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Lipid management in Ischemic Stroke or Transient Ischemic Attack in China: Result from China National Stroke Registry III

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Lipid management in Ischemic Stroke or Transient Ischemic Attack in China: Result from China National Stroke Registry III

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Abstract

Background and purpose: Dyslipidaemia is a significant risk factor for ischemic stroke and transient ischemic attack (TIA). This study aimed to assess the management of LDL-C and the goal achievement and to investigate the association between baseline low-density lipoprotein cholesterol (LDL-C) level, lipid-lowering treatment (LLT), and stroke recurrence in patients with ischemic stroke or TIA.

Methods: We derived data from the Third China National Stroke Registry (CNSR-III). The primary outcome was a new stroke, LDL-C goal (LDL-C<1.8mmol/L and LDL-C<1.4mmol/L, respectively) achievement rates, and LLT compliance within 3, 6, and 12 months. The association of baseline LDL-C level, LLT at discharge, and outcomes were assessed.

Results: Among the 15,166 patients, over 90% of patients received LLT during hospitalization and 2 weeks after discharge; the LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. LDL-C goal achievement for 1.8mmol/L and 1.4mmol/L was 35.4% and 17.6% at 12 months. LLT at discharge was associated with reduced risk of ischemic stroke recurrence (HR=0.687, 95% CI: 0.480-0.985, p=0.0411) at 3 months. The rate of LDL-C reduction from baseline to 3-month follow-up was not associated with a reduced risk of stroke recurrence, and major adverse cardiovascular events (MACE) at 12 months. Patients with baseline LDL-C ≤1.4mmol/L had a numerically lower risk of stroke, ischemic stroke and MACE at both 3 months and 12 months.

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Conclusions: The goal achievement of LDL-C has increased mildly in the stroke and TIA population in mainland China. Lowered baseline LDL-C level was significantly associated with a decreased short- and long-term risk of ischemic stroke among stroke and TIA patients. LDL-C<1.4mmol/L might be a safe standard for this population.

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Introduction

Low-density lipoprotein cholesterol (LDL-C) has been well established as an independent risk factor for ischemic stroke [1]. Intensive lipid-lowering treatment (LLT) has been proven to reduce cardiovascular event recurrence in ischemic stroke/TIA patients. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study [2] showed that intensive atorvastatin treatment for five years reduced the risk of stroke recurrence up to 16% (HR 0.84, 95% CI 0.71-0.99; P＜0.03) in ischemic stroke (IS) or transient ischemic attack (TIA). Recently, TST study [3] also demonstrated that IS/TIA patients who had a target LDL-C level of less than 70 mg/dl (1.8mmol/L) had a lower risk of subsequent cardiovascular events than those who had a target range of 90 to 110 mg/dl (HR 0.78, 95% CI 0.61-0.98; P=0.04). Therefore, European Stroke Organisation (ESO) and American Stroke Association (ASA) both updated the IS/TIA second prevention guideline with a recommendation of LDL-C target goal to less than 70mg/dl (1.8mmol/L) [4,5].

However, there are still clinical questions not thoroughly investigated. Firstly, SPARCL and Treat Stroke to Target (TST) trials are randomized controlled trials conducted mainly in the Caucasian population [2,6], while studies focusing on the Asian population on lipid management in stroke patients are limited. Since there are more intracranial artery stenosis (ICAS) [7,8] and cerebral small vessel disease (CSVD) patients in Asia [9,10], especially in east Asia, the conclusions of these two trials in Asia should be discreet. Secondly, there were inconsistencies and conflicts about whether the lower LDL-C level could increase the risk of intracranial hemorrhage (ICH),

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especially during the acute or subacute phase. In the SPARCL study, subgroup analysis indicated that atorvastatin treatment might increase the risk of ICH, which led to a big concern for statin usage during the acute phase of IS/TIA [11]. In contrast, the TST study showed that the incidence of ICH did not differ significantly between the lower- and higher-target groups [3]. Thirdly, with emerging evidence from non-stain therapies such as IMPROVE-IT [12], FOURIER [13], and ODYSSEY [14], a lower LDL-C target of less than 1.4mmol/L or even 1.0mmol/L has been recommended by international guidelines. However, the benefit of a lower LDL-C target other than 1.8mmol/L has not been investigated.

The Third China National Stroke Registry (CNSR-III) is one of the world's most extensive IS/TIA cohort studies, which included comprehensive medical history, centralized the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification judication, and follow-up outcomes. We aim to collect data from CNSR-III to investigate China's current lipid management situation and the association between LDL-C level, LLT, and stroke recurrence in ischemic stroke or TIA patients.

Methods

Patient and Public Involvement

The development and organization of the study depended on stroke center organizations and networks in China. Our co-investigators conducted a series of meetings and discussions with national stroke patients. Patient education is always an important work of the organization. We provided standard educational materials and a

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research tutorial to each stroke center, to help to encourage familiarity with research concepts and terminology. The discussion of study design and research method were conveyed to the patients by co-investigators, using laypersons' language to facilitate common understanding, and we solicited patients' feedback. We also conduct quality control regularly to provide advice and service for patients. When results emerged, we reviewed the results with patient co-investigators to obtain their perspectives and feedback to ensure that we presented the findings in the most effective way beyond the research community to general populations.

Study design and participants

We derived data from the CNSR-III database. The CNSR-III is a nationwide clinical registry of ischemic stroke or transient ischemic attack (TIA) based on etiology, imaging, and biological markers in China from August 2015 to March 2018 [15]. Consecutive patients were recruited consecutively if they were: (1) aged>18 years; (2) patients with physician-diagnosed ischemic stroke or TIA; (3) within 7 days from the onset of symptoms to enrolment; (4) patients who have provided consent to participant in the study. Patients were excluded if they had silent cerebral infarction with no symptoms or signs, or those who refused to participate in the registry. The study protocol of the CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centres. Every participant provided written informed consent before participation.

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Among all the clinical centers included in CNSR-III, 169 centers voluntarily participated in the prespecified blood biomarker substudy. All the patients at these centers participated in this biomarker substudy. Patients participating in the biomarker substudy provided a separate written informed consent form, including consent for blood sample collection and further study of biomarkers.

A total of 15166 patients were eligible and had complete information at baseline.

Data Collection and Management

Patient information, including demographics, risk factors, comorbidities, medications, selected laboratory tests, and hospital-level characteristics, were collected systematically during hospitalization and at discharge by trained research coordinators at each participating hospital. National Institutes of Health Stroke Scale (NIHSS) score at admission, and ischemic stroke recurrence, composite vascular event, and modified Rankin Scale (mRS) at 3 months and 1 year after stroke onset were also collected.

Venous blood samples were collected from fasting patients within 24 hours from admission. Serum specimens were extracted, aliquoted, and transported through the cold chain to the central laboratory in Beijing Tiantan Hospital and stored at -80°C. LDL-C measurements were centrally and blindly assayed by enzymatic method on the Cobas 8000 analyzer c702 module (Roche Diagnostics, Mannheim, Germany).

Follow-Up and Clinical Outcome Evaluations

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Patients were followed up by face-to-face interviews at 3 months and by telephone interviews at 6 and 12 months by trained research coordinators based on a standardized interview protocol. Information collected at each follow-up included cardio-/cerebrovascular events, all causes of death, and medications use. Vascular events were confirmed from the treating hospital, and death was either confirmed on a death certificate from the attended hospital or the local civil registry.

The primary outcome was a new stroke (defined as a new neurological deficit lasting more than 24 hours or re-hospitalization with a diagnosis of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage), LDL-C goal (LDL-C<1.4mmol/L, and LDL-C<1.8mmol/L, respectively) achievement rates and LLT compliance in China within 3, 6, and 12 months. The secondary outcomes included major adverse cardiovascular events (including stroke, myocardial infarction, or vascular death) and all caused death at 3 months and 12 months.

All reported efficacy and safety outcomes were verified by a central independent adjudication committee blinded to study treatment assignments and baseline LDL-C level.

Patients were categorized into four groups according to baseline LDL-C levels and lipid-lowering treatment during hospitalization and after discharge: LDL-C≤1.4mmol/L, 1.4mmol/L<LDL-C ≤1.8mmol/L, 1.8 mmol/L<LDL≤2.6mmol/L, LDL>2.6mmol/L.

LLT compliance was defined as the continuation of LLT medication from discharge to 3, 6, or 12 months after the onset of symptoms. Patients assigned to LLT at

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discharge but later discontinuing LLT at any follow-up point within 3, 6, or 12 months were considered “non-persistent”. Patients were considered persistent if they discontinued one medication but took another statin medication within 3, 6, or 12 months.

Statistical analysis

Baseline variables were presented as median with interquartile range (IQR) for continuous variables and percentages for categorical variables.

To analyze the association of baseline LDL-C levels and outcomes, we only included those subjects who provided 3-month or 12-month bio-sample. Univariate and multivariate Cox proportional hazard regression models were used. The model included the following covariates: age, sex, education, current smoking, heavy drinking, medical history, stroke severity on the NIHSS, history of stroke, history of diabetes, and history of hypertension. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The dose-response-relationship curves were also presented.

To analyze the effect of discharge LLT on outcomes, we excluded subjects who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) during hospitalization. We performed a univariate model and multivariable analysis by adjusting for age, sex, education, current smoking, heavy drinking, medical history, stroke severity on the NIHSS, history of stroke, history of diabetes, and history of hypertension.

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In addition, to analyze the association of 3-month LDL-C change with stroke recurrence and MACE in 12 months, we excluded subjects who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) within 3 months.

Related statistical analyses in the study was performed by SAS 9.4 software. All statistical analysis adopted a two-sided test which will be performed at a 5% significance level.

Results

Characteristics of study participants

From August 2015 to March 2018, a total of 15166 patients with acute stroke and TIA were recruited to the CNSR-III trial and entered our final analysis. The average age of 62.2±11.3 years, 31.7% of patients were women, 14146 (93.3%) had an index event of stroke, and 1020 (6.7%) had a TIA [15].

Baseline LDL-C levels

There were 10,738 patients in LDL-C analysis set: 1407 (13.1%), 1636 (15.2%), 3655 (34.0%), and 4040 (37.6%) patients with an LDL-C ≤1.4mmol/L, LDL-C 1.4–1.8mmol/L, LDL-C 1.8–2.6mmol/L, LDL-C ≥ 2.6mmol/L, respectively **(Table 1)**.

Table 1. Baseline Characteristics for the LDL-C analysis set

Variables	LDL≤1.4mmol/L N=1407	1.4 < LDL≤1.8mmol/L N=1636	1.8 < LDL≤2.6mmol/L N=3655	LDL>2.6mmol/L N=4040	P Value*
Women, n (%)	378 (26.9)	439 (26.8)	1057 (28.9)	1517 (37.6)	<0.001
Mean age, years (SD)	60.8±11.9	62.4±11.3	62.2±11.3	62.8±11.1	<0.001
Ethnicity (non-Han), n (%)	30 (2.1)	49 (3.0)	122 (3.3)	104 (2.6)	0.07
Current smoker, n (%)	435 (30.9)	525 (32.1)	1239 (33.9)	1198 (29.7)	<0.001
Heavy drinker, n (%)*	185 (13.2)	210 (12.8)	545 (14.9)	589 (14.6)	0.12

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Triglycerides (IQR)	1.3 (0.9-1.9)	1.3 (1.0-1.8)	1.3 (1.0-1.8)	1.5 (1.1-2.0)	<0.001
TC, mmol/L	2.7 (2.4-3.1)	3.2 (3.0-3.5)	3.8 (3.5-4.1)	4.9 (4.5-5.5)	<0.001
HDL-C, mmol/L	0.8 (0.7-1.0)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	1.0 (0.8-1.2)	<0.001
LDL-C, mmol/L	1.2 (1.0-1.3)	1.6 (1.5-1.7)	2.2 (2.0-2.4)	3.2 (2.9-3.8)	<0.001
BMI	24.4 (22.5-26.4)	24.5 (22.7-26.6)	24.4 (22.5-26.4)	24.5 (22.7-26.7)	0.06
Systolic pressure, mmHg	145.0 (132.5-160.0)	146.5 (133.0-161.0)	148.5 (135.0-163.5)	150.0 (136.0-166.5)	<0.001
Medical history, n (%)					
Ischemic stroke	369 (26.2)	429 (26.2)	715 (19.6)	748 (18.5)	<0.001
TIA	44 (3.1)	46 (2.8)	115 (3.6)	102 (2.5)	0.38
Coronary heart diseases	147 (10.5)	193 (11.8)	366 (10.0)	449 (11.1)	0.20
Atrial fibrillation	93 (6.6)	124 (7.6)	272 (7.4)	257 (6.4)	0.19
Hypertension	897 (63.8)	1045 (63.9)	2295 (62.8)	2516 (62.3)	0.62
Diabetes mellitus	386 (27.4)	394 (24.1)	824 (22.5)	960 (23.8)	0.004
Hypercholesterolemia	119 (8.5)	120 (7.3)	302 (8.3)	341 (8.4)	0.56
NIHSS at admission, median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	<0.001
NIHSS 0–3	743 (52.8)	914 (55.9)	1974 (54.0)	2073 (51.3)	0.009
NIHSS≥4	664 (47.2)	722 (44.1)	1681 (46.0)	1967 (48.7)	
mRS (IQR)	0 (0-1.0)	0 (0-1.0)	0 (0-1.0)	0 (0-0)	<0.001
Stroke subtype, n (%)					
LAA	303 (21.5)	390 (23.8)	933 (25.5)	1092 (27.0)	0.0095
CE	81 (5.8)	96 (5.9)	251 (6.9)	256 (6.3)	
SAO	312 (22.2)	359 (21.9)	740 (20.3)	819 (20.3)	
Other	21 (1.5)	16 (1.0)	38 (1.0)	47 (1.2)	
Unknown	690 (49.0)	775 (47.4)	1693 (46.3)	1826 (45.2)	
Antiplatelet therapy, n (%)	1357 (97.4)	1569 (97.1)	3504 (96.7)	3894 (97.0)	0.57
LLT, n (%)	1359 (97.6)	1558 (96.4)	3498 (96.5)	3897 (97.1)	0.15
Statin, n (%)	1355 (97.3)	1556 (96.3)	3491 (96.3)	3887 (96.9)	0.27

TC: total cholesterol. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. BMI: body mass index. TIA: transient ischemic attack. NIHSS: National Institutes of Health Stroke Scale. mRS: modified Rankin Scale. LAA: large artery atherosclerosis. CE: cardiogenic embolism. SAO: small artery occlusion. LLT: lipid-lowering therapy.

Patients in the lower baseline LDL-C level group (≤1.4 mmol/L) were more likely to be younger (p<0.0001) and had a greater prevalence of cardiovascular risk factors (previous stroke, hypertension, hypercholesterolemia, diabetes mellitus, and history of stroke) (p<0.0001) and a lower level of triglycerides, total cholesterol and high-density lipoprotein (HDL) (p<0.0001). About 97% of included patients had medication history of antiplatelet and lipid-lowering therapy, and the rates showed no difference among the four groups.

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Association between baseline LDL-C levels and outcomes at 3 months and 12 months

There were 656 (6.11%) new stroke occurrences at 3 months and 1037 (9.66%) at 12 months **(Table 2)**.

Table 2. Association between baseline LDL-C levels and outcomes at 3 months and 12 months

	Total	Events (n%)	HR (95% CI) Unadjusted	*P* value	HR (95% CI) Adjusted	*P* value
3 months						
Stroke recurrence						
LDL≤1.4mmol/L	1407	69 (4.9)	0.72 (0.55-0.94)	0.01	0.74 (0.57-0.97)	0.03
1.4＜LDL≤1.8mmol/L	1636	95 (5.8)	0.85 (0.68-1.08)	0.18	0.89 (0.70-1.12)	0.32
1.8＜LDL≤2.6mmol/L	3655	219 (6.0)	0.88 (0.74-1.05)	0.17	0.91 (0.76-1.08)	0.28
LDL>2.6mmol/L	4040	273 (6.8)	Reference	-	Reference	-
Ischemic stroke						
LDL≤1.4mmol/L	1407	65 (4.6)	0.72 (0.55-0.95)	0.02	0.74 (0.56-0.98)	0.03
1.4＜LDL≤1.8mmol/L	1636	88 (5.4)	0.84 (0.66-1.07)	0.16	0.87 (0.68-1.11)	0.27
1.8＜LDL≤2.6mmol/L	3655	201 (5.5)	0.86 (0.72-1.04)	0.11	0.89 (0.74-1.07)	0.22
LDL>2.6mmol/L	4040	257 (6.4)	Reference	-	Reference	-
Hemorrhagic stroke						
LDL≤1.4mmol/L	1407	4 (0.3)	0.52 (0.18-1.51)	0.23	0.55 (0.19-1.61)	0.28
1.4＜LDL≤1.8mmol/L	1636	9 (0.6)	1.01 (0.46-2.19)	0.98	1.03 (0.47-2.26)	0.93
1.8＜LDL≤2.6mmol/L	3655	20 (0.6)	1.00 (0.55-1.84)	0.99	0.93 (0.50-1.73)	0.82
LDL>2.6mmol/L	4040	22 (0.5)	Reference	-	Reference	-
MACE						
LDL≤1.4mmol/L	1407	71 (5.1)	0.72 (0.56-0.94)	0.01	0.75 (0.57-0.97)	0.03
1.4＜LDL≤1.8mmol/L	1636	100 (6.1)	0.88 (0.70-1.10)	0.27	0.91 (0.72-1.15)	0.42
1.8＜LDL≤2.6mmol/L	3655	231 (6.3)	0.91 (0.77-1.08)	0.29	0.93 (0.78-1.11)	0.43
LDL>2.6mmol/L	4040	279 (6.9)	Reference	-	Reference	-
12 months						
Stroke recurrence						
LDL≤1.4mmol/L	1407	114 (8.1)	0.76 (0.62-0.93)	0.009	0.77 (0.62-0.95)	0.01
1.4＜LDL≤1.8mmol/L	1636	158 (9.7)	0.91 (0.76-1.08)	0.30	0.92 (0.76-1.10)	0.36
1.8＜LDL≤2.6mmol/L	3655	339 (9.7)	0.87 (0.76-1.01)	0.06	0.89 (0.77-1.03)	0.12
LDL>2.6mmol/L	4040	426 (10.5)	Reference	-	Reference	-
Ischemic stroke						
LDL≤1.4mmol/L	1407	102 (7.6)	0.72 (0.58-0.90)	0.004	0.73 (0.59-0.91)	0.005
1.4＜LDL≤1.8mmol/L	1636	145 (8.9)	0.89 (0.73-1.07)	0.22	0.90 (0.74-1.09)	0.27
1.8＜LDL≤2.6mmol/L	3655	304 (8.3)	0.83 (0.72-0.97)	0.02	0.86 (0.74-1.00)	0.04
LDL>2.6mmol/L	4040	400 (9.9)	Reference	-	Reference	-
Hemorrhagic stroke						
LDL≤1.4mmol/L	1407	12 (0.9)	0.96 (0.50-1.84)	0.89	0.97 (0.50-1.88)	0.93
1.4＜LDL≤1.8mmol/L	1636	15 (0.9)	1.03 (0.56-1.87)	0.94	1.02 (0.56-1.88)	0.95
1.8＜LDL≤2.6mmol/L	3655	37 (1.0)	1.13 (0.72-1.80)	0.59	1.10 (0.69-1.75)	0.69
LDL>2.6mmol/L	4040	36 (0.9)	Reference	-	Reference	-

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MACE						
LDL≤1.4mmol/L	1407	119 (8.5)	0.76 (0.62-0.93)	0.008	0.77 (0.62-0.94)	0.01
1.4＜LDL≤1.8mmol/L	1636	170 (10.4)	0.94 (0.79-1.12)	0.47	0.94 (0.79-1.13)	0.50
1.8＜LDL≤2.6mmol/L	3655	363 (9.9)	0.90 (0.78-1.03)	0.13	0.91 (0.79-1.05)	0.20
LDL>2.6mmol/L	4040	444 (11.0)	Reference	-	Reference	-

LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events.

Compared with patients with other LDL-C level subgroups, patients with LDL-C ≤1.4mmol/L had a numerically lower risk of stroke (HR=0.742, 95% CI: 0.568-0.970, p=0.0291), ischaemic stroke (HR=0.741, 95% CI: 0.562-0.976, p=0.0329) and MACE (HR=0.746, 95% CI: 0.573-0.972, p=0.0297) at 3 months. Similar results were found for the outcome of stroke (HR=0.767, 95% CI: 0.622-0.946, p=0.0131), ischaemic stroke (HR=0.731, 95% CI: 0.587-0.911, p=0.0052) and MACE (HR=0.766, 95% CI: 0.624-0.940, p=0.0106) in 12 months. Lower baseline LDL-C level was not associated with an increased risk of hemorrhagic stroke at both 3 months and 12 months **(Table 2)**. Using a Cox regression model with restricted cubic splines, a larger magnitude of associations was also found between baseline LDL-C level and risk of stroke, ischemic stroke, hemorrhagic stroke, and MACE (**Figure 1**).

Lipid-lowering management, LLT compliance, and association of discharge LLT and outcomes

LLT management and compliance of the included patients during hospitalization, at discharge, 3 months, 6 months, and 12 months were shown in **Table 3**.

Table 3. Lipid-lowering Treatment (LLT) and the compliance of patients in CNSR-III

	Hospitalization	Discharge	3 months	6 months	12 months
Non LLT	547 (3.6)	1300 (8.6)	2590 (17.4)	3007 (22.4)	3754 (26.0)
LLT	14506 (96.4)	13831 (91.4)	12271 (82.6)	11726 (77.6)	10682 (74.0)
Compliance					

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Non-Persistent	/	/	2147 (15.5)	3382 (24.5)	4863 (35.2)
Persistent	/	/	11684 (84.5)	10449 (75.6)	8968 (64.8)

Over 90% of patients received LLT during hospitalization and 2 weeks after discharge. The LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. The drug regimens of lipid-lowering treatment of the patients in CNSR-III in 3 months, 6 months, and 12 months were shown in **Table 4**.

Table 4. Lipid-lowering Treatment of the included patients in CNSR-III at 3-month, 6-month, 12-month follow-up (n=15166)

Treatment	Patients with statins, N (%)				
	Hospitalization	Discharge	3 months	6 months	12 months
Atorvastatin	10527 (69.41)	9851 (64.95)	8656 (57.08)	8228 (54.25)	7470 (49.25)
<40mg	7442 (70.71)	8770 (89.03)	8284 (95.7)	7963 (96.78)	7269 (97.35)
≥40mg	3083 (29.29)	1081 (10.97)	372 (4.3)	265 (3.22)	198 (2.65)
Rosuvastatin	3546 (23.38)	3395 (22.39)	2903 (19.14)	2779 (18.32)	2489 (16.41)
<20mg	2876 (81.15)	2983 (87.86)	2650 (91.38)	2536 (91.29)	2313 (92.93)
≥20mg	668 (18.85)	412 (12.14)	250 (8.62)	242 (8.71)	176 (7.07)
Simvastatin	272 (1.79)	239 (1.58)	390 (2.57)	411 (2.71)	444 (2.93)
Pravastatin	166 (1.09)	165 (1.09)	137 (0.9)	128 (0.84)	100 (0.66)
lovastatin	25 (0.16)	24 (0.16)	33 (0.22)	33 (0.22)	30 (0.2)
Fluvastatin	54 (0.36)	53 (0.35)	52 (0.34)	43 (0.28)	47 (0.31)
Pravastatin	61 (0.40)	78 (0.51)	70 (0.46)	64 (0.42)	61 (0.4)

Compared with the non-discharge LLT group, LLT at discharge was associated with reduced risk of ischemic stroke (HR=0.65, 95% CI: 0.45-0.94, p=0.02) and stroke recurrence (HR=0.69, 95% CI: 0.48-0.99, p=0.04) at 3 months **(Table 5)**.

Table 5. The association of Discharge Lipid Lowering Therapy (LLT) and outcomes

	Total	Events, (n%)	HR (95% CI) Unadjusted	*P* value	HR (95% CI) Adjusted	*P* value
3 months						
Stroke recurrence						
Discharge LLT	13248	269 (2.0%)	0.68(0.48-0.96)	0.03	0.69(0.48-0.99)	0.04
Non discharge LLT	1181	35 (3.0%)	Reference		Reference	
Ischemic stroke						
Discharge LLT	13263	245 (1.9%)	0.68(0.47-0.98)	0.04	0.65(0.45-0.94)	0.02
Non discharge LLT	1188	32 (2.7%)	Reference		Reference	
Hemorrhagic stroke						

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Discharge LLT	13740	31 (0.2%)	0.71(0.25-2.01)	0.52	1.19(0.36-3.98)	0.78
Non discharge LLT	1266	4 (0.3%)	Reference		Reference	
MACE						
Discharge LLT	13248	299 (2.3%)	0.71(0.51-1.003)	0.052	0.74(0.52-1.04)	0.08
Non discharge LLT	1181	37 (3.1%)	Reference		Reference	
12 months						
Stroke recurrence						
Discharge LLT	13248	758 (5.7%)	0.88(0.7-1.12)	0.30	0.89(0.7-1.14)	0.36
Non discharge LLT	1181	75 (6.4%)	Reference		Reference	
Ischemic stroke						
Discharge LLT	13263	683 (5.2%)	0.87(0.68-1.11)	0.26	0.86(0.67-1.10)	0.23
Non discharge LLT	1188	69 (5.8%)	Reference		Reference	
Hemorrhagic stroke						
Discharge LLT	13740	86 (0.6%)	0.97(0.47-2.00)	0.94	1.23(0.56-2.69)	0.60
Non discharge LLT	1266	8 (0.6%)	Reference		Reference	
MACE						
Discharge LLT	13248	838 (6.3%)	0.94(0.75-1.19)	0.60	0.96(0.76-1.21)	0.72
Non discharge LLT	1181	78(6.6%)	Reference		Reference	

Patients who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) during hospitalization were excluded.

LDL-C goal achievement and change of LDL-C from baseline to 3 months with outcomes at 12 months

The overall blood lipid level at baseline, 3-month, and 12-month follow-up were shown in **Table 6**. LDL-C goal achievement for 1.8mmol/L were 28.3% at baseline, 46.7% at 3 months, and 35.4% at 12 months, respectively; while LDL-C goal achievement for 1.4mmol/L were 13.1% at baseline, 25.6% at 3 months, and 17.6% at 12 months, respectively.

Table 6. Blood Lipid Level of the included patients at baseline, 3 months and 1 year in CNSR-III

Lipids, mmol/L	Baseline N=10738	3M N=6034	12M N=4899
Median triglycerides (IQR), mmol/L	1.37(1.03-1.87)	1.32(0.98-1.81)	1.46(1.04-2.16)
Total cholesterol, mmol/L	3.97(3.31-4.72)	3.74(3.13-4.54)	3.92(3.25-4.76)
HDL-C, mmol/L	0.93(0.78-1.12)	1.02(0.86-1.21)	0.99(0.79-1.2)
LDL-C, mmol/L	2.31(1.73-2.97)	1.87(1.39-2.55)	2.14(1.57-2.87)
LDL <1.4mmol/L, n (%)	1407 (13.1)	1547 (25.6)	862 (17.6)
1.4 < LDL≤1.8mmol/L, n (%)	1636 (15.2)	1272 (21.1)	872 (17.8)

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1.8 < LDL≤2.6mmol/L, n (%)	3655 (34.0)	1785 (29.6)	1533 (31.3)
LDL>2.6mmol/L, n (%)	4040 (37.6)	1430 (23.7)	1632 (33.3)

HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol.

We did not find that the LDL-C reduction rate from baseline to 3-month follow-up was associated with reduced risk of stroke and MACE at 12 months **(Table 7)**.

Table 7. Association of change of LDL-C from baseline to 3 months with outcomes at 12 months

Percentage of LDL level decrease (compared to baseline)	Total	Events, (n%)	HR (95% CI) unadjusted	*P* value	HR (95% CI) adjusted	*P* value
12 months						
Stroke recurrence*						
<30%, n (%)	3526	137 (3.9)	1.48 (0.92-2.39)	0.11	1.42 (0.87-2.30)	0.16
30-50%, n (%)	1146	45 (3.9)	1.50 (0.88-2.56)	0.14	1.44 (0.84-2.47)	0.19
>50%, n (%)	718	19 (2.7)	Reference		Reference	
MACE‡						
<30%, n (%)	3526	149 (4.2)	1.46 (0.92-2.20)	0.11	1.39 (0.88-2.21)	0.16
30-50%, n (%)	1146	47 (4.1)	1.41 (0.84-2.36)	0.19	1.36 (0.81-2.28)	0.24
>50%, n (%)	718	21 (2.9)	Reference		Reference	

* Patients with stroke recurrence, death, and loss to follow-up within 3 months were excluded.

‡ Patients with MACE, death, and loss to follow-up within 3 months were excluded.

Discussion

This national hospital-based study described the current LDL level and LLT of stroke patients in the real world. We described the LLT management and LDL-C goal achievement and found that lowered baseline LDL-C level was associated with a decreased risk of new ischaemic stroke and MACE at both 3 months and 12 months, without increasing risk of intracranial hemorrhage. In addition, LLT at discharge was associated with a reduced risk of CV events at 3 and 12 months. Our study may have important clinical implications with the large sample size of LDL-C levels of stroke patients and comprehensive prognostic characteristics recorded.

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Firstly, LDL-C of 1.4 mmol/l might be a reasonable target for the high-risk population. Our study indicated that the LDL≤1.4 mmol/L group, with the highest risk factors, developed the lowest stroke and MACE at 3 and 12 months. The paradox of high risk of stroke with low LDL-C level could be due to the previous intensive LLT and rigid LDL-C control. It is consistent with the previous study that fixed-dose statin regimens are less effective than targeting LDL-C levels of 1.8 or 1.4 mmol/l when pre-treatment LDL-C levels exceed 4 mmol/L [16]. The target LDL-C of 1.4 mmol/l recently advocated in particularly high-risk patients is most effective when pre-treatment LDL-C exceeds about 3 mmol/l [16]. The TST trial found that an intensive LDL-C lowering target of less than 1.8 mmol/L further reduced the risk of cardiovascular events by approximately 20% during a median follow-up of 3.5 years in patients with ischaemic stroke within 3 months or a TIA within 15 days, compared with the higher target of 2.3–2.8mmol/L.[3] 2019 ESC/EAS Guidelines for the management of dyslipidaemias set the most aggressive target of less than 1.4 mmol/L and a reduction of more than 50% in LDL-C [17].

Secondly, our findings proved the safety of the LDL-C level lower than 1.4mmol/L in Chinese people: it did not associate with an increased risk of hemorrhagic stroke. Studies of LDL-C and ICH have reported conflicting results. In a twenty-year epidemiologic study, an excess risk of hemorrhagic stroke was observed in patients with uncontrolled hypertension and LDL-C <70 mg/dL (1.8mmol/L) [18]. However, in subgroup analysis of FOURIER trial [19], among patients with prior stroke, the risk of hemorrhagic stroke did not increase, even when the median LDL-C decreased from

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2.4 mmol/L at randomization to 0.8 (0.5–1.2) mmol/L at 48 weeks in the evolocumab group. All stroke and ischemic stroke were reduced, with no difference in hemorrhagic stroke. Meanwhile, in a systematic review and meta-analysis, the higher level of LDL-C seemed to be associated with a lower risk of hemorrhagic stroke [20]. Our study proved the efficacy and safety of that baseline LDL-C of <1.4 mmol/L in stroke patients, providing evidence for the first and second prevention strategies. Thirdly, we described the epidemiological characteristics of LDL-C levels and LLT of Chinese stroke patients. Compared to the study conducted in 2013 [21], our study indicated some progress in blood lipid management in mainland China. In our study, about 97% of patients had a medication history of LLT before onset. Compared to the LLT rate of 79.6% in 2013, over 90% of patients received LLT during hospitalization and at discharge; the LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. In addition, LDL-C goal achievement for 1.8mmol/L had improved mildly, increasing from 27.4% to 35.4%, while LDL-C goal achievement for 1.4mmol/L was 17.6% at 12 months. The non-ideal LLT compliance and LDL-C control rate might be due to statin intolerance in Asian people, including statin-associated myopathy and hemorrhagic stroke [22,23]. A meta-analysis indicated that statins increase the risk of hemorrhagic stroke in a medication dose-dependent and type of index brain vascular injury-dependent manner, while PCSK9 inhibitors do not increase hemorrhagic stroke risk[24]. Thus, statins, rather than low-leveled LDL-C, might closely relate to hemorrhagic stroke. PCSK9 inhibitors might be a more promising lipid-lowering medication class in patients with an elevated risk of

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hemorrhagic stroke. In addition, our analysis revealed a significant association between LLT at discharge and 3-month outcomes, indicating the importance of early LLT.

Fourthly, we did not observe the correlation between the 3-month LDL-C decrease amplitude and 12-month outcomes. To analyze the association of 3-month LDL-C change with 12-month outcomes, we excluded subjects who reached the end point within 3 months, which led to a limited sample size and loss of a considerable amount of target events, for most stroke recurrences happened within 3 months [25]. Another critical factor was that we could not adjust some risk factors in the model, such as IL-6 level and relevant intracranial artery stenosis (ICAS). They were independent risk factors of the residual risk. Although substantially reduced by secondary prevention treatment, there was still 8.3% residual risk of 12-month recurrent stroke even in patients with persistent adherence to guideline-based secondary stroke prevention [26].

Our study has several limitations. First, only LLT medication use at the follow-up time point was recorded, not the details of use during the whole trial, such as continuous use, intermittent use, and the change of dose; thus, lipid-lowering agents use at 3 months and 12 months could not represent the actual situation. Second, statin use before admission was not recorded in the trial and may confound the results. Details of medication use, such as class, dose, duration, and adherence of lipid-lowering agents, did not enter the regression model. Third, there could be some undetected confounding factors except for residual risk. Additionally, the trial was conducted exclusively on Chinese patients. The finding in this study needs to be

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further validated in studies with a larger sample size and non-Asian populations.

Conclusions

The LDL-C goal achievement has increased mildly in the stroke and TIA population in mainland China and improving of the LDL-C goal achievement is still an essential task for secondary prevention of stroke. The lowered baseline LDL-C level was significantly associated with a decreased short-and long-term risk of ischemic stroke among stroke and TIA patients. LDL-C<1.4mmol/L could be a safe standard for this population.

Ethics Approval Statement

The study protocol of the CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centers. Every participant provided written informed consent before participation.

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Competing Interests

The authors have no conflicts of interest to declare.

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Contributorship statement

(I) Conception and design: Drs. YY Xu and WQ Chen

(II) Administrative support: Drs. X Meng

(III) Provision of study materials or patients: Drs. X Meng, ZX Li

(IV) Collection and assembly of data: Drs. X Meng, XQ Zhao, LP Liu, and YL Wang

(V) Data analysis and interpretation: Drs. MX Wang and YS Pan

(VI) Manuscript writing: All authors.

(VII) Final approval of manuscript: All authors.

Data sharing statement

The datasets used in this study are not publicly available, but these can be provided on reasonable request after the approval.

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Figure 1. Dose-response-relationship curves

Adjusted odds ratio of events and MACE at 3 months and 12 months according to LDL-C at baseline in patients. (a) stroke at 3 months; (b) ischemic stroke at 3 months; (c) hemorrhagic stroke at 3 months; (d) MACE at 3 months; (e) stroke at 12 months; (f) ischemic stroke at 12 months; (g) hemorrhagic stroke at 12 months; (h) MACE at 12 months. The full line indicates the adjusted hazard ratio and the dashed lines the 95% confidence interval bands. Reference is LDL-C >2.6mmol/L. Data were fitted using a logistic regression model of restricted cubic spline with three knots (the 5th, 50th, 90th percentiles) for LDL-C level, adjusting for potential covariates.

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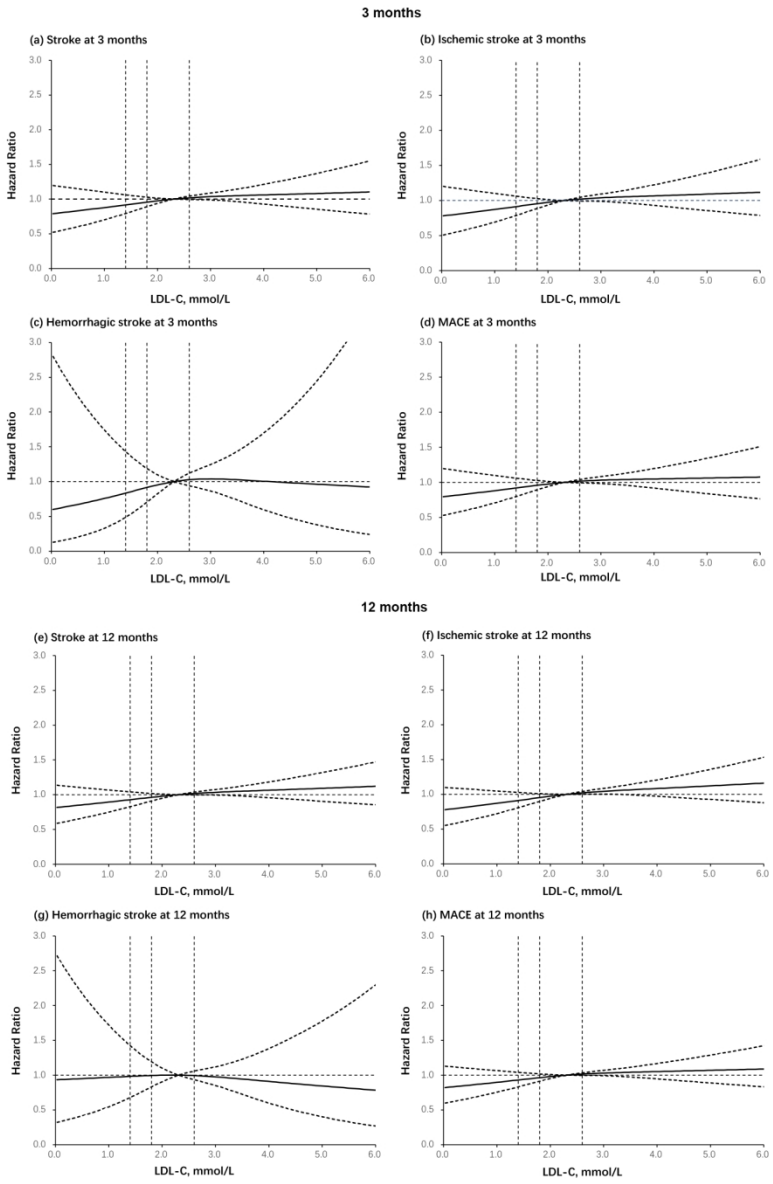

Dose-response-relationship curves

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13 13 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Lipid Management in Ischemic Stroke or Transient Ischemic Attack in China: Result from China National Stroke Registry III

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Lipid Management in Ischemic Stroke or Transient Ischemic Attack in China: Result from China National Stroke Registry III

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Running title: Lipid management in Ischemic Stroke or TIA

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Number of Figures: 1

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Keywords: low-density lipoprotein cholesterol, lipid-lowering treatment, ischemic stroke, second prevention

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Abstract

Background and purpose: Dyslipidaemia is a significant risk factor for ischemic stroke and transient ischemic attack (TIA). The aims of the study were to assess the management of low-density lipoprotein cholesterol (LDL-C) and the goal achievement, as well as to investigate the association between baseline LDL-C level, lipid-lowering treatment (LLT), and stroke recurrence in patients with ischemic stroke or TIA.

Methods: We derived data from the Third China National Stroke Registry (CNSR-III). The primary outcome was a new stroke, LDL-C goal (LDL-C<1.8mmol/L and LDL-C<1.4mmol/L, respectively) achievement rates, and LLT compliance within 3, 6, and 12 months. The associations among the baseline LDL-C level, LLT at discharge, and outcomes were also assessed.

Results: Among the 15,166 patients, over 90% of patients received LLT during hospitalization and 2 weeks after discharge; the LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. At 12 months, LDL-C goal achievement rate for 1.8mmol/L and 1.4mmol/L was 35.4% and 17.6%, respectively. LLT at discharge was associated with reduced risk of ischemic stroke recurrence (HR=0.687, 95% CI: 0.480-0.985, p=0.0411) at 3 months. The rate of LDL-C reduction from baseline to 3-month follow-up was not associated with a reduced risk of stroke recurrence or major adverse cardiovascular events (MACE) at 12 months. Patients with baseline LDL-C ≤1.4mmol/L had a numerically lower risk of stroke, ischemic stroke and MACE at both 3 months and 12 months.

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Conclusions: The LDL-C goal achievement rate has increased mildly in the stroke and TIA population in mainland China. Lowered baseline LDL-C level was significantly associated with a decreased short- and long-term risk of ischemic stroke among stroke and TIA patients. LDL-C<1.4mmol/L might be a safe standard for this population.

Strengths and limitations of this study

1. This hospital-based study analyzed the low-density lipoprotein cholesterol (LDL-C) levels and lipid-lowering therapy (LLT) in patients with ischemic stroke (IS)/transient ischemic attack (TIA) in the general population of mainland China.
2. The study included the largest sample of IS/TIA patients and recorded detailed prognostic characteristics.
3. The design of the cohort study did not allow for further detailed analysis of lipid-lowering medication use, such as dose change and duration.
4. Some undetected confounding factors, including residual risk, were not able to be assessed in this study.

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Introduction

Low-density lipoprotein cholesterol (LDL-C) has been well established as an independent risk factor for ischemic stroke [1]. Intensive lipid-lowering treatment (LLT) has been proven to reduce cardiovascular event recurrence in ischemic stroke (IS)/ transient ischemic attack (TIA) patients. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study [2] showed that intensive atorvastatin treatment for five years reduced the risk of stroke recurrence up to 16% (HR 0.84, 95% CI 0.71-0.99; P＜0.03) in IS/TIA. Recently, Treat Stroke to Target (TST) study [3] also demonstrated that IS/TIA patients who had a target LDL-C level of less than 70 mg/dl (1.8mmol/L) had a lower risk of subsequent cardiovascular events than those who had a target range of 90 to 110 mg/dl (HR 0.78, 95% CI 0.61-0.98; P=0.04). Therefore, European Stroke Organisation (ESO) and American Stroke Association (ASA) both updated the IS/TIA second prevention guideline with a recommendation of LDL-C target goal to be less than 70mg/dl (1.8mmol/L) [4,5].

However, there are still clinical questions not thoroughly investigated. Firstly, SPARCL and TST trials are randomized controlled trials conducted mainly in the Caucasian population [2,6], whereas studies focusing on the Asian population on lipid management in stroke patients are limited. Since there are more intracranial artery stenosis (ICAS) [7,8] and cerebral small vessel disease (CSVD) patients in Asia [9,10], especially in east Asia, the applicability of the conclusions of these two trials to Asian people should be discreet. Secondly, there are inconsistencies and conflicts about whether the reduced LDL-C level, especially during the acute or subacute phase,

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could increase the risk of intracranial hemorrhage (ICH). In the SPARCL study, subgroup analysis indicated that atorvastatin treatment might increase the risk of ICH, which led to a big concern for statin usage during the acute phase of IS/TIA [11]. In contrast, the TST study showed that the incidence of ICH did not differ significantly between the lower- and higher-target groups [3]. Thirdly, with emerging evidence from non-stain therapies such as IMPROVE-IT [12], FOURIER [13], and ODYSSEY [14], a lower LDL-C target of less than 1.4mmol/L or even 1.0mmol/L has been recommended for adoption as international guidelines. However, the benefits of a lower LDL-C target lower than 1.8mmol/L have not been investigated.

The Third China National Stroke Registry (CNSR-III) is one of the world's most extensive IS/TIA cohort studies and it includes comprehensive medical histories, centralized the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification judication, and follow-up outcomes. We aimed to collect data from CNSR-III to investigate the China's current lipid management practices and the associations between LDL-C level, LLT, and stroke recurrence in ischemic stroke or TIA patients.

Methods

Study design and participants

The study was based on the CNSR-III database. The CNSR-III is a nationwide clinical registry of ischemic stroke or transient ischemic attack (TIA) based on etiology, imaging, and biological markers in China from August 2015 to March 2018 [15]. 201 participating hospitals were selected in China, and 15,166 patients were

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eligible and had complete information at baseline. The total 15,166 patients were included in the analysis.

Among all the clinical centers included in CNSR-III, 169 centers voluntarily participated in the prespecified blood biomarker substudy, with all the patients at these centers participating in the biomarker substudy. Such patients provided a separate written informed consent form that included their consent for blood sample collection and further study of biomarkers.

The study protocol of the CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centres. Every participant provided written informed consent before participation.

Data Collection and Management

Patient information, including demographics, risk factors, comorbidities, medications, selected laboratory tests, and hospital-level characteristics, were collected systematically during hospitalization and at discharge by trained research coordinators at each participating hospital. National Institutes of Health Stroke Scale (NIHSS) score at admission, and ischemic stroke recurrence, composite vascular event, and modified Rankin Scale (mRS) at 3 months and 1 year after stroke onset were also collected.

Venous blood samples were collected from fasting patients within 24 hours from admission. Serum specimens were extracted, aliquoted, and transported through the cold chain to the central laboratory in Beijing Tiantan Hospital and stored at -80°C.

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LDL-C measurements were centrally and blindly assayed by enzymatic method on the Cobas 8000 analyzer c702 module (Roche Diagnostics, Mannheim, Germany).

Follow-Up and Clinical Outcome Evaluations

Patients were followed up through face-to-face interviews at 3 months and by telephone interviews at 6 and 12 months by trained research coordinators who followed a standardized interview protocol. Information collected at each follow-up included cardio- and cerebrovascular events, all causes of death, and medications use. Vascular events were confirmed with the treating hospital, and death was either confirmed based on a death certificate issued by the attended hospital or the local civil registry.

The primary outcome was a new stroke (defined as a new neurological deficit lasting more than 24 hours or re-hospitalization with a diagnosis of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage), LDL-C goal (LDL-C<1.4mmol/L, and LDL-C<1.8mmol/L, respectively) achievement rates and LLT compliance in China within 3, 6, and 12 months. The secondary outcomes included major adverse cardiovascular events (including stroke, myocardial infarction, or vascular death) and all caused death at 3 months and 12 months.

All reported efficacy and safety outcomes were verified by a central independent adjudication committee blinded to study treatment assignments and baseline LDL-C level.

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Patients were categorized into four groups according to the baseline LDL-C levels and lipid-lowering treatment during hospitalization and after discharge: LDL-C≤1.4mmol/L, 1.4mmol/L<LDL-C ≤1.8mmol/L, 1.8 mmol/L<LDL≤2.6mmol/L, LDL>2.6mmol/L.

LLT compliance was defined as the continuation of LLT medication from discharge to 3, 6, or 12 months after the onset of symptoms. Patients assigned to LLT at discharge but later discontinuing LLT at any follow-up point within 3, 6, or 12 months were considered "non-persistent". Patients were considered persistent if they discontinued one medication but replaced it with another statin medication that they continued taking through 3, 6, or 12 months after enrollment.

Statistical analysis

Baseline variables were presented as median with interquartile range (IQR) for continuous variables and percentages for categorical variables.

To analyze the association of baseline LDL-C levels and outcomes, we only included those subjects who provided 3-month or 12-month bio-sample. Univariate and multivariate Cox proportional hazard regression models were used. The model included the following covariates: age, sex, education, current smoking, heavy drinking, medical history, stroke severity on the NIHSS, history of stroke, history of diabetes, and history of hypertension. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The dose-response-relationship curves were also presented.

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To analyze the effect of discharge LLT on outcomes, we excluded subjects who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) during hospitalization. We performed a univariate model and multivariate analysis by adjusting for age, sex, education, current smoking, heavy drinking, medical history, stroke severity on the NIHSS, history of stroke, history of diabetes, and history of hypertension.

In addition, to analyze the association of 3-month LDL-C change with stroke recurrence and MACE within 12 months, we excluded subjects who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) within 3 months.

All statistical analyses in the study were performed by SAS 9.4 software. All statistical analysis adopted a two-sided test which was performed at a 5% significance level.

Patient and Public Involvement

This registry study was designed and conducted without patient and public involvement. Our results will be disseminated to the public through publication in this journal.

Results

Characteristics of study participants

From August 2015 to March 2018, a total of 15166 patients with acute stroke and TIA were recruited to the CNSR-III trial and entered our final analysis. The average age of

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patients was 62.2±11.3 years, 31.7% of patients were women, 14,146 (93.3%) had an index event of stroke, and 1020 (6.7%) had a TIA [15].

Baseline LDL-C levels

There were 10,738 patients in LDL-C analysis set: 1,407 (13.1%), 1,636 (15.2%), 3,655 (34.0%), and 4,040 (37.6%) patients with the baseline LDL-C ≤1.4mmol/L, 1.4–1.8mmol/L, 1.8–2.6mmol/L, ≥ 2.6mmol/L, respectively **(Table 1)**.

Table 1. Baseline Characteristics for the LDL-C analysis set

Variables	LDL≤1.4mmol/L N=1407	1.4 < LDL≤1.8mmol/L N=1636	1.8 < LDL≤2.6mmol/L N=3655	LDL>2.6mmol/L N=4040	P Value*
Women, n (%)	378 (26.9)	439 (26.8)	1057 (28.9)	1517 (37.6)	<0.001
Mean age, years (SD)	60.8±11.9	62.4±11.3	62.2±11.3	62.8±11.1	<0.001
Ethnicity (non-Han), n (%)	30 (2.1)	49 (3.0)	122 (3.3)	104 (2.6)	0.07
Current smoker, n (%)	435 (30.9)	525 (32.1)	1239 (33.9)	1198 (29.7)	<0.001
Heavy drinker, n (%)*	185 (13.2)	210 (12.8)	545 (14.9)	589 (14.6)	0.12
Triglycerides (IQR)	1.3 (0.9-1.9)	1.3 (1.0-1.8)	1.3 (1.0-1.8)	1.5 (1.1-2.0)	<0.001
TC, mmol/L	2.7 (2.4-3.1)	3.2 (3.0-3.5)	3.8 (3.5-4.1)	4.9 (4.5-5.5)	<0.001
HDL-C, mmol/L	0.8 (0.7-1.0)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	1.0 (0.8-1.2)	<0.001
LDL-C, mmol/L	1.2 (1.0-1.3)	1.6 (1.5-1.7)	2.2 (2.0-2.4)	3.2 (2.9-3.8)	<0.001
BMI	24.4 (22.5-26.4)	24.5 (22.7-26.6)	24.4 (22.5-26.4)	24.5 (22.7-26.7)	0.06
Systolic pressure, mmHg	145.0 (132.5-160.0)	146.5 (133.0-161.0)	148.5 (135.0-163.5)	150.0 (136.0-166.5)	<0.001
Medical history, n (%)					
Ischemic stroke	369 (26.2)	429 (26.2)	715 (19.6)	748 (18.5)	<0.001
TIA	44 (3.1)	46 (2.8)	115 (3.6)	102 (2.5)	0.38
Coronary heart diseases	147 (10.5)	193 (11.8)	366 (10.0)	449 (11.1)	0.20
Atrial fibrillation	93 (6.6)	124 (7.6)	272 (7.4)	257 (6.4)	0.19
Hypertension	897 (63.8)	1045 (63.9)	2295 (62.8)	2516 (62.3)	0.62
Diabetes mellitus	386 (27.4)	394 (24.1)	824 (22.5)	960 (23.8)	0.004
Hypercholesterolemia	119 (8.5)	120 (7.3)	302 (8.3)	341 (8.4)	0.56
NIHSS at admission, median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	<0.001
NIHSS 0–3	743 (52.8)	914 (55.9)	1974 (54.0)	2073 (51.3)	0.009
NIHSS≥4	664 (47.2)	722 (44.1)	1681 (46.0)	1967 (48.7)	
mRS (IQR)	0 (0-1.0)	0 (0-1.0)	0 (0-1.0)	0 (0-0)	<0.001
Stroke subtype, n (%)					
LAA	303 (21.5)	390 (23.8)	933 (25.5)	1092 (27.0)	0.0095
CE	81 (5.8)	96 (5.9)	251 (6.9)	256 (6.3)	
SAO	312 (22.2)	359 (21.9)	740 (20.3)	819 (20.3)	
Other	21 (1.5)	16 (1.0)	38 (1.0)	47 (1.2)	
Unknown	690 (49.0)	775 (47.4)	1693 (46.3)	1826 (45.2)	
Prestroke antiplatelet therapy, n (%)	1357 (97.4)	1569 (97.1)	3504 (96.7)	3894 (97.0)	0.57

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Prestroke LLT, n (%)	1359 (97.6)	1558 (96.4)	3498 (96.5)	3897 (97.1)	0.15
Statin, n (%)	1355 (97.3)	1556 (96.3)	3491 (96.3)	3887 (96.9)	0.27

TC: total cholesterol. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. BMI: body mass index. TIA: transient ischemic attack. NIHSS: National Institutes of Health Stroke Scale. mRS: modified Rankin Scale. LAA: large artery atherosclerosis. CE: cardiogenic embolism. SAO: small artery occlusion. LLT: lipid-lowering therapy.

Patients in the lower baseline LDL-C level group (≤1.4 mmol/L) were more likely to be younger (p<0.0001) and had a greater prevalence of cardiovascular risk factors (previous stroke, hypertension, hypercholesterolemia, diabetes mellitus, and history of stroke) (p<0.0001) and lower levels of triglycerides, total cholesterol and high-density lipoprotein (HDL) (p<0.0001). About 97% of the patients had a history of antiplatelet and lipid-lowering therapy, and the rates showed no difference among the four baseline LDL-C groups.

Association between baseline LDL-C levels and outcomes at 3 months and 12 months

There were 656 (6.11%) new stroke occurrences at 3 months and 1037 (9.66%) at 12 months **(Table 2)**.

Table 2. Association between baseline LDL-C levels and outcomes at 3 months and 12 months

	Total	Events (n%)	HR (95% CI) Unadjusted	*P* value	HR (95% CI) Adjusted	*P* value
3 months						
Stroke recurrence						
LDL≤1.4mmol/L	1407	69 (4.9)	0.72 (0.55-0.94)	0.01	0.74 (0.57-0.97)	0.03
1.4<LDL≤1.8mmol/L	1636	95 (5.8)	0.85 (0.68-1.08)	0.18	0.89 (0.70-1.12)	0.32
1.8<LDL≤2.6mmol/L	3655	219 (6.0)	0.88 (0.74-1.05)	0.17	0.91 (0.76-1.08)	0.28
LDL>2.6mmol/L	4040	273 (6.8)	Reference	-	Reference	-
Ischemic stroke						
LDL≤1.4mmol/L	1407	65 (4.6)	0.72 (0.55-0.95)	0.02	0.74 (0.56-0.98)	0.03
1.4<LDL≤1.8mmol/L	1636	88 (5.4)	0.84 (0.66-1.07)	0.16	0.87 (0.68-1.11)	0.27
1.8<LDL≤2.6mmol/L	3655	201 (5.5)	0.86 (0.72-1.04)	0.11	0.89 (0.74-1.07)	0.22
LDL>2.6mmol/L	4040	257 (6.4)	Reference	-	Reference	-
Hemorrhagic stroke						
LDL≤1.4mmol/L	1407	4 (0.3)	0.52 (0.18-1.51)	0.23	0.55 (0.19-1.61)	0.28

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1.4＜LDL≤1.8mmol/L	1636	9 (0.6)	1.01 (0.46-2.19)	0.98	1.03 (0.47-2.26)	0.93
1.8＜LDL≤2.6mmol/L	3655	20 (0.6)	1.00 (0.55-1.84)	0.99	0.93 (0.50-1.73)	0.82
LDL>2.6mmol/L	4040	22 (0.5)	Reference	-	Reference	-
MACE						
LDL≤1.4mmol/L	1407	71 (5.1)	0.72 (0.56-0.94)	0.01	0.75 (0.57-0.97)	0.03
1.4＜LDL≤1.8mmol/L	1636	100 (6.1)	0.88 (0.70-1.10)	0.27	0.91 (0.72-1.15)	0.42
1.8＜LDL≤2.6mmol/L	3655	231 (6.3)	0.91 (0.77-1.08)	0.29	0.93 (0.78-1.11)	0.43
LDL>2.6mmol/L	4040	279 (6.9)	Reference	-	Reference	-
12 months						
Stroke recurrence						
LDL≤1.4mmol/L	1407	114 (8.1)	0.76 (0.62-0.93)	0.009	0.77 (0.62-0.95)	0.01
1.4＜LDL≤1.8mmol/L	1636	158 (9.7)	0.91 (0.76-1.08)	0.30	0.92 (0.76-1.10)	0.36
1.8＜LDL≤2.6mmol/L	3655	339 (9.7)	0.87 (0.76-1.01)	0.06	0.89 (0.77-1.03)	0.12
LDL>2.6mmol/L	4040	426 (10.5)	Reference	-	Reference	-
Ischemic stroke						
LDL≤1.4mmol/L	1407	102 (7.6)	0.72 (0.58-0.90)	0.004	0.73 (0.59-0.91)	0.005
1.4＜LDL≤1.8mmol/L	1636	145 (8.9)	0.89 (0.73-1.07)	0.22	0.90 (0.74-1.09)	0.27
1.8＜LDL≤2.6mmol/L	3655	304 (8.3)	0.83 (0.72-0.97)	0.02	0.86 (0.74-1.00)	0.04
LDL>2.6mmol/L	4040	400 (9.9)	Reference	-	Reference	-
Hemorrhagic stroke						
LDL≤1.4mmol/L	1407	12 (0.9)	0.96 (0.50-1.84)	0.89	0.97 (0.50-1.88)	0.93
1.4＜LDL≤1.8mmol/L	1636	15 (0.9)	1.03 (0.56-1.87)	0.94	1.02 (0.56-1.88)	0.95
1.8＜LDL≤2.6mmol/L	3655	37 (1.0)	1.13 (0.72-1.80)	0.59	1.10 (0.69-1.75)	0.69
LDL>2.6mmol/L	4040	36 (0.9)	Reference	-	Reference	-
MACE						
LDL≤1.4mmol/L	1407	119 (8.5)	0.76 (0.62-0.93)	0.008	0.77 (0.62-0.94)	0.01
1.4＜LDL≤1.8mmol/L	1636	170 (10.4)	0.94 (0.79-1.12)	0.47	0.94 (0.79-1.13)	0.50
1.8＜LDL≤2.6mmol/L	3655	363 (9.9)	0.90 (0.78-1.03)	0.13	0.91 (0.79-1.05)	0.20
LDL>2.6mmol/L	4040	444 (11.0)	Reference	-	Reference	-

LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events.

Compared with patients with other LDL-C level subgroups, the patients with LDL-C ≤1.4mmol/L had a numerically lower risk of stroke (HR=0.742, 95% CI: 0.568-0.970, p=0.0291), ischaemic stroke (HR=0.741, 95% CI: 0.562-0.976, p=0.0329) and MACE (HR=0.746, 95% CI: 0.573-0.972, p=0.0297) at 3 months. Similar results were found for the outcome of stroke (HR=0.767, 95% CI: 0.622-0.946, p=0.0131), ischaemic stroke (HR=0.731, 95% CI: 0.587-0.911, p=0.0052) and MACE (HR=0.766, 95% CI: 0.624-0.940, p=0.0106) at 12 months after the initial event. Lower baseline LDL-C level was not associated with an increased risk of hemorrhagic stroke at either 3 months or 12 months **(Table 2)**. Using a Cox regression model with restricted cubic

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splines, a strong association was also found between baseline LDL-C level and risk of stroke, ischemic stroke, hemorrhagic stroke, and MACE (**Figure 1**).

Lipid-lowering management, LLT compliance, and association of discharge LLT and outcomes

LLT management and compliance of the included patients during hospitalization, at discharge, 3 months, 6 months, and 12 months after the initial event were shown in **Table 3**.

Table 3. Lipid-lowering Treatment (LLT) and the compliance of patients in CNSR-III

	Hospitalization	Discharge	3 months	6 months	12 months
Non LLT	547 (3.6)	1300 (8.6)	2590 (17.4)	3007 (22.4)	3754 (26.0)
LLT	14506 (96.4)	13831 (91.4)	12271 (82.6)	11726 (77.6)	10682 (74.0)
Compliance					
Non-Persistent	/	/	2147 (15.5)	3382 (24.5)	4863 (35.2)
Persistent	/	/	11684 (84.5)	10449 (75.6)	8968 (64.8)

Over 90% of patients received LLT during hospitalization and for 2 weeks after discharge. The LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. The drug regimens of LLT for the patients in CNSR-III at 3 months, 6 months, and 12 months were shown in **Table 4**.

Table 4. Lipid-lowering Treatment of the included patients in CNSR-III at 3-month, 6-month, 12-month follow-up (n=15166)

Treatment	Patients with statins, N (%)				
	Hospitalization	Discharge	3 months	6 months	12 months
Atorvastatin	10527 (69.41)	9851 (64.95)	8656 (57.08)	8228 (54.25)	7470 (49.25)
<40mg	7442 (70.71)	8770 (89.03)	8284 (95.7)	7963 (96.78)	7269 (97.35)
≥40mg	3083 (29.29)	1081 (10.97)	372 (4.3)	265 (3.22)	198 (2.65)
Rosuvastatin	3546 (23.38)	3395 (22.39)	2903 (19.14)	2779 (18.32)	2489 (16.41)
<20mg	2876 (81.15)	2983 (87.86)	2650 (91.38)	2536 (91.29)	2313 (92.93)
≥20mg	668 (18.85)	412 (12.14)	250 (8.62)	242 (8.71)	176 (7.07)
Simvastatin	272 (1.79)	239 (1.58)	390 (2.57)	411 (2.71)	444 (2.93)
Pravastatin	166 (1.09)	165 (1.09)	137 (0.9)	128 (0.84)	100 (0.66)

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lovastatin	25 (0.16)	24 (0.16)	33 (0.22)	33 (0.22)	30 (0.2)
Fluvastatin	54 (0.36)	53 (0.35)	52 (0.34)	43 (0.28)	47 (0.31)
Pravastatin	61 (0.40)	78 (0.51)	70 (0.46)	64 (0.42)	61 (0.4)

Compared with the non-discharge LLT group, LLT at discharge was associated with reduced risk of ischemic stroke (HR=0.65, 95% CI: 0.45-0.94, p=0.02) and stroke recurrence (HR=0.69, 95% CI: 0.48-0.99, p=0.04) at 3 months **(Table 5)**.

Table 5. The association of Discharge Lipid Lowering Therapy (LLT) and outcomes

	Total	Events, (n%)	HR (95% CI) Unadjusted	*P* value	HR (95% CI) Adjusted	*P* value
3 months						
Stroke recurrence						
Discharge LLT	13248	269 (2.0%)	0.68(0.48-0.96)	0.03	0.69(0.48-0.99)	0.04
Non discharge LLT	1181	35 (3.0%)	Reference		Reference	
Ischemic stroke						
Discharge LLT	13263	245 (1.9%)	0.68(0.47-0.98)	0.04	0.65(0.45-0.94)	0.02
Non discharge LLT	1188	32 (2.7%)	Reference		Reference	
Hemorrhagic stroke						
Discharge LLT	13740	31 (0.2%)	0.71(0.25-2.01)	0.52	1.19(0.36-3.98)	0.78
Non discharge LLT	1266	4 (0.3%)	Reference		Reference	
MACE						
Discharge LLT	13248	299 (2.3%)	0.71(0.51-1.003)	0.052	0.74(0.52-1.04)	0.08
Non discharge LLT	1181	37 (3.1%)	Reference		Reference	
12 months						
Stroke recurrence						
Discharge LLT	13248	758 (5.7%)	0.88(0.7-1.12)	0.30	0.89(0.7-1.14)	0.36
Non discharge LLT	1181	75 (6.4%)	Reference		Reference	
Ischemic stroke						
Discharge LLT	13263	683 (5.2%)	0.87(0.68-1.11)	0.26	0.86(0.67-1.10)	0.23
Non discharge LLT	1188	69 (5.8%)	Reference		Reference	
Hemorrhagic stroke						
Discharge LLT	13740	86 (0.6%)	0.97(0.47-2.00)	0.94	1.23(0.56-2.69)	0.60
Non discharge LLT	1266	8 (0.6%)	Reference		Reference	
MACE						
Discharge LLT	13248	838 (6.3%)	0.94(0.75-1.19)	0.60	0.96(0.76-1.21)	0.72
Non discharge LLT	1181	78(6.6%)	Reference		Reference	

Patients who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) during hospitalization were excluded.

LDL-C goal achievement and the association of LDL-C changes (from baseline to 3 months) with outcomes at 12 months

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The overall blood lipid levels at baseline and at 3-month, and 12-month follow-up were shown in **Table 6**. LDL-C goal of 1.8mmol/L was achieved by 28.3% of patients at baseline, 46.7% at 3 months, and 35.4% at 12 months; LDL-C goal of 1.4mmol/L was achieved by 13.1% of patients at baseline, 25.6% at 3 months, and 17.6% at 12 months.

Table 6. Blood Lipid Level of the included patients at baseline, 3 months and 1 year in CNSR-III

Lipids, mmol/L	Baseline N=10738	3M N=6034	12M N=4899
Median triglycerides (IQR), mmol/L	1.37(1.03-1.87)	1.32(0.98-1.81)	1.46(1.04-2.16)
Total cholesterol, mmol/L	3.97(3.31-4.72)	3.74(3.13-4.54)	3.92(3.25-4.76)
HDL-C, mmol/L	0.93(0.78-1.12)	1.02(0.86-1.21)	0.99(0.79-1.2)
LDL-C, mmol/L	2.31(1.73-2.97)	1.87(1.39-2.55)	2.14(1.57-2.87)
LDL <1.4mmol/L, n (%)	1407 (13.1)	1547 (25.6)	862 (17.6)
1.4 < LDL≤1.8mmol/L, n (%)	1636 (15.2)	1272 (21.1)	872 (17.8)
1.8 < LDL≤2.6mmol/L, n (%)	3655 (34.0)	1785 (29.6)	1533 (31.3)
LDL>2.6mmol/L, n (%)	4040 (37.6)	1430 (23.7)	1632 (33.3)

HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol.

We did not find any significant association between the LDL-C reduction rate from baseline to 3-month follow-up and the risk of stroke and MACE at 12 months **(Table 7)**.

Table 7. Association of LDL-C changes (from baseline to 3 months) with outcomes at 12 months

Percentage of LDL level decrease (compared to baseline)	Total	Events, (n%)	HR (95% CI) unadjusted	*P* value	HR (95% CI) adjusted	*P* value
12 months						
Stroke recurrence*						
<30%, n (%)	3526	137 (3.9)	1.48 (0.92-2.39)	0.11	1.42 (0.87-2.30)	0.16
30-50%, n (%)	1146	45 (3.9)	1.50 (0.88-2.56)	0.14	1.44 (0.84-2.47)	0.19
>50%, n (%)	718	19 (2.7)	Reference		Reference	
MACE‡						

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<30%, n (%)	3526	149 (4.2)	1.46 (0.92-2.20)	0.11	1.39 (0.88-2.21)	0.16
30-50%, n (%)	1146	47 (4.1)	1.41 (0.84-2.36)	0.19	1.36 (0.81-2.28)	0.24
>50%, n (%)	718	21 (2.9)	Reference		Reference	

* Patients with stroke recurrence, death, and loss to follow-up within 3 months were excluded.

‡ Patients with MACE, death, and loss to follow-up within 3 months were excluded.

Discussion

This national hospital-based study described the current LDL-C level and LLT of IS/TIA patients in the real world. We described the LLT management and LDL-C goal achievement. We also found that a lowered baseline LDL-C level was associated with a decreased risk of new ischemic stroke and MACE at both 3 months and 12 months after the initial event, without an increased risk of intracranial hemorrhage. In addition, LLT at discharge was associated with a reduced risk of CV events at 3 and 12 months. Given the large sample size of LDL-C levels of IS/TIA patients and comprehensive prognostic characteristics recorded, these findings may have important clinical implications.

Firstly, LDL-C of 1.4 mmol/l might be a reasonable target for the high-risk population. Our study indicated that the LDL ≤1.4 mmol/L group, with the highest risk factors, had the lowest stroke and MACE rates at 3 and 12 months. The paradox of high risk of stroke with low LDL-C level could be due to the previous intensive LLT and rigid LDL-C control. It is consistent with the previous study that fixed-dose statin regimens are less effective than targeting LDL-C levels of 1.8 or 1.4 mmol/l when pre-treatment LDL-C levels exceed 4 mmol/L [16]; and the target of 1.4 mmol/l recently advocated in particularly high-risk patients is most effective when pre-treatment LDL-C exceeds 3 mmol/l [16]. In addition, 2019 ESC/EAS Guidelines for the management of dyslipidaemias set the most aggressive target of less than 1.4 mmol/L

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and a reduction of more than 50% in LDL-C [17].

Secondly, our findings suggested that the safety of the LDL-C ≤1.4mmol/L at least in Chinese population, because this level was not associate with an increased risk of hemorrhagic stroke. Studies of LDL-C and ICH have reported conflicting results. In a twenty-year epidemiologic study, an excess risk of hemorrhagic stroke was observed in patients with uncontrolled hypertension and LDL-C <70 mg/dL (1.8mmol/L) [18]. However, in a subgroup analysis of FOURIER trial [19], among patients with prior stroke, the risk of hemorrhagic stroke did not increase, even when the median LDL-C decreased from 2.4 mmol/L at randomization to 0.8 (0.5–1.2) mmol/L at 48 weeks in the evolocumab group. All stroke and ischemic stroke rates were reduced, and the rate of hemorrhagic stroke was not significantly changed. Meanwhile, in a systematic review and meta-analysis, the higher level of LDL-C tended to be associated with a lower risk of hemorrhagic stroke [20]. Thus, our study indicated the efficacy and safety of the baseline LDL-C of <1.4 mmol/L in IS/TIA patients, providing evidence for the first and second prevention strategies.

Thirdly, we described the epidemiological characteristics of Chinese IS/TIA patients in relation to their LDL-C levels and LLT. Compared to the study conducted in 2013 [21], our study indicated some progress in blood lipid management in mainland China. Notably, about 97% of patients had LLT medication history prior to the entry into our study. Also, compared to the LLT rate of 79.6% in 2013, over 90% of patients in our cohort received LLT during hospitalization and at discharge; the LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. In addition, LDL-C

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goal achievement for 1.8mmol/L had improved mildly, from 27.4% to 35.4%, and LDL-C goal achievement for 1.4mmol/L was 17.6% at 12 months. The less than perfect LLT compliance and LDL-C control rate might be due to statin intolerance in Asian people, including statin-associated myopathy and hemorrhagic stroke [22,23]. An earlier meta-analysis indicated that statins increase the risk of hemorrhagic stroke in a medication dose-dependent and type of index brain vascular injury-dependent manner, while PCSK9 inhibitors do not increase hemorrhagic stroke risk [24]. Thus, statins, rather than low-level of LDL-C, might closely relate to the risk of hemorrhagic stroke. Accordingly, PCSK9 inhibitors might be a more promising lipid-lowering medication class in patients with an elevated risk of hemorrhagic stroke. In addition, our analysis revealed a significant association between LLT at discharge and 3-month outcomes, indicating the importance of early LLT implementation.

Fourthly, we did not observe the correlation between the 3-month LDL-C decrease amplitude and 12-month outcomes. To analyze the association of 3-month LDL-C change with 12-month outcomes, we excluded subjects who reached the end point within 3 months, which led to a reduction of our sample size and a loss of a considerable number of target events, for most stroke recurrences occurred within 3 months [25]. Another critical factor was that we could not adjust some risk factors in the model, such as IL-6 level or the evidence of relevant intracranial artery stenosis (ICAS), which were independent risk factors of the residual risk. Although substantially reduced by secondary prevention treatment, there was still 8.3% residual

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risk of 12-month recurrent stroke even in patients with persistent adherence to guideline-based secondary stroke prevention [26].

Our study has several limitations. First, only LLT medication use at the follow-up time points was recorded, whereas additional details of use during the whole trial, such as continuous use, intermittent use, and the dose changes were not subjected to specific analysis. Thus, lipid-lowering agents use at 3 months and 12 months provided only a partial picture of the course of medication during the trial. Second, statin use before admission was not recorded in the trial which may confound the results. Furthermore, details of medication use, such as class, dose, duration, and adherence of lipid-lowering agents, did not enter the regression model. Third, there could be some undetected confounding factors in addition to those regarded as the residual risk. Forth, the use of dual antiplatelet therapy may reduce the risk of a 3-month recurrence of stroke for more than half of the patients presented with an initial NIHSS score of ≤3. Fifth, the trial was conducted exclusively on Chinese patients. The finding in this study needs to be further validated in studies with a larger sample size and non-Asian populations.

Conclusions

The LDL-C goal achievement has increased mildly in the stroke and TIA population in mainland China, and its further improvement is still an essential task for secondary prevention of stroke. The lowered baseline LDL-C level was significantly associated with a decreased short-and long-term risk of ischemic stroke among stroke and TIA patients. LDL-C<1.4mmol/L could be a safe standard for this population.

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Ethics Approval Statement

The study protocol of the CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centers. Every participant provided written informed consent before participation.

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Competing Interests

The authors have no conflicts of interest to declare.

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Contributorship statement

Drs. YY Xu and X Meng conceived and designed the study. Drs. X Meng and YJ Wang served as scientific advisors. Drs. X Meng, ZX Li, Hao Li, and YJ Wang critically reviewed the study proposal. Drs. X Meng, XQ Zhao, LP Liu, and YL Wang collected and assembled the data. Drs. MX Wang and YS Pan did statistical analyses. Drs. YY Xu and WQ Chen interpreted the data. Drs. YY Xu drafted the manuscript and did the language editing. Dr. X Meng is responsible for the overall content as

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guarantor. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

The datasets used in this study are not publicly available, but these can be provided on reasonable request after the approval.

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Figure 1. Dose-response-relationship curves

Adjusted odds ratio of events and MACE at 3 months and 12 months according to LDL-C at baseline in patients. (a) stroke at 3 months; (b) ischemic stroke at 3 months; (c) hemorrhagic stroke at 3 months; (d) MACE at 3 months; (e) stroke at 12 months; (f) ischemic stroke at 12 months; (g) hemorrhagic stroke at 12 months; (h) MACE at 12 months. The full line indicates the adjusted hazard ratio and the dashed lines the 95% confidence interval bands. Reference is LDL-C >2.6mmol/L. Data were fitted using a logistic regression model of restricted cubic spline with three knots (the 5th, 50th, 90th percentiles) for LDL-C level, adjusting for potential covariates.

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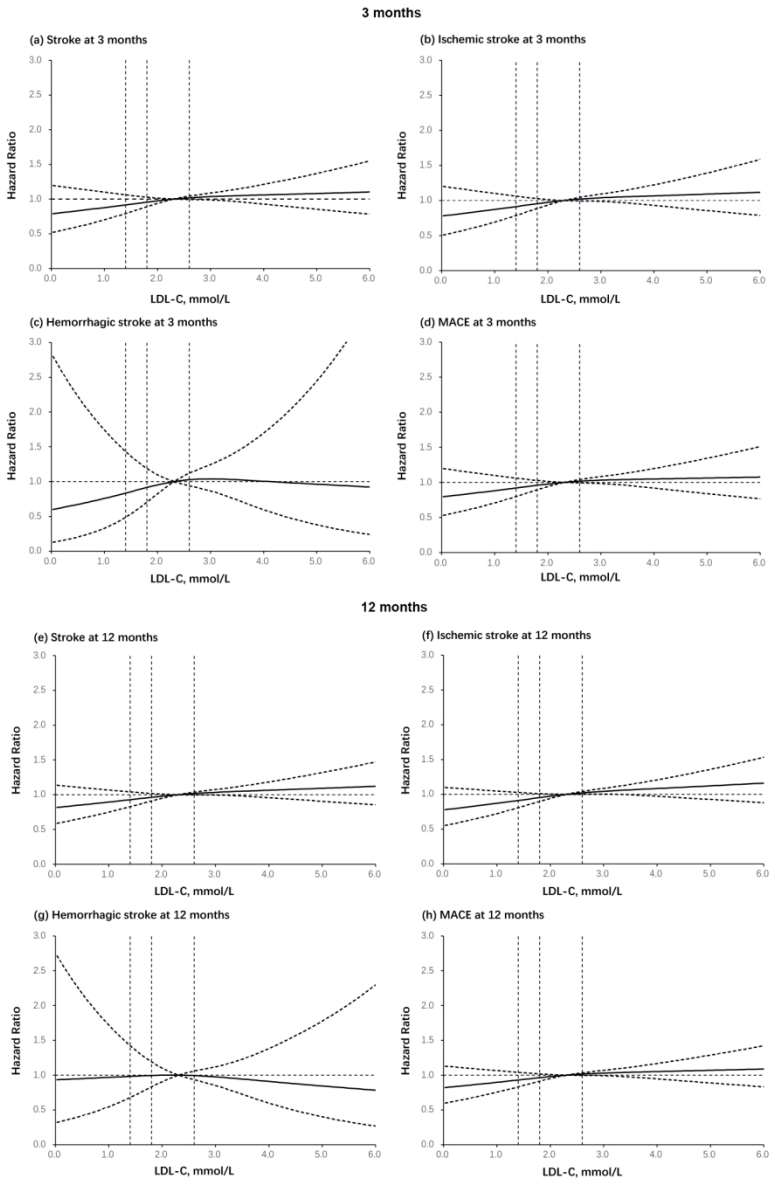

Dose-response-relationship curves

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13 13 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Lipid Management in Ischemic Stroke or Transient Ischemic Attack in China: Result from China National Stroke Registry III

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Lipid Management in Ischemic Stroke or Transient Ischemic Attack in China: Result from China National Stroke Registry III

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Keywords: low-density lipoprotein cholesterol, lipid-lowering treatment, ischemic stroke, second prevention

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Abstract

Background and purpose: Dyslipidaemia is a significant risk factor for ischemic stroke and transient ischemic attack (TIA). The aims of the study were to assess the management of low-density lipoprotein cholesterol (LDL-C) and the goal achievement, as well as to investigate the association between baseline LDL-C level, lipid-lowering treatment (LLT), and stroke recurrence in patients with ischemic stroke or TIA.

Methods: We derived data from the Third China National Stroke Registry (CNSR-III). The primary outcome was a new stroke, LDL-C goal (LDL-C<1.8mmol/L and LDL-C<1.4mmol/L, respectively) achievement rates, and LLT compliance within 3, 6, and 12 months. The associations among the baseline LDL-C level, LLT at discharge, and outcomes were also assessed.

Results: Among the 15,166 patients, over 90% of patients received LLT during hospitalization and 2 weeks after discharge; the LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. At 12 months, LDL-C goal achievement rate for 1.8mmol/L and 1.4mmol/L was 35.4% and 17.6%, respectively. LLT at discharge was associated with reduced risk of ischemic stroke recurrence (HR=0.687, 95% CI: 0.480-0.985, p=0.0411) at 3 months. The rate of LDL-C reduction from baseline to 3-month follow-up was not associated with a reduced risk of stroke recurrence or major adverse cardiovascular events (MACE) at 12 months. Patients with baseline LDL-C ≤1.4mmol/L had a numerically lower risk of stroke, ischemic stroke and MACE at both 3 months and 12 months.

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Conclusions: The LDL-C goal achievement rate has increased mildly in the stroke and TIA population in mainland China. Lowered baseline LDL-C level was significantly associated with a decreased short- and long-term risk of ischemic stroke among stroke and TIA patients. LDL-C<1.4mmol/L might be a safe standard for this population.

Strengths and limitations of this study

1. This hospital-based study analyzed the low-density lipoprotein cholesterol (LDL-C) levels and lipid-lowering therapy (LLT) in patients with ischemic stroke (IS)/transient ischemic attack (TIA) in the general population of mainland China.
2. The study included the largest sample of IS/TIA patients and recorded detailed prognostic characteristics.
3. The design of the cohort study did not allow for further detailed analysis of lipid-lowering medication use, such as dose change and duration.
4. Some undetected confounding factors, including residual risk, were not able to be assessed in this study.

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Introduction

Low-density lipoprotein cholesterol (LDL-C) has been well established as an independent risk factor for ischemic stroke [1]. Intensive lipid-lowering treatment (LLT) has been proven to reduce cardiovascular event recurrence in ischemic stroke (IS)/ transient ischemic attack (TIA) patients. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study [2] showed that intensive atorvastatin treatment for five years reduced the risk of stroke recurrence up to 16% (HR 0.84, 95% CI 0.71-0.99; P＜0.03) in IS/TIA. Recently, Treat Stroke to Target (TST) study [3] also demonstrated that IS/TIA patients who had a target LDL-C level of less than 70 mg/dl (1.8mmol/L) had a lower risk of subsequent cardiovascular events than those who had a target range of 90 to 110 mg/dl (HR 0.78, 95% CI 0.61-0.98; P=0.04). Therefore, European Stroke Organisation (ESO) and American Stroke Association (ASA) both updated the IS/TIA second prevention guideline with a recommendation of LDL-C target goal to be less than 70mg/dl (1.8mmol/L) [4,5].

However, there are still clinical questions not thoroughly investigated. Firstly, SPARCL and TST trials are randomized controlled trials conducted mainly in the Caucasian population [2,6], whereas studies focusing on the Asian population on lipid management in stroke patients are limited. Since there are more intracranial artery stenosis (ICAS) [7,8] and cerebral small vessel disease (CSVD) patients in Asia [9,10], especially in east Asia, the applicability of the conclusions of these two trials to Asian people should be discreet. Secondly, there are inconsistencies and conflicts about whether the reduced LDL-C level, especially during the acute or subacute phase,

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could increase the risk of intracranial hemorrhage (ICH). In the SPARCL study, subgroup analysis indicated that atorvastatin treatment might increase the risk of ICH, which led to a big concern for statin usage during the acute phase of IS/TIA [11]. In contrast, the TST study showed that the incidence of ICH did not differ significantly between the lower- and higher-target groups [3]. Thirdly, with emerging evidence from non-stain therapies such as IMPROVE-IT [12], FOURIER [13], and ODYSSEY [14], a lower LDL-C target of less than 1.4mmol/L or even 1.0mmol/L has been recommended for adoption as international guidelines. However, the benefits of a lower LDL-C target lower than 1.8mmol/L have not been investigated.

The Third China National Stroke Registry (CNSR-III) is one of the world's most extensive IS/TIA cohort studies and it includes comprehensive medical histories, centralized the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification judication, and follow-up outcomes. We aimed to collect data from CNSR-III to investigate the China's current lipid management practices and the associations between LDL-C level, LLT, and stroke recurrence in ischemic stroke or TIA patients.

Methods

Study design and participants

This study was based on the CNSR-III database. The CNSR-III is a nationwide clinical registry of ischemic stroke or transient ischemic attack (TIA) based on etiology, imaging, and biological markers in China from August 2015 to March 2018 [15]. 201 participating hospitals were selected in China, and 15,166 patients were

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eligible and had complete information at baseline. The total 15,166 patients were included in the analysis. Among all the clinical centers included in CNSR-III, 169 centers voluntarily participated in the prespecified blood biomarker substudy, with all the patients at these centers participating in the biomarker substudy. Such patients provided a separate written informed consent form that included their consent for blood sample collection and further study of biomarkers. The study protocol of the CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centres. Every participant provided written informed consent before participation.

To eligible for this second analysis research, patients had to meet the following criteria: (1) age 18 or older; (2) hospitalized with a primary diagnosis of acute ischemic stroke or transient ischemic attack; (3) direct hospital admission from a physician's clinic or an emergency department; and (4) informed consent provided by the patient or legally authorized representative. Patients with intracranial hemorrhage, subarachnoid hemorrhage, or undetermined stroke were not included in this study. This study was approved by ethics committee at Beijing Tiantan Hospital (KY2019-109-01).

Data Collection and Management

Patient information, including demographics, risk factors, comorbidities, medications, selected laboratory tests, and hospital-level characteristics, were collected systematically during hospitalization and at discharge by trained research coordinators

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at each participating hospital. National Institutes of Health Stroke Scale (NIHSS) score at admission, and ischemic stroke recurrence, composite vascular event, and modified Rankin Scale (mRS) at 3 months and 1 year after stroke onset were also collected.

Venous blood samples were collected from fasting patients within 24 hours from admission. Serum specimens were extracted, aliquoted, and transported through the cold chain to the central laboratory in Beijing Tiantan Hospital and stored at -80°C. LDL-C measurements were centrally and blindly assayed by enzymatic method on the Cobas 8000 analyzer c702 module (Roche Diagnostics, Mannheim, Germany).

Follow-Up and Clinical Outcome Evaluations

Patients were followed up through face-to-face interviews at 3 months and by telephone interviews at 6 and 12 months by trained research coordinators who followed a standardized interview protocol. Information collected at each follow-up included cardio- and cerebrovascular events, all causes of death, and medications use. Vascular events were confirmed with the treating hospital, and death was either confirmed based on a death certificate issued by the attended hospital or the local civil registry.

The primary outcome was a new stroke (defined as a new neurological deficit lasting more than 24 hours or re-hospitalization with a diagnosis of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage), LDL-C goal (LDL-C<1.4mmol/L, and LDL-C<1.8mmol/L, respectively) achievement rates and LLT

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compliance in China within 3, 6, and 12 months. The secondary outcomes included major adverse cardiovascular events (including stroke, myocardial infarction, or vascular death) and all caused death at 3 months and 12 months.

All reported efficacy and safety outcomes were verified by a central independent adjudication committee blinded to study treatment assignments and baseline LDL-C level.

Patients were categorized into four groups according to the baseline LDL-C levels and lipid-lowering treatment during hospitalization and after discharge: LDL-C≤1.4mmol/L, 1.4mmol/L<LDL-C ≤1.8mmol/L, 1.8 mmol/L<LDL≤2.6mmol/L, LDL>2.6mmol/L.

LLT compliance was defined as the continuation of LLT medication from discharge to 3, 6, or 12 months after the onset of symptoms. Patients assigned to LLT at discharge but later discontinuing LLT at any follow-up point within 3, 6, or 12 months were considered “non-persistent”. Patients were considered persistent if they discontinued one medication but replaced it with another statin medication that they continued taking through 3, 6, or 12 months after enrollment.

Statistical analysis

Baseline variables were presented as median with interquartile range (IQR) for continuous variables and percentages for categorical variables.

To analyze the association of baseline LDL-C levels and outcomes, we only included those subjects who provided 3-month or 12-month bio-sample. Univariate and

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multivariate Cox proportional hazard regression models were used. The model included the following covariates: age, sex, education, current smoking, heavy drinking, medical history, stroke severity on the NIHSS, history of stroke, history of diabetes, and history of hypertension. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The dose-response-relationship curves were also presented.

To analyze the effect of discharge LLT on outcomes, we excluded subjects who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) during hospitalization. We performed a univariate model and multivariate analysis by adjusting for age, sex, education, current smoking, heavy drinking, medical history, stroke severity on the NIHSS, history of stroke, history of diabetes, and history of hypertension.

In addition, to analyze the association of 3-month LDL-C change with stroke recurrence and MACE within 12 months, we excluded subjects who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) within 3 months.

All statistical analyses in the study were performed by SAS 9.4 software. All statistical analysis adopted a two-sided test which was performed at a 5% significance level.

Patient and Public Involvement

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This registry study was designed and conducted without patient and public involvement. Our results will be disseminated to the public through publication in this journal.

Results

Characteristics of study participants

From August 2015 to March 2018, a total of 15166 patients with acute stroke and TIA were recruited to the CNSR-III and entered our final analysis. The average age of patients was 62.2±11.3 years, 31.7% of patients were women, 14,146 (93.3%) had an index event of stroke, and 1020 (6.7%) had a TIA [15].

Baseline LDL-C levels

There were 10,738 patients in LDL-C analysis set: 1,407 (13.1%), 1,636 (15.2%), 3,655 (34.0%), and 4,040 (37.6%) patients with the baseline LDL-C ≤1.4mmol/L, 1.4–1.8mmol/L, 1.8–2.6mmol/L, ≥ 2.6mmol/L, respectively **(Table 1)**.

Table 1. Baseline Characteristics for the LDL-C analysis set

Variables	LDL≤1.4mmol/L N=1407	1.4 < LDL≤1.8mmol/L N=1636	1.8 < LDL≤2.6mmol/L N=3655	LDL>2.6mmol/L N=4040	P Value*
Women, n (%)	378 (26.9)	439 (26.8)	1057 (28.9)	1517 (37.6)	<0.001
Mean age, years (SD)	60.8±11.9	62.4±11.3	62.2±11.3	62.8±11.1	<0.001
Ethnicity (non-Han), n (%)	30 (2.1)	49 (3.0)	122 (3.3)	104 (2.6)	0.07
Current smoker, n (%)	435 (30.9)	525 (32.1)	1239 (33.9)	1198 (29.7)	<0.001
Heavy drinker, n (%)*	185 (13.2)	210 (12.8)	545 (14.9)	589 (14.6)	0.12
Triglycerides (IQR)	1.3 (0.9-1.9)	1.3 (1.0-1.8)	1.3 (1.0-1.8)	1.5 (1.1-2.0)	<0.001
TC, mmol/L	2.7 (2.4-3.1)	3.2 (3.0-3.5)	3.8 (3.5-4.1)	4.9 (4.5-5.5)	<0.001
HDL-C, mmol/L	0.8 (0.7-1.0)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	1.0 (0.8-1.2)	<0.001
LDL-C, mmol/L	1.2 (1.0-1.3)	1.6 (1.5-1.7)	2.2 (2.0-2.4)	3.2 (2.9-3.8)	<0.001
BMI	24.4 (22.5-26.4)	24.5 (22.7-26.6)	24.4 (22.5-26.4)	24.5 (22.7-26.7)	0.06
Systolic pressure, mmHg	145.0 (132.5-160.0)	146.5 (133.0-161.0)	148.5 (135.0-163.5)	150.0 (136.0-166.5)	<0.001
Medical history, n (%)					
Ischemic stroke	369 (26.2)	429 (26.2)	715 (19.6)	748 (18.5)	<0.001

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TIA	44 (3.1)	46 (2.8)	115 (3.6)	102 (2.5)	0.38
Coronary heart diseases	147 (10.5)	193 (11.8)	366 (10.0)	449 (11.1)	0.20
Atrial fibrillation	93 (6.6)	124 (7.6)	272 (7.4)	257 (6.4)	0.19
Hypertension	897 (63.8)	1045 (63.9)	2295 (62.8)	2516 (62.3)	0.62
Diabetes mellitus	386 (27.4)	394 (24.1)	824 (22.5)	960 (23.8)	0.004
Hypercholesterolemia	119 (8.5)	120 (7.3)	302 (8.3)	341 (8.4)	0.56
NIHSS at admission, median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	<0.001
NIHSS 0–3	743 (52.8)	914 (55.9)	1974 (54.0)	2073 (51.3)	0.009
NIHSS≥4	664 (47.2)	722 (44.1)	1681 (46.0)	1967 (48.7)	
mRS (IQR)	0 (0-1.0)	0 (0-1.0)	0 (0-1.0)	0 (0-0)	<0.001
Stroke subtype, n (%)					
LAA	303 (21.5)	390 (23.8)	933 (25.5)	1092 (27.0)	0.0095
CE	81 (5.8)	96 (5.9)	251 (6.9)	256 (6.3)	
SAO	312 (22.2)	359 (21.9)	740 (20.3)	819 (20.3)	
Other	21 (1.5)	16 (1.0)	38 (1.0)	47 (1.2)	
Unknown	690 (49.0)	775 (47.4)	1693 (46.3)	1826 (45.2)	
Prestroke antiplatelet therapy, n (%)	1357 (97.4)	1569 (97.1)	3504 (96.7)	3894 (97.0)	0.57
Prestroke LLT, n (%)	1359 (97.6)	1558 (96.4)	3498 (96.5)	3897 (97.1)	0.15
Statin, n (%)	1355 (97.3)	1556 (96.3)	3491 (96.3)	3887 (96.9)	0.27

TC: total cholesterol. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. BMI: body mass index. TIA: transient ischemic attack. NIHSS: National Institutes of Health Stroke Scale. mRS: modified Rankin Scale. LAA: large artery atherosclerosis. CE: cardiogenic embolism. SAO: small artery occlusion. LLT: lipid-lowering therapy.

Patients in the lower baseline LDL-C level group (≤1.4 mmol/L) were more likely to be younger (p<0.0001) and had a greater prevalence of cardiovascular risk factors (previous stroke, hypertension, hypercholesterolemia, diabetes mellitus, and history of stroke) (p<0.0001) and lower levels of triglycerides, total cholesterol and high-density lipoprotein (HDL) (p<0.0001). About 97% of the patients had a history of antiplatelet and lipid-lowering therapy, and the rates showed no difference among the four baseline LDL-C groups.

Association between baseline LDL-C levels and outcomes at 3 months and 12 months

There were 656 (6.11%) new stroke occurrences at 3 months and 1037 (9.66%) at 12 months **(Table 2)**.

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Table 2. Association between baseline LDL-C levels and outcomes at 3 months and 12 months

	Total	Events (n%)	HR (95% CI) Unadjusted	*P* value	HR (95% CI) Adjusted	*P* value
3 months						
Stroke recurrence						
LDL≤1.4mmol/L	1407	69 (4.9)	0.72 (0.55-0.94)	0.01	0.74 (0.57-0.97)	0.03
1.4＜LDL≤1.8mmol/L	1636	95 (5.8)	0.85 (0.68-1.08)	0.18	0.89 (0.70-1.12)	0.32
1.8＜LDL≤2.6mmol/L	3655	219 (6.0)	0.88 (0.74-1.05)	0.17	0.91 (0.76-1.08)	0.28
LDL>2.6mmol/L	4040	273 (6.8)	Reference	-	Reference	-
Ischemic stroke						
LDL≤1.4mmol/L	1407	65 (4.6)	0.72 (0.55-0.95)	0.02	0.74 (0.56-0.98)	0.03
1.4＜LDL≤1.8mmol/L	1636	88 (5.4)	0.84 (0.66-1.07)	0.16	0.87 (0.68-1.11)	0.27
1.8＜LDL≤2.6mmol/L	3655	201 (5.5)	0.86 (0.72-1.04)	0.11	0.89 (0.74-1.07)	0.22
LDL>2.6mmol/L	4040	257 (6.4)	Reference	-	Reference	-
Hemorrhagic stroke						
LDL≤1.4mmol/L	1407	4 (0.3)	0.52 (0.18-1.51)	0.23	0.55 (0.19-1.61)	0.28
1.4＜LDL≤1.8mmol/L	1636	9 (0.6)	1.01 (0.46-2.19)	0.98	1.03 (0.47-2.26)	0.93
1.8＜LDL≤2.6mmol/L	3655	20 (0.6)	1.00 (0.55-1.84)	0.99	0.93 (0.50-1.73)	0.82
LDL>2.6mmol/L	4040	22 (0.5)	Reference	-	Reference	-
MACE						
LDL≤1.4mmol/L	1407	71 (5.1)	0.72 (0.56-0.94)	0.01	0.75 (0.57-0.97)	0.03
1.4＜LDL≤1.8mmol/L	1636	100 (6.1)	0.88 (0.70-1.10)	0.27	0.91 (0.72-1.15)	0.42
1.8＜LDL≤2.6mmol/L	3655	231 (6.3)	0.91 (0.77-1.08)	0.29	0.93 (0.78-1.11)	0.43
LDL>2.6mmol/L	4040	279 (6.9)	Reference	-	Reference	-
12 months						
Stroke recurrence						
LDL≤1.4mmol/L	1407	114 (8.1)	0.76 (0.62-0.93)	0.009	0.77 (0.62-0.95)	0.01
1.4＜LDL≤1.8mmol/L	1636	158 (9.7)	0.91 (0.76-1.08)	0.30	0.92 (0.76-1.10)	0.36
1.8＜LDL≤2.6mmol/L	3655	339 (9.7)	0.87 (0.76-1.01)	0.06	0.89 (0.77-1.03)	0.12
LDL>2.6mmol/L	4040	426 (10.5)	Reference	-	Reference	-
Ischemic stroke						
LDL≤1.4mmol/L	1407	102 (7.6)	0.72 (0.58-0.90)	0.004	0.73 (0.59-0.91)	0.005
1.4＜LDL≤1.8mmol/L	1636	145 (8.9)	0.89 (0.73-1.07)	0.22	0.90 (0.74-1.09)	0.27
1.8＜LDL≤2.6mmol/L	3655	304 (8.3)	0.83 (0.72-0.97)	0.02	0.86 (0.74-1.00)	0.04
LDL>2.6mmol/L	4040	400 (9.9)	Reference	-	Reference	-
Hemorrhagic stroke						
LDL≤1.4mmol/L	1407	12 (0.9)	0.96 (0.50-1.84)	0.89	0.97 (0.50-1.88)	0.93
1.4＜LDL≤1.8mmol/L	1636	15 (0.9)	1.03 (0.56-1.87)	0.94	1.02 (0.56-1.88)	0.95
1.8＜LDL≤2.6mmol/L	3655	37 (1.0)	1.13 (0.72-1.80)	0.59	1.10 (0.69-1.75)	0.69
LDL>2.6mmol/L	4040	36 (0.9)	Reference	-	Reference	-
MACE						
LDL≤1.4mmol/L	1407	119 (8.5)	0.76 (0.62-0.93)	0.008	0.77 (0.62-0.94)	0.01
1.4＜LDL≤1.8mmol/L	1636	170 (10.4)	0.94 (0.79-1.12)	0.47	0.94 (0.79-1.13)	0.50
1.8＜LDL≤2.6mmol/L	3655	363 (9.9)	0.90 (0.78-1.03)	0.13	0.91 (0.79-1.05)	0.20
LDL>2.6mmol/L	4040	444 (11.0)	Reference	-	Reference	-

LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events.

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Compared with patients with other LDL-C level subgroups, the patients with LDL-C ≤1.4mmol/L had a numerically lower risk of stroke (HR=0.742, 95% CI: 0.568-0.970, p=0.0291), ischaemic stroke (HR=0.741, 95% CI: 0.562-0.976, p=0.0329) and MACE (HR=0.746, 95% CI: 0.573-0.972, p=0.0297) at 3 months. Similar results were found for the outcome of stroke (HR=0.767, 95% CI: 0.622-0.946, p=0.0131), ischaemic stroke (HR=0.731, 95% CI: 0.587-0.911, p=0.0052) and MACE (HR=0.766, 95% CI: 0.624-0.940, p=0.0106) at 12 months after the initial event. Lower baseline LDL-C level was not associated with an increased risk of hemorrhagic stroke at either 3 months or 12 months **(Table 2)**. Using a Cox regression model with restricted cubic splines, a strong association was also found between baseline LDL-C level and risk of stroke, ischemic stroke, hemorrhagic stroke, and MACE (**Figure 1**).

Lipid-lowering management, LLT compliance, and association of discharge LLT and outcomes

LLT management and compliance of the included patients during hospitalization, at discharge, 3 months, 6 months, and 12 months after the initial event were shown in **Table 3**.

Table 3. Lipid-lowering Treatment (LLT) and the compliance of patients in CNSR-III

	Hospitalization	Discharge	3 months	6 months	12 months
Non LLT	547 (3.6)	1300 (8.6)	2590 (17.4)	3007 (22.4)	3754 (26.0)
LLT	14506 (96.4)	13831 (91.4)	12271 (82.6)	11726 (77.6)	10682 (74.0)
Compliance					
Non-Persistent	/	/	2147 (15.5)	3382 (24.5)	4863 (35.2)
Persistent	/	/	11684 (84.5)	10449 (75.6)	8968 (64.8)

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Over 90% of patients received LLT during hospitalization and for 2 weeks after discharge. The LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. The drug regimens of LLT for the patients in CNSR-III at 3 months, 6 months, and 12 months were shown in **Table 4**.

Table 4. Lipid-lowering Treatment of the included patients in CNSR-III at 3-month, 6-month, 12-month follow-up (n=15166)

Treatment	Patients with statins, N (%)				
	Hospitalization	Discharge	3 months	6 months	12 months
Atorvastatin	10527 (69.41)	9851 (64.95)	8656 (57.08)	8228 (54.25)	7470 (49.25)
<40mg	7442 (70.71)	8770 (89.03)	8284 (95.7)	7963 (96.78)	7269 (97.35)
≥40mg	3083 (29.29)	1081 (10.97)	372 (4.3)	265 (3.22)	198 (2.65)
Rosuvastatin	3546 (23.38)	3395 (22.39)	2903 (19.14)	2779 (18.32)	2489 (16.41)
<20mg	2876 (81.15)	2983 (87.86)	2650 (91.38)	2536 (91.29)	2313 (92.93)
≥20mg	668 (18.85)	412 (12.14)	250 (8.62)	242 (8.71)	176 (7.07)
Simvastatin	272 (1.79)	239 (1.58)	390 (2.57)	411 (2.71)	444 (2.93)
Pravastatin	166 (1.09)	165 (1.09)	137 (0.9)	128 (0.84)	100 (0.66)
lovastatin	25 (0.16)	24 (0.16)	33 (0.22)	33 (0.22)	30 (0.2)
Fluvastatin	54 (0.36)	53 (0.35)	52 (0.34)	43 (0.28)	47 (0.31)
Pravastatin	61 (0.40)	78 (0.51)	70 (0.46)	64 (0.42)	61 (0.4)

Compared with the non-discharge LLT group, LLT at discharge was associated with reduced risk of ischemic stroke (HR=0.65, 95% CI: 0.45-0.94, p=0.02) and stroke recurrence (HR=0.69, 95% CI: 0.48-0.99, p=0.04) at 3 months **(Table 5)**.

Table 5. The association of Discharge Lipid Lowering Therapy (LLT) and outcomes

	Total	Events, (n%)	HR (95% CI) Unadjusted	*P* value	HR (95% CI) Adjusted	*P* value
3 months						
Stroke recurrence						
Discharge LLT	13248	269 (2.0%)	0.68(0.48-0.96)	0.03	0.69(0.48-0.99)	0.04
Non discharge LLT	1181	35 (3.0%)	Reference		Reference	
Ischemic stroke						
Discharge LLT	13263	245 (1.9%)	0.68(0.47-0.98)	0.04	0.65(0.45-0.94)	0.02
Non discharge LLT	1188	32 (2.7%)	Reference		Reference	
Hemorrhagic stroke						
Discharge LLT	13740	31 (0.2%)	0.71(0.25-2.01)	0.52	1.19(0.36-3.98)	0.78
Non discharge LLT	1266	4 (0.3%)	Reference		Reference	

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MACE						
Discharge LLT	13248	299 (2.3%)	0.71(0.51-1.003)	0.052	0.74(0.52-1.04)	0.08
Non discharge LLT	1181	37 (3.1%)	Reference		Reference	
12 months						
Stroke recurrence						
Discharge LLT	13248	758 (5.7%)	0.88(0.7-1.12)	0.30	0.89(0.7-1.14)	0.36
Non discharge LLT	1181	75 (6.4%)	Reference		Reference	
Ischemic stroke						
Discharge LLT	13263	683 (5.2%)	0.87(0.68-1.11)	0.26	0.86(0.67-1.10)	0.23
Non discharge LLT	1188	69 (5.8%)	Reference		Reference	
Hemorrhagic stroke						
Discharge LLT	13740	86 (0.6%)	0.97(0.47-2.00)	0.94	1.23(0.56-2.69)	0.60
Non discharge LLT	1266	8 (0.6%)	Reference		Reference	
MACE						
Discharge LLT	13248	838 (6.3%)	0.94(0.75-1.19)	0.60	0.96(0.76-1.21)	0.72
Non discharge LLT	1181	78(6.6%)	Reference		Reference	

Patients who reached the end point (stroke recurrence or MACE, death, and loss to follow-up) during hospitalization were excluded.

LDL-C goal achievement and the association of LDL-C changes (from baseline to 3 months) with outcomes at 12 months

The overall blood lipid levels at baseline and at 3-month, and 12-month follow-up were shown in **Table 6**. LDL-C goal of 1.8mmol/L was achieved by 28.3% of patients at baseline, 46.7% at 3 months, and 35.4% at 12 months; LDL-C goal of 1.4mmol/L was achieved by 13.1% of patients at baseline, 25.6% at 3 months, and 17.6% at 12 months.

Table 6. Blood Lipid Level of the included patients at baseline, 3 months and 1 year in CNSR-III

Lipids, mmol/L	Baseline N=10738	3M N=6034	12M N=4899
Median triglycerides (IQR), mmol/L	1.37(1.03-1.87)	1.32(0.98-1.81)	1.46(1.04-2.16)
Total cholesterol, mmol/L	3.97(3.31-4.72)	3.74(3.13-4.54)	3.92(3.25-4.76)
HDL-C, mmol/L	0.93(0.78-1.12)	1.02(0.86-1.21)	0.99(0.79-1.2)
LDL-C, mmol/L	2.31(1.73-2.97)	1.87(1.39-2.55)	2.14(1.57-2.87)
LDL <1.4mmol/L, n (%)	1407 (13.1)	1547 (25.6)	862 (17.6)
1.4 < LDL≤1.8mmol/L, n (%)	1636 (15.2)	1272 (21.1)	872 (17.8)
1.8 < LDL≤2.6mmol/L, n (%)	3655 (34.0)	1785 (29.6)	1533 (31.3)
LDL>2.6mmol/L, n (%)	4040 (37.6)	1430 (23.7)	1632 (33.3)

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HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol.

We did not find any significant association between the LDL-C reduction rate from baseline to 3-month follow-up and the risk of stroke and MACE at 12 months **(Table 7)**.

Table 7. Association of LDL-C changes (from baseline to 3 months) with outcomes at 12 months

Percentage of LDL level decrease (compared to baseline)	Total	Events, (n%)	HR (95% CI) unadjusted	*P* value	HR (95% CI) adjusted	*P* value
12 months						
Stroke recurrence*						
<30%, n (%)	3526	137 (3.9)	1.48 (0.92-2.39)	0.11	1.42 (0.87-2.30)	0.16
30-50%, n (%)	1146	45 (3.9)	1.50 (0.88-2.56)	0.14	1.44 (0.84-2.47)	0.19
>50%, n (%)	718	19 (2.7)	Reference		Reference	
MACE‡						
<30%, n (%)	3526	149 (4.2)	1.46 (0.92-2.20)	0.11	1.39 (0.88-2.21)	0.16
30-50%, n (%)	1146	47 (4.1)	1.41 (0.84-2.36)	0.19	1.36 (0.81-2.28)	0.24
>50%, n (%)	718	21 (2.9)	Reference		Reference	

* Patients with stroke recurrence, death, and loss to follow-up within 3 months were excluded.

‡ Patients with MACE, death, and loss to follow-up within 3 months were excluded.

Discussion

This national hospital-based study described the current LDL-C level and LLT of IS/TIA patients in the real world. We described the LLT management and LDL-C goal achievement. We also found that a lowered baseline LDL-C level was associated with a decreased risk of new ischemic stroke and MACE at both 3 months and 12 months after the initial event, without an increased risk of intracranial hemorrhage. In addition, LLT at discharge was associated with a reduced risk of CV events at 3 and 12 months. Given the large sample size of LDL-C levels of IS/TIA patients and comprehensive prognostic characteristics recorded, these findings may have important clinical implications.

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Firstly, LDL-C of 1.4 mmol/l might be a reasonable target for the high-risk population. Our study indicated that the LDL ≤1.4 mmol/L group, with the highest risk factors, had the lowest stroke and MACE rates at 3 and 12 months. The paradox of high risk of stroke with low LDL-C level could be due to the previous intensive LLT and rigid LDL-C control. It is consistent with the previous study that fixed-dose statin regimens are less effective than targeting LDL-C levels of 1.8 or 1.4 mmol/l when pre-treatment LDL-C levels exceed 4 mmol/L [16]; and the target of 1.4 mmol/l recently advocated in particularly high-risk patients is most effective when pre-treatment LDL-C exceeds 3 mmol/l [16]. In addition, 2019 ESC/EAS Guidelines for the management of dyslipidaemias set the most aggressive target of less than 1.4 mmol/L and a reduction of more than 50% in LDL-C [17].

Secondly, our findings suggested that the safety of the LDL-C ≤1.4mmol/L at least in Chinese population, because this level was not associate with an increased risk of hemorrhagic stroke. Studies of LDL-C and ICH have reported conflicting results. In a twenty-year epidemiologic study, an excess risk of hemorrhagic stroke was observed in patients with uncontrolled hypertension and LDL-C <70 mg/dL (1.8mmol/L) [18]. However, in a subgroup analysis of FOURIER trial [19], among patients with prior stroke, the risk of hemorrhagic stroke did not increase, even when the median LDL-C decreased from 2.4 mmol/L at randomization to 0.8 (0.5–1.2) mmol/L at 48 weeks in the evolocumab group. All stroke and ischemic stroke rates were reduced, and the rate of hemorrhagic stroke was not significantly changed. Meanwhile, in a systematic review and meta-analysis, the higher level of LDL-C tended to be associated with a

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lower risk of hemorrhagic stroke [20]. Thus, our study indicated the efficacy and safety of the baseline LDL-C of <1.4 mmol/L in IS/TIA patients, providing evidence for the first and second prevention strategies.

Thirdly, we described the epidemiological characteristics of Chinese IS/TIA patients in relation to their LDL-C levels and LLT. Compared to the study conducted in 2013 [21], our study indicated some progress in blood lipid management in mainland China. Notably, about 97% of patients had LLT medication history prior to the entry into our study. Also, compared to the LLT rate of 79.6% in 2013, over 90% of patients in our cohort received LLT during hospitalization and at discharge; the LLT compliance was 84.5% at 3 months, 75.6% at 6 months, and 64.8% at 12 months. In addition, LDL-C goal achievement for 1.8mmol/L had improved mildly, from 27.4% to 35.4%, and LDL-C goal achievement for 1.4mmol/L was 17.6% at 12 months. The less than perfect LLT compliance and LDL-C control rate might be due to statin intolerance in Asian people, including statin-associated myopathy and hemorrhagic stroke [22,23]. An earlier meta-analysis indicated that statins increase the risk of hemorrhagic stroke in a medication dose-dependent and type of index brain vascular injury-dependent manner, while PCSK9 inhibitors do not increase hemorrhagic stroke risk [24]. Thus, statins, rather than low-level of LDL-C, might closely relate to the risk of hemorrhagic stroke. Accordingly, PCSK9 inhibitors might be a more promising lipid-lowering medication class in patients with an elevated risk of hemorrhagic stroke. In addition, our analysis revealed a significant association between LLT at discharge and 3-month outcomes, indicating the importance of early LLT implementation.

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Fourthly, we did not observe the correlation between the 3-month LDL-C decrease amplitude and 12-month outcomes. To analyze the association of 3-month LDL-C change with 12-month outcomes, we excluded subjects who reached the end point within 3 months, which led to a reduction of our sample size and a loss of a considerable number of target events, for most stroke recurrences occurred within 3 months [25]. Another critical factor was that we could not adjust some risk factors in the model, such as IL-6 level or the evidence of relevant intracranial artery stenosis (ICAS), which were independent risk factors of the residual risk. Although substantially reduced by secondary prevention treatment, there was still 8.3% residual risk of 12-month recurrent stroke even in patients with persistent adherence to guideline-based secondary stroke prevention [26].

Our study has several limitations. First, only LLT medication use at the follow-up time points was recorded, whereas additional details of use during the whole study, such as continuous use, intermittent use, and the dose changes were not subjected to specific analysis. Thus, lipid-lowering agents use at 3 months and 12 months provided only a partial picture of the course of medication during the study. Second, statin use before admission was not recorded in the study which may confound the results. Furthermore, details of medication use, such as class, dose, duration, and adherence of lipid-lowering agents, did not enter the regression model. Third, there could be some undetected confounding factors in addition to those regarded as the residual risk. Forth, the use of dual antiplatelet therapy may reduce the risk of a 3-month recurrence of stroke for more than half of the patients presented with an initial NIHSS score of

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≤3. Fifth, the study was conducted exclusively on Chinese patients. The finding in this study needs to be further validated in studies with a larger sample size and non-Asian populations.

Conclusions

The LDL-C goal achievement has increased mildly in the stroke and TIA population in mainland China, and its further improvement is still an essential task for secondary prevention of stroke. The lowered baseline LDL-C level was significantly associated with a decreased short-and long-term risk of ischemic stroke among stroke and TIA patients. LDL-C<1.4mmol/L could be a safe standard for this population.

Ethics Approval Statement

The study protocol of the CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centers. Every participant provided written informed consent before participation.

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Competing Interests

The authors have no conflicts of interest to declare.

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Contributorship statement

Drs. YY Xu and X Meng conceived and designed the study. Drs. X Meng and YJ Wang served as scientific advisors. Drs. X Meng, ZX Li, Hao Li, and YJ Wang critically reviewed the study proposal. Drs. X Meng, XQ Zhao, LP Liu, and YL Wang collected and assembled the data. Drs. MX Wang and YS Pan did statistical analyses. Drs. YY Xu and WQ Chen interpreted the data. Drs. YY Xu drafted the manuscript and did the language editing. Dr. X Meng is responsible for the overall content as guarantor. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

The datasets used in this study are not publicly available, but these can be provided on reasonable request after the approval.

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Figure 1. Dose-response-relationship curves

Adjusted odds ratio of events and MACE at 3 months and 12 months according to LDL-C at baseline in patients. (a) stroke at 3 months; (b) ischemic stroke at 3 months; (c) hemorrhagic stroke at 3 months; (d) MACE at 3 months; (e) stroke at 12 months; (f) ischemic stroke at 12 months; (g) hemorrhagic stroke at 12 months; (h) MACE at 12 months. The full line indicates the adjusted hazard ratio and the dashed lines the 95% confidence interval bands. Reference is LDL-C >2.6mmol/L. Data were fitted using a logistic regression model of restricted cubic spline with three knots (the 5th, 50th, 90th percentiles) for LDL-C level, adjusting for potential covariates.

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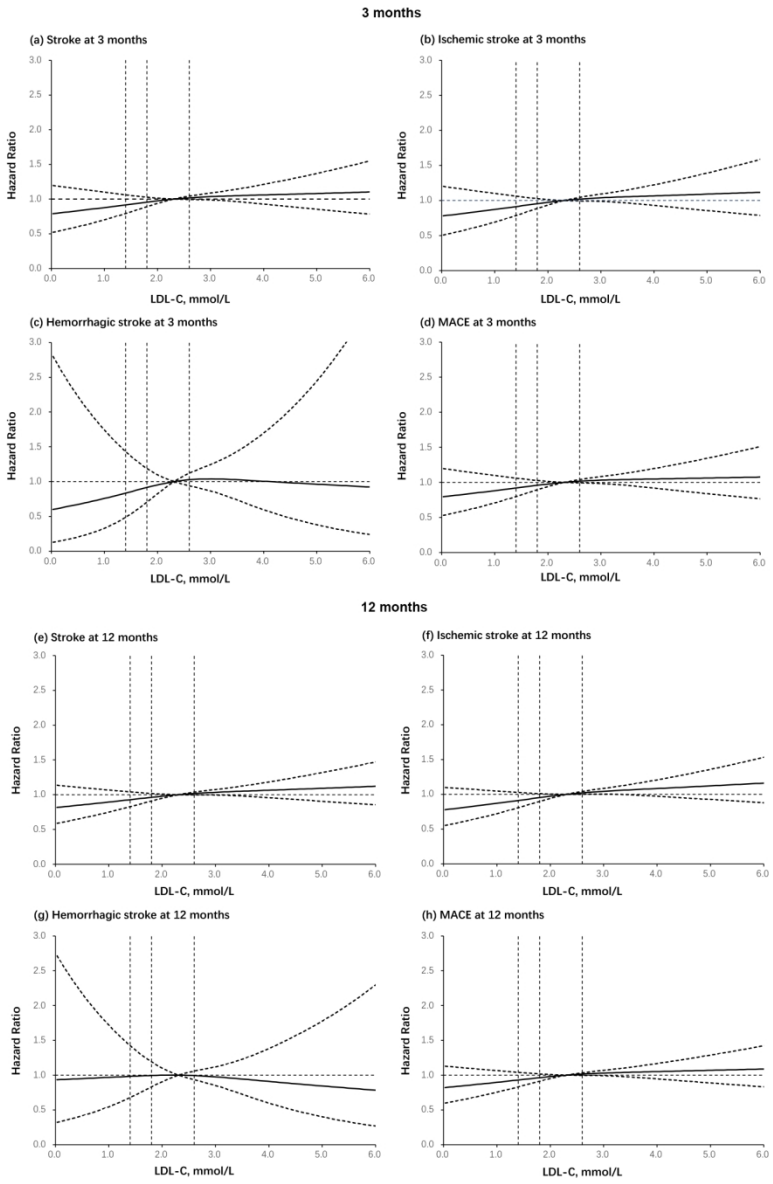

Dose-response-relationship curves

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13 13 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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