BMJ Open

Lipid management in ischaemic stroke or transient ischaemic attack in China: result from China National Stroke Registry III

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To cite: Xu Y-Y, Chen W-Q, Wang M-X, *et al*. Lipid management in ischaemic stroke or transient ischaemic attack in China: result from China National Stroke Registry III. *BMJ Open* 2023;**13**:e069465. doi:10.1136/bmjopen-2022-069465

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069465).

Received 11 November 2022
Accepted 18 January 2023

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ABSTRACT

Objectives 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 ischaemic stroke or transient ischaemic attack (TIA).

Design Our study was a post hoc analysis of the Third China National Stroke Registry (CNSR-III).

Setting We derived data from the CNSR-III - a nationwide clinical registry of ischaemic stroke and TIA based on 201 participating hospitals in mainland China.

Participants 15,166 patients were included in this study with demographic characteristics, etiology, imaging, and biological markers from August 2015 to March 2018.

Primary and secondary outcome measures 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 secondary outcomes included major adverse cardiovascular events (MACE) and all caused death at 3 and 12 months.

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=0.69, 95% CI: 0.48-0.99, p=0.04) 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.

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

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

INTRODUCTION

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

However, there are still clinical questions not thoroughly investigated. First, SPARCL and TST trials are randomised controlled trials conducted mainly in the Caucasian population,[2 6] whereas studies focusing on the Asian population on lipid management in patients who had a stroke are limited. Since there are more patients with intracranial artery stenosis (ICAS)[7 8] and cerebral small vessel disease in Asia,[9 10] especially in east Asia, the applicability of the conclusions of these two trials to Asian people should be discreet. Second, there are inconsistencies and conflicts about whether the reduced LDL-C level, especially during the acute or subacute phase, could increase the risk of intracranial haemorrhage (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-target and higher-target groups.[3] Third, 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 1.4 mmol/L or even 1.0 mmol/L has been recommended for adoption as international guidelines. However, the benefits of a lower LDL-C target lower than 1.8 mmol/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, centralised the Trial of Org 10172 in Acute Stroke Treatment classification judication and follow-up outcomes. We aimed to collect data from CNSR-III to investigate China's current lipid management practices and the associations between LDL-C level, LLT and stroke recurrence in patients with IS or TIA.

METHODS

Study design and participants

This study was based on the CNSR-III database. The CNSR-III is a nationwide clinical registry of IS or TIA based on aetiology, imaging and biological markers in China from August 2015 to March 2018.[15] Two hundred one participating hospitals were selected in China, and 15 166 patients were eligible and had complete information at baseline. The total 15 166 patients were included in the analysis. Among all the clinical centres included in CNSR-III, 169 centres voluntarily participated in the prespecified blood biomarker substudy, with all the patients at these centres 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.

To be eligible for this second analysis research, patients had to meet the following criteria: (1) age 18 years or older; (2) hospitalised with a primary diagnosis of acute IS or TIA; (3) direct hospital admission from a physician's clinic or an emergency department; and (4) informed consent provided by the patient or legally authorised representative. Patients with ICH, subarachnoid haemorrhage or undetermined stroke were not included in this study.

Data collection and management

Patient information, including demographics, risk factors, comorbidities, medications, selected laboratory tests and hospital-level characteristics, was collected systematically during hospitalisation and at discharge by trained research coordinators at each participating hospital. National Institutes of Health Stroke Scale (NIHSS) score at admission, and IS recurrence, composite vascular event, and modified Rankin Scale 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 analyser 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 standardised interview protocol. Information collected at each follow-up included cardiovascular and cerebrovascular events, all causes of death and medication 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 rehospitalisation with a diagnosis of IS, ICH or subarachnoid haemorrhage), LDL-C goal (LDL-C <1.4 mmol/L and LDL-C <1.8 mmol/L, respectively) achievement rates and LLT compliance in China within 3, 6 and 12 months. The secondary outcomes included major adverse cardiovascular events (MACE) (including stroke, myocardial infarction or vascular death) and all-cause 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 categorised into four groups according to the baseline LDL-C levels and LLT during hospitalisation and after discharge: LDL-C ≤1.4 mmol/L, 1.4 mmol/L<LDL-C≤1.8 mmol/L, 1.8 mmol/L<LDL≤2.6 mmol/L, LDL >2.6 mmol/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

Table 1 Baseline characteristics for the LDL-C analysis set

Variables	LDL ≤1.4 mmol/L N=1407	1.4<LDL≤1.8 mmol/L N=1636	1.8<LDL≤2.6 mmol/L N=3655	LDL >2.6 mmol/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, mm Hg	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 (%)					
Ischaemic 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
Hypercholesterolaemia	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

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

one medication but replaced it with another statin medication that they continued taking through 3, 6 or 12 months after enrolment.

Statistical analysis

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

To analyse the association of baseline LDL-C levels and outcomes, we only included those subjects who provided 3-month or 12-month biosample. 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 (HR) with 95% confidence intervals (CI) were calculated. The dose–response relationship curves were also presented.

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

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

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

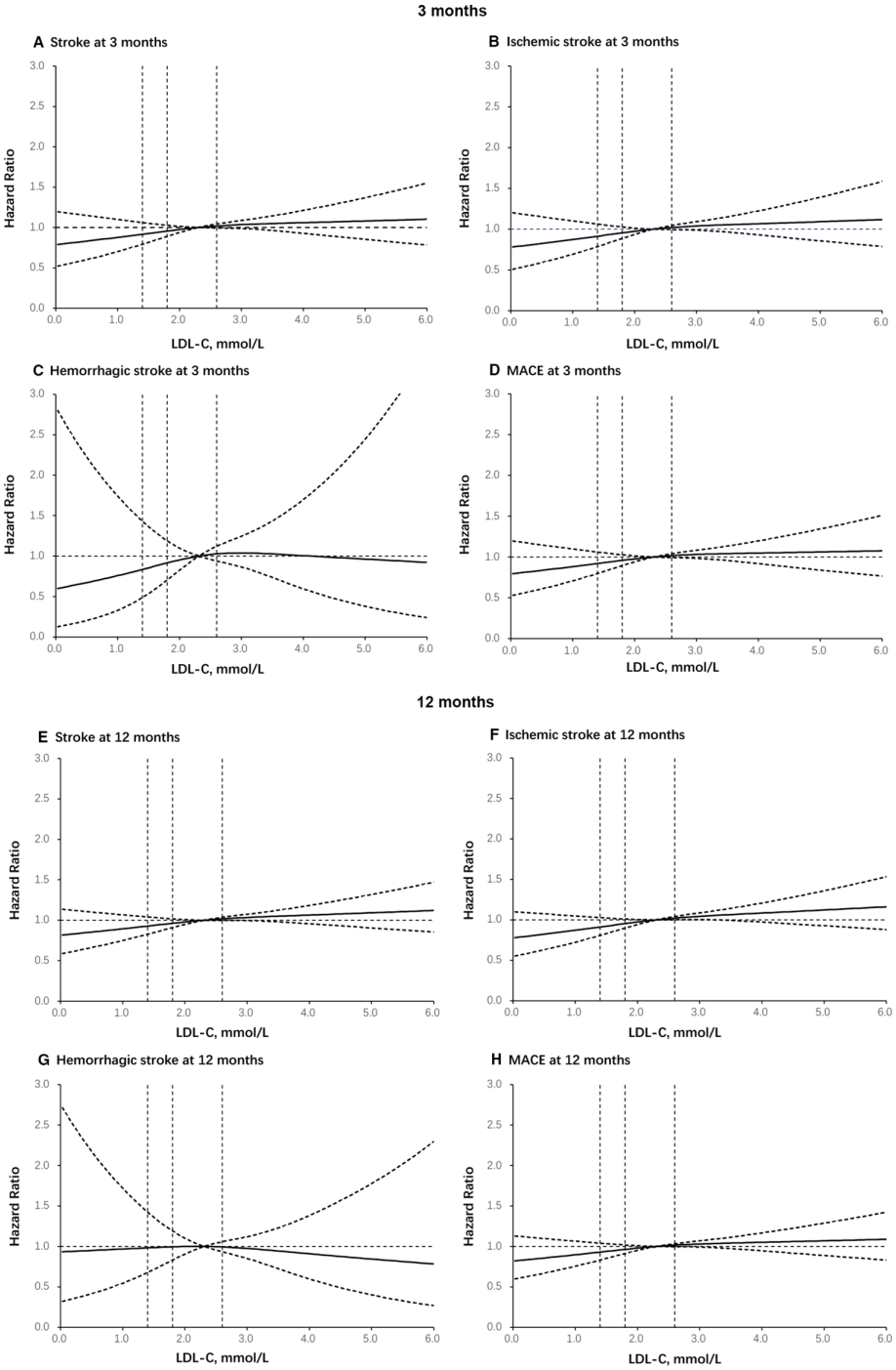

Figure 1 Dose–response relationship curves. Adjusted OR of events and MACE at 3 months and 12 months according to LDL-C at baseline in patients: (A) stroke at 3 months; (B) ischaemic stroke at 3 months; (C) haemorrhagic stroke at 3 months; (D) MACE at 3 months; (E) stroke at 12 months; (F) ischaemic stroke at 12 months; (G) haemorrhagic stroke at 12 months; (H) MACE at 12 months. The full line indicates the adjusted HR and the dashed lines the 95% CI bands. Reference is LDL-C >2.6 mmol/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. LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events.

stroke severity on the NIHSS, history of stroke, history of diabetes and history of hypertension.

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

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

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

	Hospitalisation	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)

CNSR-III, Third China National Stroke Registry.

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 and entered our final analysis. The average age of patients was 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 10738 patients in LDL-C analysis set: 1407 (13.1%), 1636 (15.2%), 3655 (34.0%) and 4040 (37.6%) patients with the baseline LDL-C ≤1.4 mmol/L, 1.4–1.8 mmol/L, 1.8–2.6 mmol/L, and ≥2.6 mmol/L, respectively (table 1).

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, hypercholesterolaemia, diabetes mellitus and history of stroke) (p<0.0001) and lower levels of triglycerides, total cholesterol and high-density lipoprotein (p<0.0001). About 97% of the patients had a history of antiplatelet and LLT, 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 (6.1%) new stroke occurrences at 3 months and 1037 (9.7%) at 12 months (table 2).

Compared with patients with other LDL-C level subgroups, the patients with LDL-C ≤1.4 mmol/L had a numerically lower risk of stroke (HR=0.742, 95% CI: 0.568 to 0.970, p=0.0291), IS (HR=0.741, 95% CI: 0.562 to 0.976, p=0.0329) and MACE (HR=0.746, 95% CI: 0.573 to 0.972, p=0.0297) at 3 months. Similar results were found for the outcome of stroke (HR=0.767, 95% CI: 0.622 to 0.946, p=0.0131), IS (HR=0.731, 95% CI: 0.587 to 0.911, p=0.0052) and MACE (HR=0.766, 95% CI: 0.624 to 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 haemorrhagic 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, IS, haemorrhagic stroke and MACE (figure 1).

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

	Patients with statins, N (%)				
Treatment	Hospitalisation	Discharge	3 months	6 months	12 months
Atorvastatin	10527 (69.4)	9851 (65.0)	8656 (57.1)	8228 (54.3)	7470 (49.3)
<40 mg	7442 (70.7)	8770 (89.0)	8284 (95.7)	7963 (96.8)	7269 (97.4)
≥40 mg	3083 (29.3)	1081 (11.0)	372 (4.3)	265 (3.2)	198 (2.7)
Rosuvastatin	3546 (23.4)	3395 (22.4)	2903 (19.1)	2779 (18.3)	2489 (16.4)
<20 mg	2876 (81.2)	2983 (87.9)	2650 (91.4)	2536 (91.3)	2313 (93.0)
≥20 mg	668 (18.9)	412 (12.1)	250 (8.6)	242 (8.7)	176 (7.1)
Simvastatin	272 (1.8)	239 (1.6)	390 (2.6)	411 (2.7)	444 (2.9)
Pravastatin	166 (1.1)	165 (1.1)	137 (0.9)	128 (0.8)	100 (0.7)
Lovastatin	25 (0.2)	24 (0.2)	33 (0.2)	33 (0.2)	30 (0.2)
Fluvastatin	54 (0.4)	53 (0.4)	52 (0.3)	43 (0.3)	47 (0.3)
Pravastatin	61 (0.4)	78 (0.5)	70 (0.5)	64 (0.4)	61 (0.4)

CNSR-III, Third China National Stroke Registry.

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 to 0.96)	0.03	0.69 (0.48 to 0.99)	0.04
Non-discharge LLT	1181	35 (3.0)	Reference		Reference	
Ischaemic stroke						
Discharge LLT	13263	245 (1.9)	0.68 (0.47 to 0.98)	0.04	0.65 (0.45 to 0.94)	0.02
Non-discharge LLT	1188	32 (2.7)	Reference		Reference	
Haemorrhagic stroke						
Discharge LLT	13740	31 (0.2)	0.71 (0.25 to 2.01)	0.52	1.19 (0.36 to 3.98)	0.78
Non-discharge LLT	1266	4 (0.3)	Reference		Reference	
MACE						
Discharge LLT	13248	299 (2.3)	0.71 (0.51 to 1.003)	0.052	0.74 (0.52 to 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 to 1.12)	0.30	0.89 (0.7 to 1.14)	0.36
Non-discharge LLT	1181	75 (6.4)	Reference		Reference	
Ischaemic stroke						
Discharge LLT	13263	683 (5.2)	0.87 (0.68 to 1.11)	0.26	0.86 (0.67 to 1.10)	0.23
Non-discharge LLT	1188	69 (5.8)	Reference		Reference	
Haemorrhagic stroke						
Discharge LLT	13740	86 (0.6)	0.97 (0.47 to 2.00)	0.94	1.23 (0.56 to 2.69)	0.60
Non-discharge LLT	1266	8 (0.6)	Reference		Reference	
MACE						
Discharge LLT	13248	838 (6.3)	0.94 (0.75 to 1.19)	0.60	0.96 (0.76 to 1.21)	0.72
Non-discharge LLT	1181	78 (6.6)	Reference		Reference	

Patients who reached the endpoint (stroke recurrence or MACE, death and loss to follow-up) during hospitalisation were excluded.
MACE, major adverse cardiovascular events.

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

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

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	3 months N=6034	1 year 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 <1.4 mmol/L, n (%)	1407 (13.1)	1547 (25.6)	862 (17.6)
1.4<LDL≤1.8 mmol/L, n (%)	1636 (15.2)	1272 (21.1)	872 (17.8)
1.8<LDL≤2.6 mmol/L, n (%)	3655 (34.0)	1785 (29.6)	1533 (31.3)
LDL >2.6 mmol/L, n (%)	4040 (37.6)	1430 (23.7)	1632 (33.3)

CNSR-III, Third China National Stroke Registry; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

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

Percentage of LDL level decrease (compared with 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 to 2.39)	0.11	1.42 (0.87 to 2.30)	0.16
30%–50%, n (%)	1146	45 (3.9)	1.50 (0.88 to 2.56)	0.14	1.44 (0.84 to 2.47)	0.19
>50%, n (%)	718	19 (2.7)	Reference		Reference	
MACE†						
<30%, n (%)	3526	149 (4.2)	1.46 (0.92 to 2.20)	0.11	1.39 (0.88 to 2.21)	0.16
30%–50%, n (%)	1146	47 (4.1)	1.41 (0.84 to 2.36)	0.19	1.36 (0.81 to 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.
LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events.

Over 90% of patients received LLT during hospitalisation 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.

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

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 1.8 mmol/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 1.4 mmol/L was achieved by 13.1% of patients at baseline, 25.6% at 3 months and 17.6% at 12 months.

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).

DISCUSSION

This national hospital-based study described the current LDL-C level and LLT of patients with IS/TIA 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 IS and MACE at both 3 months and 12 months after the initial event, without an increased risk of ICH. In addition, LLT at discharge was associated with a reduced risk of cardiovascular events at 3 and 12 months. Given the large sample size of LDL-C levels of patients with IS/TIA and comprehensive prognostic characteristics recorded, these findings may have important clinical implications.

First, 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 pretreatment 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 pretreatment LDL-C exceeds 3 mmol/L.[16] In addition, 2019 European Society of Cardiology/European Atherosclerosis Society 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]

Second, our findings suggested the safety of the LDL-C ≤1.4 mmol/L at least in Chinese population, because this level was not associated with an increased risk of haemorrhagic stroke. Studies of LDL-C and ICH have reported conflicting results. In a 20-year epidemiological study, an excess risk of haemorrhagic stroke was observed in patients with uncontrolled hypertension and LDL-C <70 mg/dL (1.8 mmol/L).[18] However, in a subgroup analysis of FOURIER trial,[19] among patients with prior stroke, the risk of haemorrhagic stroke did not increase, even when the median LDL-C decreased from 2.4 mmol/L at randomisation to 0.8 (0.5–1.2) mmol/L at 48 weeks in the evolocumab group. All stroke and IS rates were reduced, and the rate of haemorrhagic 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 haemorrhagic stroke.[20] Thus, our study indicated the efficacy and safety of the baseline LDL-C of <1.4 mmol/L in patients with IS/TIA,

providing evidence for the first and second prevention strategies.

Third, we described the epidemiological characteristics of Chinese patients with IS/TIA in relation to their LDL-C levels and LLT. Compared with 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 with the LLT rate of 79.6% in 2013, over 90% of patients in our cohort received LLT during hospitalisation 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 1.8 mmol/L had improved mildly, from 27.4% to 35.4%, and LDL-C goal achievement for 1.4 mmol/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 haemorrhagic stroke.[22 23] An earlier meta-analysis indicated that statins increase the risk of haemorrhagic stroke in a medication dose-dependent and type of index brain vascular injury-dependent manner, while proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors do not increase haemorrhagic stroke risk.[24] Thus, statins, rather than low level of LDL-C, might closely relate to the risk of haemorrhagic stroke. Accordingly, PCSK9 inhibitors might be a more promising lipid-lowering medication class in patients with an elevated risk of haemorrhagic stroke. In addition, our analysis revealed a significant association between LLT at discharge and 3-month outcomes, indicating the importance of early LLT implementation.

Fourth, we did not observe the correlation between the 3-month LDL-C decrease amplitude and 12-month outcomes. To analyse the association of 3-month LDL-C change with 12-month outcomes, we excluded subjects who reached the endpoint 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 interleukin-6 level or the evidence of relevant 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 agent 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 to 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. Fourth, 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 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 population who had a stroke and with TIA 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 IS among patients who had a stroke and with TIA. LDL-C <1.4 mmol/L could be a safe standard for this population.

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Acknowledgements We thank Dr Feng Sheng for his important intellectual contributions to the article. We thank all participating hospitals, their physicians and nurses. We appreciate all the patients who took part in the CNSR-III.

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Funding This work was supported by the National Key R&D Program of China (no. 2018YFC1312903), National Natural Science Foundation of China (no. 81870905, 82071295, 81801139) and Beijing Hospitals Authority Innovation Studio of Young Staff Funding Support (code: 202113).

Competing interests None declared.

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.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethics committee at Beijing Tiantan Hospital (KY2019-109-01). 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. 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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