, NIHSS: the National Institutes of Health Stroke Scale evaluated at admission.