Associations between low-density lipoprotein cholesterol and haemorrhagic stroke

Yun-Yan XIE¹,* , Shi-Meng LIU²-3,* , Qian ZHANG¹ , Yu JIA¹ , Jian-Ping DING¹,✉

1. Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China; 2. Department of Neurology, University of California, Irvine, Irvine, California, USA; 3. Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

*The authors contributed equally to this manuscript

✉Correspondence to: djp192001@aliyun.com

https://doi.org/10.11909/j.issn.1671-5411.2021.03.011

ABSTRACT

OBJECTIVE To investigate the associations between the blood concentrations of low-density lipoprotein cholesterol (LDL-C) and the clinical features of haemorrhagic stroke.

METHODS This study analysed the data from patients with acute haemorrhagic stroke at a comprehensive stroke centre from 2013 to 2018. Patients were stratified into three groups according to their baseline LDL-C levels: < 70, 70 to < 100 and ≥ 100 mg/dL. We used multivariate logistic regression models to analyse the associations between LDL-C and the risks of having severe neurological deficits (National Institute Health Stroke Scale [NIHSS] scores ≥ 15) and unfavourable outcomes (modified Rankin Scale [mRS] scores >2) at discharge.

RESULTS Six-hundred and six patients were analysed. Their median age was 58 years. Among the patients, 75 (12%) patients had LDL-C levels < 70 mg/dL, 194 (32%) patients had LDL-C levels between 70 to < 100 mg/dL and the other 337 (56%) patients had LDL-C levels ≥ 100 mg/dL. Patients with higher LDL-C levels were less likely to suffer severe neurological deficits (LDL-C: 70 to < 100 vs. < 70 mg/dL, adjusted odds ratio [OR]: 0.29, 95% CI: 0.15–0.57; LDL-C: ≥ 100 vs. < 70 mg/dL, adjusted OR = 0.27, 95% CI: 0.15–0.51) and to have unfavourable outcomes at discharge (LDL-C: 70 to < 100 vs. < 70 mg/dL, adjusted OR = 0.50, 95% CI: 0.29–0.87 and LDL-C: ≥ 100 vs. < 70 mg/dL, adjusted OR = 0.46, 95% CI: 0.28–0.78).

CONCLUSIONS An LDL-C level < 70 mg/dL was independently associated with severe neurological deficits of haemorrhagic stroke and may increase the risks of unfavourable outcomes at discharge.

Hyperlipidaemia, especially increased levels of low-density lipoprotein cholesterol (LDL-C), is an independent risk factor for acute ischaemic stroke (AIS).[1, 2] In a cohort study with 27,937 healthy women, subjects with LDL-C ≥ 151 mg/dL had a hazard ratio (HR) of 1.85 to experience an AIS within 11 years relative to those with an LDL-C < 100 mg/dL, where the 95% confidence interval (CI) was 1.22 to 2.80.[3]

Lipid-lowering therapy is one of the critical strategies for both primary and secondary prevention of AIS.[4,5] A meta-analysis of the AIS prevention studies indicated that lipid-lowering therapy was associated with lower risks of AIS in the primary (risk ratio [RR]: 0.70, 95% CI: 0.60–0.82; P < 0.001) and the secondary (RR: 0.80, 95% CI: 0.70-0.90; P < 0.001) prevention settings.[6] Additionally, a meta-analysis in the setting of atherosclerosis coronary heart disease (CHD) also showed that with every 39 mg/dL decrease in the LDL-C levels, the risks of major adverse cardiovascular events (including CHD death, nonfatal myocardial infarction, AIS or unstable angina requiring hospitalization) appeared to be 24% lower (adjusted HR = 0.76, 95% CI: 0.63–0.91; P = 0.002 5).[7] Our prior study found that achieving an LDL-C < 70 mg/dL may be effective in inhibiting the progression of carotid atherosclerosis plaques in patients with AIS.[8]

However, lower LDL-C levels might increase the risks of intracranial haemorrhage (ICH). LDL-C <
90 mg/dL was associated with a higher risk of haemorrhage transformation after AIS, which was attributable to large artery atherothrombosis: the risks were increased by 54.0% with each 39 mg/dL decrease in the LDL-C levels (adjusted odds ratio (OR): 0.46 per 39 mg/dL increase, 95% CI: 0.22–0.98). A case-control study found the LDL-C level was significantly lower in patients with ICH compared to the controls (114 vs. 128 mg/dL; P = 0.016). A post hoc analysis of the SPARCL study also found that patients with LDL-C < 70 mg/dL had a trend of increased risks of ICH relative to those with LDL-C ≥ 100 mg/dL (HR = 1.28, 95% CI: 0.78–2.09). Above all, the target value of LDL-C to be achieved through lipid-lowering therapy is still unclear due to the potential risks of ICH.

We carried out a single-centre retrospective cohort study to investigate the associations between the LDL-C levels (< 70, 70 to < 100 and ≥ 100 mg/dL) and the outcomes of haemorrhagic stroke to provide preliminary information about safe targets for lipid-lowering therapy.

METHODS

Patients

We retrospectively analysed the data of consecutive patients with haemorrhagic stroke treated at a comprehensive stroke centre, Xuanwu Hospital, Capital Medical University in Beijing, China, from January 1st, 2013 to January 1st, 2018. The inclusion criteria were: (1) patients ≥ 18 years old; (2) with an initial diagnosis of intracerebral haemorrhage; and (3) symptoms onset within seven days. We excluded patients with traumatic ICH. Diagnosis and stroke subtypes were determined based on clinical features, laboratory examinations, brain imaging and angiography. This study was approved by the institutional review board (IRB) at Xuanwu Hospital.

Patients were categorized into three groups according to their baseline LDL-C levels: < 70, 70 to < 100 and ≥ 100 mg/dL. LDL-C < 70 mg/dL was used as the reference level to test the associations of intensive lipid-lowering therapy (achieving an LDL-C < 70 mg/dL) with the outcomes of ICH.

The scores of the National Institute of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS) were recorded in the emergency room to evaluate the baseline severity of the indexed events. The modified Rankin Scale (mRS) was tested at discharge to describe the prognosis of the haemorrhagic event. The baseline scores of the NIHSS were stratified by the cut-off values of 15 and 24. The GCS scores were stratified with the cut-off points of 4 and 12. An mRS score > 2 was defined as having unfavourable outcomes at discharge.

Statistical Analysis

We first compared the distributions of sex, age, risk factors of stroke, medication history and laboratory results among the three groups. We used χ² tests or Fisher’s exact tests to examine the distributions of each categorical variable and Kruskal-Wallis tests to examine the distributions of the medians (for the non-normally distributed numerical variables), with a significance level of P < 0.05. Univariate and multivariate logistic regression models were used to determine the crude ORs and the adjusted ORs (95% CI). The ORs of having initial NIHSS scores ≥ 15 and mRS scores > 2 at discharge were tested, with the patients with LDL-C < 70 mg/dL as the reference group. The multivariate analysis first included only sex and age for the adjustments. Further analysis included variables significant at P < 0.05 in the baseline comparisons. When we used mRS scores (> 2 vs. 0–1) at discharge to evaluate the clinical outcomes of the indexed events, the analysis was adjusted by the initial NIHSS scores (≥ 15 vs. 0–14) to exclude the confounding effects caused by the baseline severity.

The SAS statistical package (version 9.4; SAS Institute, Cary, NC, USA) was used to perform the data analysis.

RESULTS

From January 1st, 2013 to January 1st, 2018, 641 patients with a diagnosis of haemorrhagic stroke were admitted at the comprehensive stroke centre, Xuanwu Hospital, Capital Medical University. Thirty-five of them were excluded due to the lack of lipid levels at admission. Six-hundred and six patients were included in the final analysis, including 420 men and 186 women with a median age of 58 years old.
Baseline Characteristics

Among the 606 patients, 75 (12%) patients had LDL-C concentrations less than 70 mg/dL, 194 (32%) patients had LDL-C concentrations between 70 to < 100 mg/dL and the other 337 (56%) patients had LDL-C ≥ 100 mg/dL at baseline. Patients with an LDL-C < 70 mg/dL were generally older (LDL-C < 70 vs. 70 to < 100 vs. ≥ 100 mg/dL: median age, 62 vs. 59 vs. 57 years, P = 0.01). The proportion of patients having a prior disability (pre-mRS scores > 2) was higher in patients with LDL-C < 70 mg/dL (LDL-C < 70 vs. 70 to < 100 vs. ≥ 100 mg/dL: 11% vs. 3% vs. 3%, P = 0.01). More patients had diabetes mellitus in the group with LDL-C < 70 mg/dL (< 70 vs. 70 to < 100 vs. ≥ 100 mg/dL: 38% vs. 21% vs. 16%, P < 0.01). More patients with LDL-C < 70 mg/dL (n = 20, 27%) suffered an AIS or transient ischaemic attack (TIA) prior to the indexed haemorrhagic events (P < 0.01). We did not find any significant differences regarding the distributions of sex, other medical histories or pre-medication histories, including stain use. Serum lipids significantly varied across the groups, while glucose levels were similar (Table 1).

Descriptions of the Haemorrhagic Stroke Events

The median (interquartile range (IQR)) NIHSS scores at admission were 8 (3–16), 5 (2–10) and 5 (2–10) in the groups with LDL-C < 70, 70 to < 100, ≥ 100 mg/dL, respectively (P = 0.01). More patients with LDL-C < 70 mg/dL had mRS scores ≥ 2 at discharge (< 70 vs. 70 to < 100 vs. ≥ 100 mg/dL: 57% vs. 39% vs. 37%, P < 0.01) (Table 2). We did not find any significant differences in the median of the initial GCS scores (< 70 vs. 70 to < 100 vs. ≥ 100 mg/dL: 14 vs. 15 vs. 15; P = 0.12) or mortality in the hospital (< 70 vs. 70 to <100 vs. ≥ 100 mg/dL: 4% vs. 1% vs. 2%; P = 0.25). LDL-C levels were not associ-

| Table 1 Baseline characteristics of the study patients. | LDL-C levels | P value |
|---|---|---|
| **All patients (n = 606)** | < 70 mg/dL (n = 75) | 70 to < 100 mg/dL (n = 194) | ≥ 100 mg/dL (n = 337) |
| **Age, yrs** | 58 (49–68) | 62 (54–72) | 59 (50–68) | 57 (47–66) | 0.01 |
| **Male** | 420 (69%) | 52 (69%) | 134 (69%) | 234 (69%) | 0.10 |
| **Prior mRS scores > 2** | 25 (4%) | 8 (11%) | 6 (3%) | 11 (3%) | 0.01 |
| **Medical history** | | | | | |
| **Hypertension** | 470 (78%) | 55 (73%) | 143 (74%) | 272 (81%) | 0.11 |
| **Heart disease** | 95 (16%) | 14 (19%) | 26 (13%) | 55 (16%) | 0.50 |
| **Diabetes mellitus** | 123 (20%) | 28 (38%) | 40 (21%) | 55 (16%) | < 0.01 |
| **Previous AIS/TIA** | 96 (16%) | 20 (27%) | 36 (19%) | 39 (12%) | < 0.01 |
| **Previous ICH** | 49 (8%) | 10 (13%) | 18 (9%) | 21 (6%) | 0.10 |
| **COPD** | 13 (2%) | 3 (4%) | 3 (2%) | 7 (2%) | 0.46 |
| **Alcohol consumption** | 225 (37%) | 28 (37%) | 59 (30%) | 138 (41%) | 0.05 |
| **Pre-medications** | | | | | |
| **Statin** | 60 (10%) | 10 (13%) | 23 (12%) | 27 (8%) | 0.21 |
| **Antiplatelets** | 76 (13%) | 14 (19%) | 26 (13%) | 36 (11%) | 0.15 |
| **Anticoagulants** | 6 (1%) | 0 (0%) | 1 (1%) | 5 (1%) | 0.36 |
| **Anti-hypertensive** | 344 (57%) | 45 (60%) | 105 (54%) | 194 (58%) | 0.62 |
| **Laboratory data** | | | | | |
| **GLU, mg/dL** | 101 (88–126) | 103 (94–146) | 102 (87–123) | 115 (88–126) | 0.23 |
| **TG, mg/dL** | 120 (89–168) | 103 (80–142) | 112 (83–157) | 128 (96–192) | < 0.01 |
| **TCH, mg/dL** | 172 (146–198) | 117 (105–132) | 150 (139–163) | 193 (177–218) | < 0.01 |
| **HDL-C, mg/dL** | 47 (39–56) | 39 (31–51) | 46 (37–55) | 49 (42–58) | < 0.01 |

Data are presented as n (%) or median (IQR). AIS: acute ischaemic stroke; COPD: chronic obstructive pulmonary disease; GLU: glucose; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; mRS: modified Rankin Scale; TCH: total cholesterol; TG: triglycerides; TIA: transient ischaemic attack.
Health Stroke Scale.

Data are presented as n (%). Age was an independent risk factor for having initial NIHSS scores ≥ 15 (OR = 1.02, 95% CI: 1.00–1.03) and mRS scores >2 at discharge (OR = 1.02, 95% CI: 1.01–1.03). Sex was not related to the baseline severity or the outcomes of the haemorrhagic stroke (Table 3).

In the multivariate logistic regression models to evaluate the associations between baseline severity (NIHSS scores ≥ 15 vs. 0–14) and LDL-C levels, we adjusted for age, sex (male vs. female), prior mRS scores (≤ 2 vs. > 2), prior diabetes mellitus (yes vs. no) and prior AIS/TIA (yes vs. no). Patients with higher LDL-C levels were still less likely to suffer a severe stroke (LDL-C 70 to < 100 vs. < 70 mg/dL, adjusted OR = 0.88, 95% CI: 0.47–1.70; LDL-C ≥ 100 vs. < 70 mg/dL, adjusted OR = 0.81, 95% CI: 0.44–1.50, respectively) as the initial NIHSS scores played the dominant role (OR = 14.66, 95% CI: 7.29–29.46) (Table 3).

**Table 2** Characteristics of the indexed haemorrhagic stroke.

| Initial NIHSS scores | All patients (n = 606) | Low-density lipoprotein cholesterol levels | P-value |
|----------------------|------------------------|--------------------------------------------|---------|
|                      | < 70 mg/dL (n = 75)     | 70 to < 100 mg/dL (n = 194) | ≥ 100 mg/dL (n = 337) |
| **Median (IQR)**     |                        |                             |         |
| 0–14                 | 5 (2–11)               | 8 (3–16)                    | 5 (2–10) | 0.01 |
| 15–24                | 522 (86%)              | 51 (68%)                    | 171 (88%) | < 0.01 |
| ≥ 25                 | 26 (4%)                | 9 (12%)                     | 3 (2%)   | 14 (4%) |
| **Initial GCS scores**|                        |                             |         |
| 3–4                  | 15 (12–15)             | 14 (9–15)                   | 15 (13–15) | 0.12 |
| 5–12                 | 11 (2%)                | 2 (3%)                      | 3 (2%)   | 6 (2%) |
| ≥ 13                 | 140 (23%)              | 27 (36%)                    | 38 (20%) | 75 (23%) |
| **Bleeding locations**|                        |                             |         |
| Deep                 | 279 (46%)              | 29 (39%)                    | 86 (44%) | 164 (49%) | 0.25 |
| Lobar                | 147 (24%)              | 29 (30%)                    | 47 (24%) | 78 (23%) | 0.42 |
| Cerebellum           | 19 (3%)                | 2 (3%)                      | 6 (3%)   | 11 (3%) | 0.96 |
| Brainstem            | 55 (9%)                | 11 (15%)                    | 14 (7%)  | 30 (9%) | 0.16 |
| **Intraventricular**| 103 (17%)              | 15 (15%)                    | 28 (14%) | 760 (18%) | 0.46 |
| **mRS scores at discharge**|                        |                             |         |
| Median (IQR)         | 2 (1–4)                | 3 (1–4)                     | 2 (1–3)  | 2 (1–3) | 0.01 |
| > 2                  | 242 (40%)              | 43 (57%)                    | 76 (39%) | 123 (37%) | < 0.01 |
| Death at hospital    | 12 (2%)                | 3 (4%)                      | 2 (1%)   | 7 (2%) | 0.25 |

Data are presented as n (%) or median (IQR). IQR: interquartile range; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale.
In the study, we found LDL-C < 70 mg/dL was independently associated with higher risks of severe haemorrhagic stroke and had a trend of having unfavourable outcomes at discharge. Lower blood cholesterol may induce angionecrosis, which is accelerated by comorbidities, such as hypertension.\[15\] This may explain the worse outcomes after an ICH for patients with LDL-C < 70 mg/dL.

Our results are consistent with previous studies in different study populations. The Helsinki ICH study found significantly lower LDL-C levels in patients with ICH who died in the hospital (73 vs. 93 mg/dL; P < 0.001).\[16\] This result is consistent with our findings, except that we did not reach significant statistical levels after adjusting for age, sex, prior mRS scores, diabetes, prior AIS/TIA histories and initial NIHSS scores. Another multi-centre stroke registry study from Taiwan indicated that patients with total cholesterol (TC) < 160 mg/dL presented more frequently with a severe neurological deficit (NIHSS scores ≥ 15), with an adjusted OR of 1.80; and 3-month unfavourable mRS scores > 2 (adjusted OR = 1.41) when compared with the patients with TC > 200 mg/dL.\[14\] Their conclusion supported our results. We found significant relationships between LDL-C levels and severe neurological deficits, as well as unfavourable outcomes at discharge.

There are limitations of the study. First, due to the limitations of the clinical data, we were unable to provide follow-up information to show the long-term prognosis after the haemorrhagic stroke. Second, we did not acquire any reliable data to investigate the relationships between LDL-C levels and bleeding volume. We were also unable to adjust our model for blood pressure status or the presence of aneurysms. Third, the study patients were recruited from a single centre in China, which may lead to limitations in external validity. Forth, LDL-C levels are variable, and they depend on medication, exercise and diet.\[17\] The LDL-C level at admission could not reflect the patient’s long-term serum lipid status; thus, additional studies with detailed long-term serum lipid histories are necessary. Last, we did not study the underlying mechanisms of the effects of a low LDL-C on haemorrhagic events.

In summary, an LDL-C level < 70 mg/dL was independently associated with severe neurological deficits after haemorrhagic stroke and may increase

### DISCUSSION

In the study, we found LDL-C < 70 mg/dL was independently associated with higher risks of severe haemorrhagic stroke and had a trend of having unfavourable outcomes at discharge. Lower blood cholesterol may induce angionecrosis, which is accelerated by comorbidities, such as hypertension.\[15\] This may explain the worse outcomes after an ICH for patients with LDL-C < 70 mg/dL.

Our results are consistent with previous studies in different study populations. The Helsinki ICH study found significantly lower LDL-C levels in patients with ICH who died in the hospital (73 vs. 93 mg/dL; P < 0.001).\[16\] This result is consistent with our findings, except that we did not reach significant statistical levels after adjusting for age, sex, prior mRS scores, diabetes, prior AIS/TIA histories and initial NIHSS scores. Another multi-centre stroke registry study from Taiwan indicated that patients with total cholesterol (TC) < 160 mg/dL presented more frequently with a severe neurological deficit (NIHSS scores ≥ 15), with an adjusted OR of 1.80; and 3-month unfavourable mRS scores > 2 (adjusted OR = 1.41) when compared with the patients with TC > 200 mg/dL.\[14\] Their conclusion supported our results. We found significant relationships between LDL-C levels and severe neurological deficits, as well as unfavourable outcomes at discharge.

There are limitations of the study. First, due to the limitations of the clinical data, we were unable to provide follow-up information to show the long-term prognosis after the haemorrhagic stroke. Second, we did not acquire any reliable data to investigate the relationships between LDL-C levels and bleeding volume. We were also unable to adjust our model for blood pressure status or the presence of aneurysms. Third, the study patients were recruited from a single centre in China, which may lead to limitations in external validity. Forth, LDL-C levels are variable, and they depend on medication, exercise and diet.\[17\] The LDL-C level at admission could not reflect the patient’s long-term serum lipid status; thus, additional studies with detailed long-term serum lipid histories are necessary. Last, we did not study the underlying mechanisms of the effects of a low LDL-C on haemorrhagic events.

In summary, an LDL-C level < 70 mg/dL was independently associated with severe neurological deficits after haemorrhagic stroke and may increase

### Table 3  Crude and adjusted logistic regression models to assess the associations between LDL-C levels and the outcomes of haemorrhagic stroke.

|                          | Crude ORs | Age/sex adjusted ORs | Multivariate adjusted ORs |
|--------------------------|-----------|---------------------|--------------------------|
| Baseline NIHSS scores ≥ 15 |           |                     |                          |
| LDL-C 70 to < 100 vs. < 70 mg/dL | 0.29 (0.15–0.55) | 0.30 (0.15–0.57) | 0.29 (0.15–0.57) |
| LDL-C ≥ 100 vs. < 70 mg/dL | 0.26 (0.15–0.47) | 0.28 (0.15–0.51) | 0.27 (0.15–0.51) |
| Age                      | –         | 1.02 (1.00–1.03)    | 1.01 (1.00–1.04)         |
| M vs. F                  | –         | 0.82 (0.50–1.36)    | 0.82 (0.49–1.36)         |
| Prior mRS scores: 2–5 vs.0–1 | –         | –                   | 1.95 (0.71–5.34)         |
| DM vs. non-DM            | –         | –                   | 0.81 (0.45–1.47)         |
| Prior AIS/TIA: yes vs. no| –         | –                   | 0.93 (0.48–1.81)         |
| mRS scores at discharge > 2 |          |                     |                          |
| LDL-C: 70 to < 100 vs. < 70 mg/dL | 0.48 (0.28–0.82) | 0.50 (0.29–0.87) | 0.88 (0.47–1.70) |
| LDL-C: ≥ 100 vs. < 70 mg/dL | 0.43 (0.26–0.71) | 0.46 (0.28–0.78) | 0.81 (0.44–1.50) |
| Age                      | –         | 1.02 (1.01–1.03)    | 1.01 (1.00–1.03)         |
| M vs. F                  | –         | 1.01 (0.70–1.45)    | 1.06 (0.71–1.57)         |
| Prior mRS scores: 2–5 vs.0–1 | –         | –                   | 5.20 (1.77–15.25)        |
| DM vs. non-DM            | –         | –                   | 1.04 (0.65–1.65)         |
| Prior AIS/TIA: yes vs. no| –         | –                   | 1.06 (0.63–1.78)         |
| Initial NIHSS scores: ≥ 15 vs. 0–14 | –         | –                   | 14.66 (7.29–29.46)       |

AIS: acute ischaemic stroke; CI: confidence interval; DM: diabetes mellitus; F: female; LDL-C: low-density lipoprotein cholesterol; M: male; mRS: modified Rankin Scale; NIHSS: National Institute of Health Scale; OR: odds ratio; TIA: transient ischaemic attack.
the risks of an unfavourable prognosis at discharge. Physicians should consider the risks of bleeding before initiating intensive lipid-lowering therapy for stroke prevention.

ACKNOWLEDGEMENTS

Dr. Shi-Meng LIU would like to acknowledge the supports from UC Irvine Cheng Xiaoqi and the Liao Dongmei International Stroke Research Scholarship and the funding from the National Natural Science Foundation of China (No. 82001242).

CONFLICT OF INTERESTS

None.

STATEMENT OF AUTHORSHIP

Concepts (Ding J, Xie Y and Liu S), design (Ding J, Xie Y and Liu S), data acquisition (Xie Y, Zhang Q, Jia Y and Ding J), data analysis (Liu S), manuscript preparation (Liu S), manuscript review (Ding J and Xie Y).

REFERENCES

[1] Ebrahim S, Sung J, Song YM, et al. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. BMJ 2006; 333: 22.
[2] Ohira T, Shahar E, Chambless LE, et al. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. Stroke 2006; 37: 2493−2498.
[3] Kurth T, Everett BM, Buring JE, et al. Lipid levels and the risk of ischemic stroke in women. Neurology 2007; 68: 556−562.
[4] Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45: 2160−2236.
[5] Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42: 517−584.
[6] Milionis H, Ntafos G, Korompoki E, et al. Statin-based therapy for primary and secondary prevention of ischemic stroke: A meta-analysis and critical overview. Int J Stroke 2019: 337−384.
[7] Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control. Circulation 2016; 134: 1931−1943.
[8] Zhang Q, Liu S, Liu Y, et al. Achieving low density lipoprotein-cholesterol < 70 mg/dL may be associated with a trend of reduced progression of carotid artery atherosclerosis in ischemic stroke patients. J Neurol Sci 2017; 378: 26−29.
[9] Kim BJ, Lee SH, Ryu WS, et al. Low level of low-density lipoprotein cholesterol increases hemorrhagic transformation in large artery atherothrombosis but not in cardioembolism. Stroke 2009; 40: 1627−1632.
[10] Valappil AV, Chaudhary NV, Praveen Kumar R, et al. Low cholesterol as a risk factor for primary intracerebral hemorrhage: A case-control study. Ann Indian Acad Neurol 2012; 15: 19−22.
[11] Amarenco P, Goldstein LB, Szarek M, et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2007; 38: 3198−3204.
[12] Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke 2003; 34: 134−137.
[13] Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989; 20: 864−870.
[14] Chen YW, Li CH, Yang CD, et al. Low cholesterol level associated with severity and outcome of spontaneous intracerebral hemorrhage: Results from Taiwan Stroke Registry. PLoS One 2017; 12: e0171379.
[15] Tanaka T, Okamura T. Blood cholesterol level and risk of stroke in community-based or worksite cohort studies: a review of Japanese cohort studies in the past 20 years. Keio J Med 2012; 61: 79−88.
[16] Mustanoja S, Strbian D, Putta J, et al. Association of prestroke statin use and lipid levels with outcome of intracerebral hemorrhage. Stroke 2013; 44: 2330−2332.
[17] Rosenthal RL. Effectiveness of altering serum cholesterol levels without drugs. Proc (Bayl Univ Med Cent) 2000; 13: 351−355.

Please cite this article as: XIE YY, LIU SM, ZHANG Q, JIA Y, DING JP. Associations between low-density lipoprotein cholesterol and haemorrhagic stroke. J Geriatr Cardiol 2021; 18(3): 204−209. DOI: 10.11909/j.issn.1671-5411.2021.03.011