REPORT

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Beyond low-density lipoprotein cholesterol levels: Impact of prior statin treatment on ischemic stroke outcomes

Zi-Mo Chen,[1,2,7] Jing-Lin Mo,[1,2,7] Kai-Xuan Yang,[2,3] Ying-Yu Jiang,[2,3] Chun-Juan Wang,[2,3] Xin Yang,[2,3] Yong Jiang,[2] Xia Meng,[1,2,3,4,5,6] Jie Xu,[1,2] Hao Li,[1,2,3,4,5,6] Li-Ping Liu,[1,2] Yi-Long Wang,[1,2] Xing-Quan Zhao,[1,2] Yong-Jun Wang,[1,2,3,4,5,6] Hong-Qiu Gu,[2,3,*] and Zi-Xiao Li[1,2,3,4,5,6,*]

*Correspondence: guhongqiu@yeah.net (H.-Q.G.); lizixiao2008@hotmail.com (Z.-X.L.)

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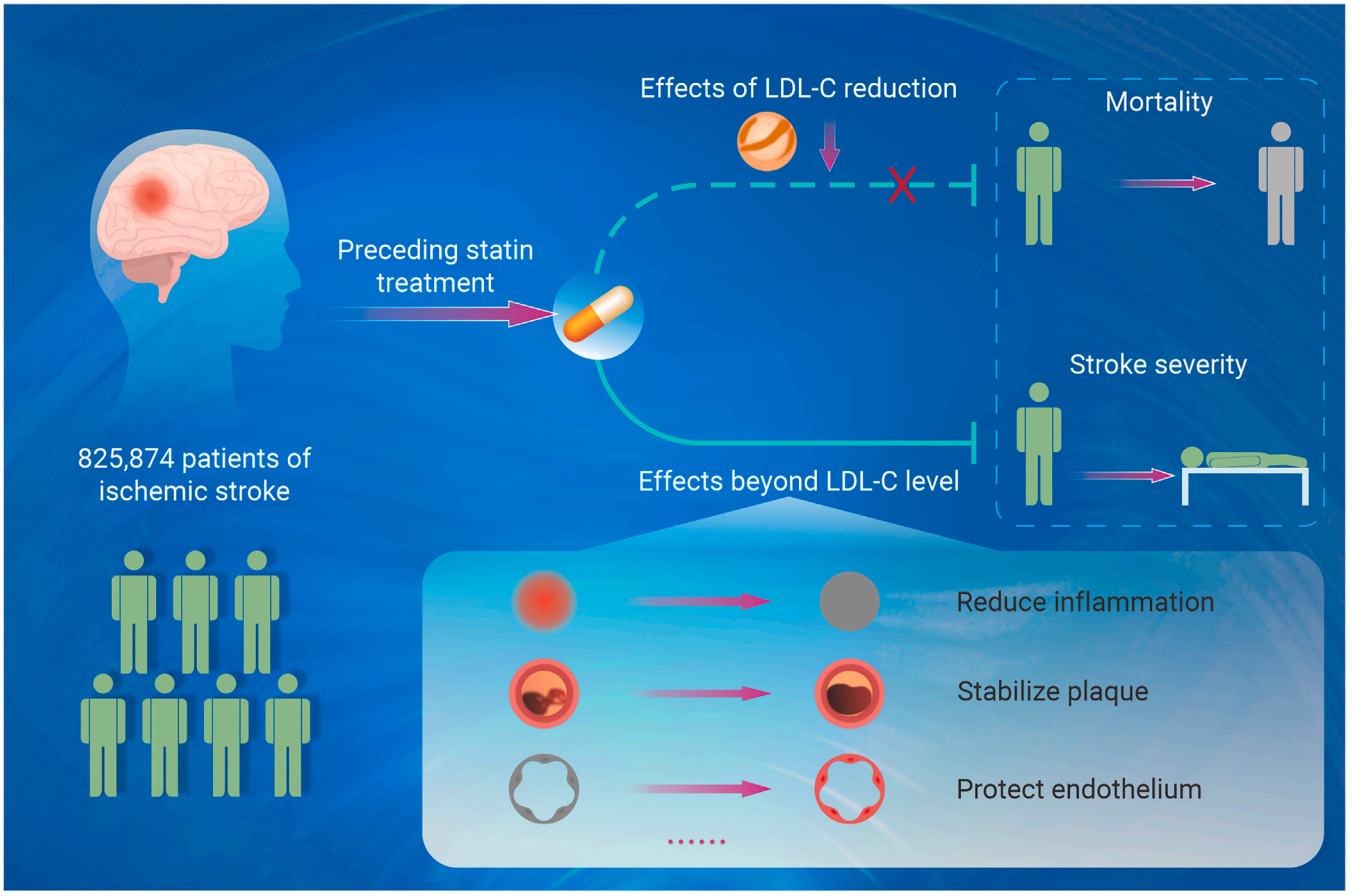
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Statins improve ischemic stroke outcomes through effects beyond LDL-C levels.
- Statins reduce stroke severity more effectively at lower LDL-C, but their impact on mortality is consistent across all levels.
- The clinical use of statins should consider their benefits beyond just LDL-C reduction.
- Further trials are required to explore the benefits of initiating statin therapy immediately following stroke.

REPORT

Beyond low-density lipoprotein cholesterol levels: Impact of prior statin treatment on ischemic stroke outcomes

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[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100071, China

[2]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing 100071, China

[3]National Center for Healthcare Quality Management in Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing 100071, China

[4]Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing 100071, China

[5]Research Unit of Artificial Intelligence in Cerebrovascular Disease, Chinese Academy of Medical Sciences, Beijing 100071, China

[6]Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai 200031, China

[7]These authors contributed equally

*Correspondence: guhongqiu@yeah.net (H.-Q.G.); lizixiao2008@hotmail.com (Z.-X.L.)

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Although essential for cardiovascular therapy, the pleiotropic effects of statins on ischemic stroke lack clinical evidence. This study examined the effects of statins beyond low-density lipoprotein cholesterol (LDL-C) levels on mortality and stroke severity. A total of 825,874 patients with ischemic stroke were included in this study, of whom 125,650 statin users were 1:1 matched with non-users based on their LDL-C levels (±0.05 mmol/L), forming the LDL-C-matched cohort. Associations between preceding statin treatment, in-hospital mortality, and stroke severity (National Institutes of Health Stroke Scale score ≥16) were estimated by multivariate and conditional logistic regression models in overall cohort and LDL-C-matched cohort, respectively. The overall statin effects reduced in-hospital mortality (odds ratio [OR]: 0.72, 95% confidence interval [CI]: 0.65–0.79, $p < 0.001$) and moderate-to-severe stroke (OR: 0.93, 95% CI: 0.90–0.96, $p < 0.001$). After matching for LDL-C levels, the reduction in mortality persisted (OR: 0.63, 95% CI: 0.52–0.77, $p < 0.001$) but not for moderate-to-severe stroke (OR: 0.96, 95% CI: 0.90–1.02, $p = 0.215$). Stratified by LDL-C levels, the effects of statin beyond LDL-C in reducing mortality remained consistent across all LDL-C ranges but increased with LDL-C reduction for stroke severity and achieved statistical significance at LDL-C <2.60 mmol/L. Mediation analyses showed that LDL-C reduction explained 0.35% (95% CI: 0.23–0.93, $p = 0.235$) of the statin treatment-mortality relationship and 12.47% (95% CI: 6.78–18.16, $p < 0.001$) for moderate-to-severe stroke. When examining the overall statin efficacy, LDL-C <2.60 mmol/L was not necessary for mortality reduction but for reducing stroke severity. The efficacy of statins in ischemic stroke outcomes is primarily derived from their effects beyond the LDL-C levels, suggesting that their neuroprotective effects should be considered in addition to their lipid-lowering effects.

INTRODUCTION

Ischemic stroke is a leading cause of death and disability worldwide.[1,2] 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are majorly used to treat ischemic stroke, with low-density lipoprotein cholesterol (LDL-C) recognized as the major therapeutic target.[3-5] However, compared with other lipid-lowering agents, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, the magnitude of statins in reducing adverse cardiovascular disease outcomes is slightly greater than what could be anticipated by their LDL-C-lowering effect alone.[6] A recent meta-analysis reported inconclusive results regarding the mediating association between the extent of statin-induced LDL-C reduction and cardiovascular outcomes, highlighting the need for further investigation into other potential mechanisms of statin benefits.[7]

To fully account for the clinical efficacy of statins, the concept of statin pleiotropy has emerged, which refers to the effects of statins beyond their LDL-C-lowering effects.[8,9] Elucidating the pleiotropic effects of statins could help identify new mechanisms underlying their benefits, such as their neuroprotective effects. This could enable a re-evaluation of the risk-benefit relationship of statin therapy, leading to a more informed clinical decision-making regarding statin use. For example, a double-edged role of low LDL-C levels has been reported, which is associated with an increased mortality risk.[10,11] Focusing solely on the LDL-C-lowering effects of statins, while disregarding their pleiotropic effects, may overemphasize the low LDL-C-related risk during statin treatment and introduce bias. However, there is a lack of clinical evidence regarding statin pleiotropy in ischemic stroke, and the clinical benefits of statin-induced LDL-C reduction remain controversial.[12,13]

Although a provocative rationale has been provided, assessing statin pleiotropy remains challenging because of the association between LDL-C levels and cardiovascular outcomes.[6] Taking advantage of a large sample size (>800,000 patients with ischemic stroke), which enabled matching of statin users with non-users at equivalent LDL-C levels, this study aimed to dissect the overall clinical efficacy of preceding statin treatment on ischemic stroke outcomes, from its impact on LDL-C levels to its effect beyond LDL-C reduction. Furthermore, we sought to determine the relationship between the effects beyond LDL-C levels and the clinical significance of low LDL-C levels under statin treatment.

RESULTS

Baseline characteristics of the patients according to the preceding statin treatment

In total, 825,874 patients with ischemic stroke were included, among whom 125,650 statin users were matched with 125,650 non-users to create an LDL-C-matched cohort, and 79.2% of the overall population had available National Institutes of Health Stroke Scale (NIHSS) scores. A flow diagram of the study is shown in Figure S2. A total of 3,365 patients with all-cause mortality were recorded during a median hospital stay of 11 days (interquartile range: 8–14 days). Table 1 presents the demographic and clinical characteristics of the LDL-C-matched population. In general, patients with ischemic stroke treated with statins were older and had more comorbidities, including hypertension, diabetes mellitus, ischemic stroke, and myocardial infarction, than statin non-users. Tables S2 and S3 describe the baseline characteristics of the overall population and of the included and excluded patients, respectively.

Overall effect and the effect beyond LDL-C levels of preceding statin treatment

Figure 1 shows that despite an increase in the crude incidence rate, after adjustment, preceding statin treatment reduced the all-cause mortality (odds ratio [OR]: 0.72, 95% confidence interval [CI]: 0.65–0.79, $p < 0.001$) and moderate-to-severe stroke (OR: 0.93, 95% CI: 0.90–0.96, $p < 0.001$) risk in the overall cohort. After LDL-C level matching, preceding statin treatment still reduced mortality risk (OR: 0.63, 95% CI: 0.52–0.77, $p < 0.001$). However, the reduction in moderate-to-severe stroke was no longer significant (OR: 0.96, 95% CI: 0.90–1.02, $p = 0.215$) in the LDL-C-matched cohort. Therefore, the effects of statins beyond the LDL-C reduction contribute to decreased mortality but do not appear to reduce stroke severity. Regarding secondary study outcomes, preceding statin treatment did not demonstrate any benefit (Figure S3), highlighting that its protective effect was specific to reducing mortality and stroke severity.

Sensitivity analysis

The total population with ischemic stroke was included within the Chinese Stroke Center Alliance (CSCA), and sensitivity analyses were performed, which

Table 1. Baseline characteristics of the LDL-C-matched cohort

Variables	Total (*N* = 251,300)	With preceding statin treatment (*N* = 125,650)	Without preceding statin treatment (*N* = 125,650)	*p* value
Demographic				
Age, mean ± SD	66.7 ± 11.8	67.1 ± 11.4	66.2 ± 12.1	<0.001
Women (%)	93,344 (37.1)	46,975 (37.4)	46,369 (36.9)	0.012
BMI (%)	–	–	–	<0.001
<18.5	9,268 (3.7)	4,559 (3.6)	4,709 (3.7)	–
18.5–25	161,941 (64.4)	80,319 (63.9)	81,622 (65.0)	–
25–30	66,784 (26.6)	34,122 (27.2)	32,662 (26.0)	–
≥30	10,072 (4.0)	5,503 (4.4)	4,569 (3.6)	–
Missing BMI	3,235 (1.3)	1,147 (0.9)	2,088 (1.7)	–
Medical history (%)				
Smoking	94,611 (37.6)	48,370 (38.5)	46,241 (36.8)	<0.001
Alcohol intake	59,442 (23.7)	30,092 (23.9)	29,350 (23.4)	0.001
Hypertension	174,481 (69.4)	96,462 (76.8)	78,019 (62.1)	<0.001
Diabetes mellitus	64,589 (25.7)	40,192 (32.0)	24,397 (19.4)	<0.001
Ischemic stroke	117,464 (46.7)	86,561 (68.9)	30,903 (24.6)	<0.001
Myocardial infarction	6,903 (2.7)	5,276 (4.2)	1,627 (1.3)	<0.001
Atrial fibrillation	16,785 (6.7)	10,275 (8.2)	6,510 (5.2)	<0.001
Heart failure	4,141 (1.6)	3,034 (2.4)	1,107 (0.9)	<0.001
Medication use (%)				
IV thrombolytic therapy	13,615 (5.4)	5,903 (4.7)	7,712 (6.1)	<0.001
Antithrombotic treatment	202,644 (80.6)	96,381 (76.7)	106,263 (84.6)	<0.001
LDL-C level	–	–	–	0.941
Mean ± SD	2.7 ± 1.5	2.7 ± 1.5	2.7 ± 1.5	–

LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; IV, intravenous; SD, standard deviation.

showed similar results to those of the main analysis that the effects beyond LDL-C of statins contribute to decreased mortality but do not reduce stroke severity (Table S4). The statistical significance of the overall effect of statins on reducing mortality risk remained consistent from model 1 [OR: 0.69, 95% CI: 0.63–0.77, $p < 0.001$] to model 3 [OR: 0.72, 95% CI: 0.70–0.87, $p < 0.001$], and it remained significant in each model after matching for LDL-C level (from model 1 [OR: 0.61, 95% CI: 0.50–0.75, $p < 0.001$] to model 3 [OR: 0.63, 95% CI: 0.51–0.79, $p < 0.001$]). The results of the sensitivity analysis for stroke severity were similar to those of the main analysis (Figure S4). The above sensitivity analyses confirmed the overall effect and the effect beyond the LDL-C level of the preceding statin treatment. Furthermore, in patients who received single-antiplatelet therapy during hospitalization, the overall effect and the effect beyond LDL-C levels were similar to those observed in the primary analysis. However, in patients receiving dual-antiplatelet therapy, neither the overall effect nor the effect beyond LDL-C levels was significant (Tables S5 and S6).

Subgroup analysis

Patients were stratified based on age, sex, and the presence of comorbidities, and subgroup analyses of the association between preceding statin treatment and all-cause mortality were performed in the overall and LDL-C-matched cohorts (Figure 2). The overall effects of reduction in mortality risk persisted across all subgroups. This interaction effect demonstrated a more prominent benefit in patients with a previous ischemic stroke ($p < 0.1$). After matching for LDL-C levels, the effect of preceding statin treatment was more prominent in patients with previous ischemic stroke and in those without diabetes mellitus (both $p < 0.1$).

A subgroup analysis of the association between preceding statin treatment and stroke severity was also performed in the overall and LDL-C-matched cohorts (Figure 3). The interaction effect demonstrated a more prominent overall effect in reducing stroke severity in older patients and in those with atrial fibrillation, previous ischemic stroke, hyperlipidemia, and without diabetes mellitus, with significant interaction effects (all $p < 0.1$). After matching for LDL-C levels, the effect of preceding statin therapy remained more prominent in the above subgroups (all with $p < 0.1$), except in patients with previous ischemic stroke ($p = 0.337$) and those with hyperlipidemia ($p = 0.933$), indicating that the more prominent overall statin effect in these two subgroups might be attributed to LDL-C levels.

Whether the effect beyond the LDL-C level occurs in parallel with the LDL-C reduction

Patients were further stratified by LDL-C level (<1.80, 1.80–2.59, 2.60–2.99, 3.00–4.89, and ≥4.90 mmol/L) in the LDL-C-matched cohort (Figure 4). The trend of the association between preceding statin use and all-cause mortality was consistent with the primary analysis in all the LDL-C level groups.

The effect size of statins beyond the LDL-C level on reducing moderate-to-severe stroke increased gradually with the reduction in LDL-C level with statin treatment, reaching statistical significance only when LDL-C levels were <2.60 mmol/L ($p = 0.023$) (Figure 4).

Therefore, regarding the effect of statins beyond LDL-C levels, the mortality benefit was consistent across all LDL-C strata, whereas their impact on reducing stroke severity became significant only when LDL-C levels were <2.60 mmol/L.

Mediation effect of LDL-C reduction on the overall efficacy of statins

Figure S5 shows the mediation effect of LDL-C reduction by statins on the reduction in all-cause mortality and stroke severity. For mortality protection,

Outcome	Events/Patients	Event rate	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)
The overall effect				
All-cause mortality				
With preceding statin treatment	588/125651	0.47	1.14(1.05,1.25)	0.72(0.65,0.79)
Without preceding statin treatment	2864/700223	0.41	1[reference]	1[reference]
Moderate to severe stroke				
With preceding statin treatment	5938/99121	5.99	1.21(1.18,1.25)	0.93(0.90,0.96)
Without preceding statin treatment	27992/560294	5.00	1[reference]	1[reference]
The effect beyond LDL-C levels				
All-cause mortality				
With preceding statin treatment	588/125650	0.47	1.09(0.97,1.23)	0.63(0.52,0.77)
Without preceding statin treatment	539/125650	0.43	1[reference]	1[reference]
Moderate to severe stroke				
With preceding statin treatment	4690/78983	5.94	1.14(1.09,1.19)	0.96(0.90,1.02)
Without preceding statin treatment	4148/78983	5.25	1[reference]	1[reference]

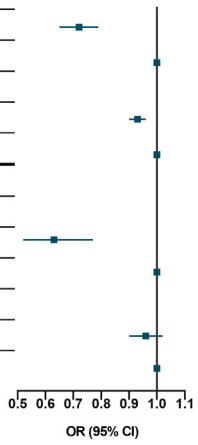


Figure 1. The overall effect and the effect beyond LDL-C levels of preceding statin treatment on in-hospital mortality and stroke severity The analyses were performed using logistic regression models and conditional logistic regression models in the overall and LDL-C-matched cohorts, respectively, after adjusting for age, sex, body mass index, smoking status, alcohol intake, history of hypertension, diabetes mellitus, ischemic stroke, myocardial infarction, atrial fibrillation and heart failure, IV thrombolytic therapy, and antithrombotic treatment. LDL-C, low-density lipoprotein cholesterol; IV, intravenous; OR, odds ratio; CI, confidence interval.

the mediation effect of LDL-C reduction was 0.35% (95% CI: −0.23 to 0.93, p = 0.235) (Figure S5A). Figure S5B shows that LDL-C reduction significantly, though modestly, mediates the relationship between preceding statin treatment and the reduction in moderate-to-severe stroke, with a mediation effect of 12.47% (95% CI: 6.78–18.16, $p < 0.001$). Therefore, LDL-C reduction by statins plays only a minor mediating role in mortality and stroke severity outcomes.

Significance of low LDL-C levels in the overall efficacy of statins

Statin users exhibited a reduced risk of all-cause mortality irrespective of LDL-C levels (either LDL-C <2.60 mmol/L or LDL-C ≥2.60 mmol/L) (Figure 5A). However, only statin users with an LDL-C level <2.60 mmol/L exhibited a reduction in moderate-to-severe stroke (OR: 0.85, 95% CI: 0.81–0.88, $p < 0.001$) (Figure 5A). The interaction effect corroborated these findings, revealing a non-significant interaction between the preceding statin treatment and LDL-C level for the outcome of mortality (p = 0.708) but a significant interaction for stroke severity ($p < 0.001$) (Figure 5B). This aligns with the above findings that the effects beyond the LDL-C level are consistent with LDL-C reduction, which should be recognized as the primary mechanism for the benefit of statins on mortality and stroke severity.

DISCUSSION

This study demonstrated that the efficacy of statins in improving the clinical outcomes of patients with ischemic stroke was primarily derived from their effects beyond the LDL-C level, which was also identified as a major beneficial mechanism during the acute stage of ischemic stroke. Thus, statins can improve clinical outcomes more substantially than that anticipated by LDL-C reduction alone, potentially because of their pleiotropic effects. Furthermore, the effect of statins beyond LDL-C levels on reducing moderate-to-severe stroke increased with the LDL-C level reduction, whereas this pattern was not observed for mortality reduction. Consequently, the relationship between overall statin efficacy and LDL-C levels differs in reducing stroke severity compared to mortality, highlighting that LDL-C levels alone may not fully reflect statin efficacy for different therapeutic objectives. Therefore, in clinical settings, it is essential to consider the effects of statins beyond the LDL-C level.

Clinical significance of the findings

Using data from >800,000 patients with ischemic stroke, this study fills a gap in clinical knowledge regarding the effects of statins beyond LDL-C levels and supports the presence of pleiotropic effects, which could be essential when evaluating the advantages and disadvantages of statin treatment when making clinical decisions. We demonstrated that reductions in mortality and moderate-to-severe stroke were the major benefits of preceding statin treatment, and that the effect beyond LDL-C levels could be recognized as the major beneficial mechanism during the acute stage of ischemic stroke. As a result, the effect of statins beyond LDL-C levels should be taken into clinical consideration, rather than being a currently postulated effect. As such, LDL-C levels should not be recognized as the only indicator of statin efficacy during the acute stage of ischemic stroke. In this context, statins should not only be regarded as lipid-lowering agents, but more importantly, their neuroprotective effects should be considered, especially in patients with a relatively high mortality risk, such as those with multiple comorbidities. Furthermore, it is also necessary to consider the potential influence of comorbid conditions such as diabetes mellitus, which may weaken the effect beyond the LDL-C level, as demonstrated in our study, to accurately assess the benefits of statin therapy and thereby design more personalized treatment approaches.

Therefore, the physiological significance of low LDL-C levels achieved with other non-statin agents may differ from that achieved with statin treatment. This may explain why the clinical benefits of statins to some extent are greater than those achieved with ezetimibe or PCSK9 inhibitors in terms of the LDL-C reduction.[6] It also explains why low LDL-C levels have been reported to be associated with an increased mortality risk, whereas statins can protect patients with ischemic stroke from mortality.[14] As a result, the potential risks related to low LDL-C levels should not be arbitrarily proposed as a reason to question the benefits of statins; rather, their efficacy in terms of their effects beyond LDL-C levels should be considered. Given these potential benefits, further clinical trials are required to explore the efficacy of initiating statin therapy immediately after stroke to improve outcomes.

Pleiotropic effects of statins

Although our study did not directly assess the pleiotropic effects of statins by randomizing patients into the statin versus ezetimibe and/or PCSK9 inhibitors groups, matching statin users with non-users at nearly equivalent LDL-C levels effectively eliminated the effects of differences in LDL-C levels. This allowed us to dissect the effects of statins beyond the LDL-C level. Therefore, our study provides evidence for the pleiotropic effects of statins.

An additional clue regarding the effects of statins beyond LDL-C levels on mortality protection included a minor LDL-C difference between statin users and non-users (2.4 vs. 2.6 mmol/L), with a significant 28% reduction in mortality. This benefit persisted even in patients with high LDL-C levels, including those with an LDL-C level of ≥4.9 mmol/L who would be diagnosed with severe hypercholesterolemia.[15] Besides, in the subgroup analyses, the overall statin effect showed no apparent link to hyperlipidemia and remained significant even in patients with atrial fibrillation, indicating that their benefit in reducing mortality was unlikely to involve lipid levels and was not limited to ischemic stroke of the presumed atherosclerotic origin.

The effect of statins in reducing stroke severity beyond LDL-C levels was also demonstrated by matching patients by LDL-C levels, albeit only when the LDL-C level was <2.6 mmol/L with statin use. In addition, in both outcomes, the mediation analyses showed that LDL-C reduction, as the other beneficial mechanism, could not explain or could only explain a small proportion of the overall statin efficacy, indicating that an effect beyond the LDL-C level is the major beneficial mechanism. Moreover, the effects beyond LDL-C levels on both outcomes were more prominent in patients without diabetes mellitus. This further supports the pleiotropic effects of statins, which can reduce inflammation and oxidation,[16,17] because diabetes mellitus often aggravates these physiological processes and may weaken the pleiotropic effects of statins.[17,18]

All-cause mortality	The overall effect			The effect beyond LDL-C levels		
	Events/Patients	Adjusted OR(95% CI)	*P* for interaction	Events/Patients	Adjusted OR(95% CI)	*P* for interaction
Age, y						
Age <65						
With preceding statin	104/49 698 (0.21)	0.65 (0.52, 0.82)		104/49 694 (0.21)	0.74 (0.48, 1.13)	
Without preceding statin	631/305 445 (0.21)	1 [reference]	0.835	112/49 694 (0.23)	1 [reference]	0.432
Age ≥65						
With preceding statin	484/75 953 (0.64)	0.73 (0.66, 0.82)		484/75 952 (0.64)	0.70 (0.57, 0.85)	
Without preceding statin	2233/394 778 (0.57)	1 [reference]		488/75 952 (0.64)	1 [reference]	
Sex						
Female						
With preceding statin	251/46 975 (0.53)	0.74 (0.64, 0.86)		251/46 973 (0.53)	0.60 (0.42, 0.87)	
Without preceding statin	1230/262 364 (0.47)	1 [reference]	0.790	202/46 973 (0.43)	1 [reference]	0.964
Male						
With preceding statin	337/78 676 (0.43)	0.70 (0.61, 0.79)		337/78 674 (0.43)	0.79 (0.61, 1.01)	
Without preceding statin	1634/437 859(0.37)	1 [reference]		308/78 674 (0.39)	1 [reference]	
Atrial fibrillation						
Yes						
With preceding statin	206/10 276 (2.00)	0.81 (0.68, 0.96)		206/10 258 (2.01)	0.79 (0.59, 1.05)	
Without preceding statin	642/33 570 (1.91)	1 [reference]	0.258	196/10 258 (1.91)	1 [reference]	0.348
No						
With preceding statin	382/115 375 (0.33)	0.67 (0.60, 0.76)		382/115 375 (0.33)	0.68 (0.54, 0.85)	
Without preceding statin	2222/666 653 (0.33)	1 [reference]		387/115 375 (0.34)	1 [reference]	
Previous ischemic stroke						
Yes						
With preceding statin	412/86 562 (0.48)	0.68 (0.60, 0.77)		412/86 506 (0.48)	0.62 (0.52, 0.74)	
Without preceding statin	972/167 650 (0.58)	1 [reference]	0.056	515/86 506 (0.60)	1 [reference]	0.035
No						
With preceding statin	176/39 089 (0.45)	0.81 (0.69, 0.95)		176/39 089 (0.45)	0.93 (0.66, 1.32)	
Without preceding statin	1892/53 2573 (0.36)	1 [reference]		134/39 089 (0.34)	1 [reference]	
Previous hemorrhagic stroke						
Yes						
With preceding statin	25/4221 (0.59)	0.76 (0.46, 1.26)		24/4213 (0.57)	0.23 (0.02, 2.88)	
Without preceding statin	93/19 648 (0.47)	1 [reference]	0.845	20/4213 (0.47)	1 [reference]	0.805
No						
With preceding statin	563/121 430 (0.46)	0.72 (0.65, 0.79)		563/121 429 (0.46)	0.67 (0.55, 0.81)	
Without preceding statin	2771/680 575 (0.41)	1 [reference]		547/121 429 (0.45)	1 [reference]	
Diabetes						
Yes						
With preceding statin	226/40 193 (0.56)	0.69 (0.58, 0.81)		226/40 157 (0.56)	0.73 (0.56, 0.96)	
Without preceding statin	715/137 094 (0.52)	1 [reference]	0.954	231/40 157 (0.58)	1 [reference]	0.043
No						
With preceding statin	362/85 458 (0.42)	0.73 (0.65, 0.83)		362/85 457 (0.42)	0.51 (0.39, 0.66)	
Without preceding statin	2149/563 129 (0.38)	1 [reference]		401/85 457 (0.47)	1 [reference]	
Hyperlipemia						
Yes						
With preceding statin	167/35 067 (0.48)	0.70 (0.55, 0.89)		140/28 459 (0.49)	0.58 (0.40, 0.84)	
Without preceding statin	143/28 961 (0.49)	1 [reference]	0.528	139/28 459 (0.49)	1 [reference]	0.275
No						
With preceding statin	421/90 584 (0.46)	0.73 (0.65, 0.81)		421/90 583 (0.46)	0.75 (0.60, 0.94)	
Without preceding statin	2721/671 262 (0.41)	1 [reference]		377/90 583 (0.42)	1 [reference]	

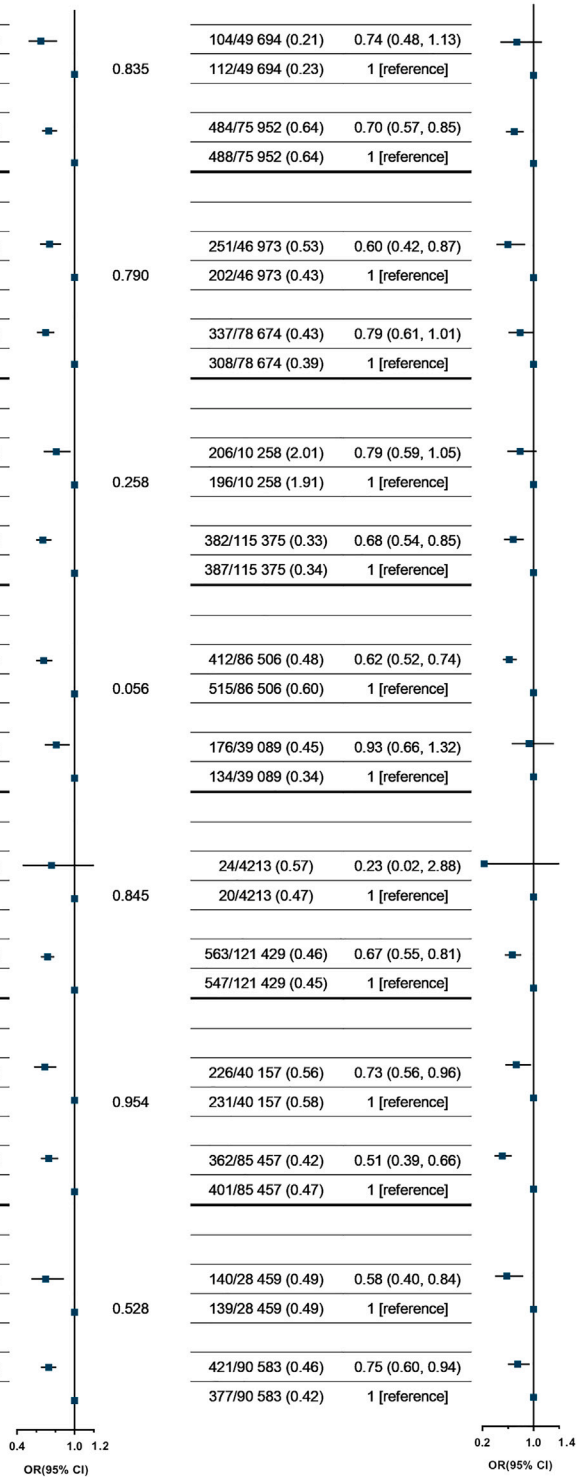


Figure 2. Subgroup analyses of the overall effect and the effect beyond LDL-C levels of preceding statin treatment on in-hospital mortality The analyses were performed using logistic regression models and conditional logistic regression models in the overall (indicating the overall effect of the preceding statin treatment) and LDL-C-matched (indicating the effect beyond LDL-C of the preceding statin treatment) cohorts, respectively, after adjusting for age, sex, body mass index, smoking status, alcohol intake, history of hypertension, diabetes mellitus, ischemic stroke, myocardial infarction, atrial fibrillation and heart failure, IV thrombolytic therapy, and antithrombotic treatment. LDL-C, low-density lipoprotein cholesterol; IV, intravenous; OR, odds ratio; CI, confidence interval.

Effects beyond LDL-C levels and the significance of low LDL-C level with statin treatment

We investigated the relationship between the effects of statin treatment beyond LDL-C levels and the clinical significance of low LDL-C levels. In terms of reducing mortality, an effect beyond LDL-C levels was observed even if a low LDL-C level was not achieved. Conversely, although LDL-C reduction did not adequately explain the overall efficacy of statins, the effect of statins beyond LDL-C levels on reducing stroke severity increased with LDL-C reduction. The

Moderate-to-severe stroke	The overall effect			The effect beyond LDL-C levels		
	Events/Patients	Adjusted OR(95% CI)	*P* for interaction	Events/Patients	Adjusted OR(95% CI)	*P* for interaction
Age, y						
Age <65						
With preceding statin	1532/39 011 (3.93)	1.01 (0.95, 1.07)		1206/31 119 (3.88)	1.06 (0.93, 1.20)	
Without preceding statin	7644/244 929 (3.12)	1 [reference]	<.0001	1001/31 119 (3.22)	1 [reference]	0.005
Age ≥65						
With preceding statin	4406/60 110 (7.33)	0.90 (0.87, 0.94)		3493/47 967 (7.28)	0.89 (0.83, 0.95)	
Without preceding statin	20 348/315 365 (6.45)	1 [reference]		3214/47 967 (6.70)	1 [reference]	
Sex						
Female						
With preceding statin	2735/36 829 (7.43)	0.91 (0.87, 0.96)		2139/29 221 (7.32)	0.94 (0.85, 1.03)	
Without preceding statin	12 943/208 760(6.20)	1 [reference]	0.958	1913/29 221 (6.55)	1 [reference]	0.445
Male						
With preceding statin	3203/62 292	0.95 (0.91, 0.99)		2513/49 913 (5.03)	1.01 (0.92, 1.09)	
Without preceding statin	15 049/351 534	1 [reference]		2209/49 913 (4.43)	1 [reference]	
Atrial fibrillation						
Yes						
With preceding statin	1495/8405 (17.79)	0.82 (0.76, 0.88)		1234/6925 (17.82)	0.84 (0.75, 0.94)	
Without preceding statin	5514/27 860 (19.79)	1 [reference]	<.0001	1398/6925 (20.19)	1 [reference]	<.0001
No						
With preceding statin	4443/90 716 (4.90)	0.96 (0.93, 1.00)		3506/72 360 (4.85)	1.01 (0.94, 1.08)	
Without preceding statin	22 478/532 434 (4.22)	1 [reference]		3176/72 360 (4.39)	1 [reference]	
Previous ischemic stroke						
Yes						
With preceding statin	4277/68 025 (6.29)	0.91 (0.88, 0.95)		3274/52 305 (6.26)	0.93 (0.88, 0.99)	
Without preceding statin	8265/129 635 (6.38)	1 [reference]	0.054	3401/52 305 (6.50)	1 [reference]	0.337
No						
With preceding statin	1661/31 096 (5.34)	0.97 (0.92, 1.02)		1337/25 146 (5.32)	1.06 (0.96, 1.18)	
Without preceding statin	19 727/430 659 (4.58)	1 [reference]		1203/25 146 (4.78)	1 [reference]	
Previous hemorrhagic stroke						
Yes						
With preceding statin	262/3175 (8.25)	0.86 (0.74, 1.01)		189/2438 (7.75)	0.87 (0.62, 1.22)	
Without preceding statin	1051/14 950 (7.03)	1 [reference]	0.564	165/2438 (6.77)	1 [reference]	0.991
No						
With preceding statin	5676/95 946 (5.92)	0.93 (0.90, 0.97)		4505/76 660 (5.88)	0.95 (0.89, 1.01)	
Without preceding statin	26941/545 344 (4.94)	1 [reference]		3964/76 660 (5.17)	1 [reference]	
Diabetes						
Yes						
With preceding statin	1826/32 140 (5.68)	0.98 (0.92, 1.04)		1453/25 888 (5.61)	1.00 (0.89, 1.11)	
Without preceding statin	4875/110 526 (4.41)	1 [reference]	0.0004	1187/25 888 (4.59)	1 [reference]	0.025
No						
With preceding statin	4112/66 981 (6.14)	0.91 (0.88, 0.95)		3276/53 273 (6.15)	0.91 (0.84, 0.98)	
Without preceding statin	23 117/449 768 (5.14)	1 [reference]		2916/53 273 (5.47)	1 [reference]	
Hyperlipemia						
Yes						
With preceding statin	1650/27 184 (6.07)	0.87(0.81,0.95)		1038/17 004 (6.10)	0.98 (0.88, 1.10)	
Without preceding statin	1356/23 227 (5.84)	1 [reference]	0.088	995/17 004 (5.85)	1 [reference]	0.933
No						
With preceding statin	4288/71 937 (5.96)	0.92(0.89,0.96)		3370/57 114 (5.90)	0.96 (0.89, 1.03)	
Without preceding statin	26 636/537 067 (4.96)	1 [reference]		2975/57 114 (5.21)	1 [reference]	

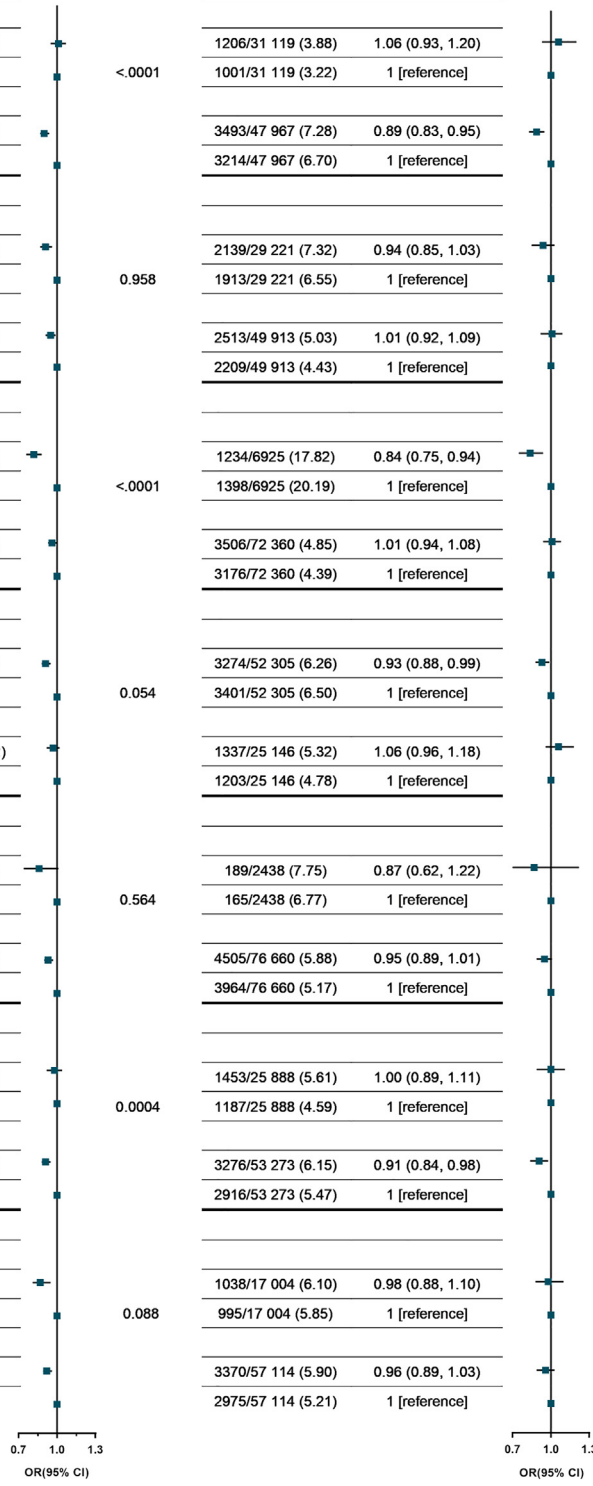


Figure 3. Subgroup analyses of the overall effect and the effect beyond LDL-C levels of preceding statin treatment on stroke severity The analyses were performed using logistic regression models and conditional logistic regression models in the overall (indicating the overall effect of the preceding statin treatment) and LDL-C-matched (indicating the effect beyond LDL-C of the preceding statin treatment) cohorts, respectively, after adjusting for age, sex, body mass index, smoking status, alcohol intake, history of hypertension, diabetes mellitus, ischemic stroke, myocardial infarction, atrial fibrillation and heart failure, IV thrombolytic therapy, and antithrombotic treatment. LDL-C, low-density lipoprotein cholesterol; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.

overall efficacy of statins, which comprises both effects, further supports these results.

Collectively, these findings suggest that LDL-C levels could indicate statin efficacy in reducing stroke severity but not mortality. Notably, the major beneficial mechanism is not LDL-C reduction itself; rather, it is an effect beyond the LDL-C level, for which the effect size can be indicated by the degree of LDL-C reduction. Therefore, besides their LDL-C-lowering effects, the clinical benefits of statins beyond LDL-C levels should be considered when determining whether

The effect beyond LDL-C levels	All-cause mortality		Moderate-to-severe stroke	
	Events/Patients	Adjusted OR(95% CI)	Events/Patients	Adjusted OR(95% CI)
LDL-C <1.80				
With preceding statin	167/26 290 (0.64)	0.59 (0.39, 0.89)	995/16 734 (5.95)	0.78 (0.68, 0.89)
Without preceding statin	168/26 290 (0.64)	1 [reference]	1090/16 734 (6.51)	1 [reference]
LDL-C = 1.80–2.59				
With preceding statin	173/40 137 (0.43)	0.71 (0.48, 1.04)	1435/25 664 (5.59)	0.87 (0.78, 0.98)
Without preceding statin	149/40 137 (0.37)	1 [reference]	1297/25 664 (5.05)	1 [reference]
LDL-C = 2.60–2.99				
With preceding statin	54/17 318 (0.31)	0.43 (0.17, 1.11)	605/11 043 (5.48)	1.03 (0.86, 1.23)
Without preceding statin	51/17 318 (0.29)	1 [reference]	503/11 043 (4.55)	1 [reference]
LDL-C = 3.00–4.89				
With preceding statin	163/36 129 (0.45)	0.63 (0.43, 0.91)	1340/22 885 (5.86)	1.16 (1.03, 1.31)
Without preceding statin	140/36 129 (0.39)	1 [reference]	1006/22 885 (4.40)	1 [reference]
LDL-C ≥4.90				
With preceding statin	31/5776 (0.54)	0.58 (0.20, 1.64)	315/2657 (11.86)	1.15 (0.89, 1.47)
Without preceding statin	31/5776 (0.54)	1 [reference]	252/2657 (9.48)	1 [reference]

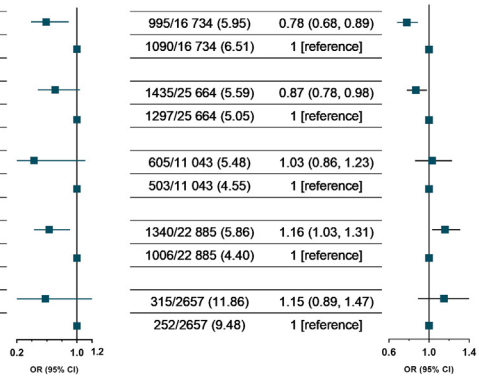


Figure 4. Associations between the effects beyond LDL-C levels and LDL-C reduction with the preceding statin treatment All analyses were performed in the LDL-C-matched cohort using conditional logistic regression models after adjusting for age, sex, body mass index, smoking status, alcohol intake, history of hypertension, diabetes mellitus, ischemic stroke, myocardial infarction, atrial fibrillation and heart failure, IV thrombolytic therapy, and antithrombotic treatment. LDL-C, low-density lipoprotein cholesterol; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.

low LDL-C levels could serve as an indicator of statin efficacy in different therapeutic contexts.

Biological explanations

The different mechanisms of statin pleiotropy may provide answers as to why the effect beyond LDL-C levels correlates with LDL-C reduction in different ways to reduce mortality and stroke severity. For instance, statins have been demonstrated to inhibit Rho kinase activity independent of LDL-C reduction, which upregulates endothelial nitric oxide synthase.[8] Additionally, it has been reported that the paraoxonase-1-enhancing effects of statins are independent of the statin dose, treatment duration, and changes in plasma LDL-C levels, which could generate a neuroprotective effect due to its antioxidant and anti-inflammatory properties.[19] However, the effect of statins on decreasing circulating CXCL12 occurs in a dose-dependent manner, as a potent mediator of angiogenesis.[20]

Strengths and limitations

One strength of this study was the large sample size, which afforded sufficient statistical power to facilitate LDL-C level matching and to effectively control and analyze confounding variables using sophisticated models. Moreover, the results exhibited specificity, signifying that the effect beyond LDL-C levels exclusively conferred protection against mortality and stroke severity (targets characterized by neuroprotective effects), rather than reducing other cardiovascular events (targets not associated with neuroprotective effects). These strengths support the reliability of the conclusions drawn in this study.

This study had certain limitations. First, the data from the CSCA program originated from in-hospital settings. Therefore, our conclusions regarding the effects of statins beyond the LDL-C levels are confined to the acute stage of ischemic stroke. However, it is important to note that this does not contradict the long-term benefits of statins in LDL-C reduction in patients with acute ischemic stroke. Second, owing to the observational design, complete elimination of the influence stemming from unmeasured covariates remains unattainable. Nevertheless, individuals using statins generally exhibit a higher prevalence of risk factors, as indicated by our baseline data. In the initial unadjusted models, statin users demonstrated an elevated risk of the study's primary outcomes. However, subsequent adjustments for potential confounding variables resulted in a noteworthy reduction in risk. Therefore, it seems unlikely that unmeasured covariates would significantly amplify the risk for non-statin users in a way that would confound the observed protective effects of statins. Third, our study lacked data on additional therapies including ezetimibe and PCSK9 inhibitors. However, a recent report indicated that among Chinese patients hospitalized for acute coronary syndrome and receiving lipid-lowering therapy, only 0.9% were prescribed a combined regimen of statin + ezetimibe upon admission, whereas 98.6% received statin monotherapy.[21] There is no available data on the rate of PCSK9 inhibitor use in China, but it is reasonable to speculate that this rate may be even lower than that of ezetimibe.

CONCLUSION

Based on the *in vitro* findings and a compelling rationale, this study provides clinical evidence of the effect of statins beyond LDL-C levels, translating it into clinical significance as a major driver of statin efficacy during the acute stage of ischemic stroke. Considering the effects of statins beyond LDL-C levels, this study empowers clinicians and patients to make more informed decisions regarding statin use, ultimately leading to improved outcomes.

MATERIALS AND METHODS

Study cohort and study population

The CSCA, a prospective, national, multicenter, and continuous quality improvement program, was launched in 2015.[22,23] Data were collected from 1,471 hospitals in China between 2015 and 2019, and 1,006,798 patients with acute ischemic stroke, transient ischemic attack, intracerebral hemorrhage, or subarachnoid hemorrhage, aged ≥18 years and with symptom onset in 7 days, were enrolled.

The Institutional Review Board waived the requirement for informed consent. All data were collected in routine clinical practice and anonymized to maintain confidentiality. Data collection did not modify the existing clinical routines. This study was approved by the Ethics Review Board of Beijing Tiantan Hospital (approval number: KY2018-061-02), and it aligned with the principles of the Declaration of Helsinki.

Data from 838,229 patients with acute ischemic stroke confirmed using computed tomography/magnetic resonance imaging were analyzed. Two cohorts were generated (the overall cohort [including the overall population] and the LDL-C-matched cohort [including statin users matched with statin non-users based on LDL-C levels from the overall population]) to define the overall statin effect and the effect beyond the LDL-C levels, respectively. Patients with missing LDL-C data were excluded (1.47% of the total patients with ischemic stroke). The correlation between preceding statin treatment and stroke severity was analyzed, and patients with ischemic stroke with missing values on the NIHSS score were excluded.

Data collection and variables of interest

In-hospital data were collected using an internet-based tool from the Beijing Medicine Innovation Research Center. Trained personnel reviewed, coded, and anonymized the data to ensure patient confidentiality. The data abstraction tool incorporated predefined logic, range validation, and user alerts to detect and prevent entry of invalid data, thereby enhancing data quality during entry.[24] Data were structured, verified, and range-checked to identify inconsistent or out-of-range data. Data collectors were trained, and automated checks flagged erroneous or illogical data entries.

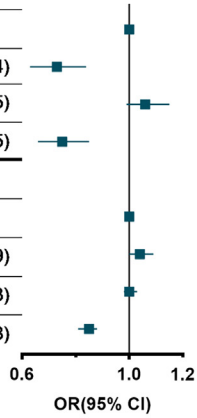
Preceding statin treatment was defined by documenting patients who had been on statin therapy in the 6 months prior to hospital arrival. LDL-C levels (mmol/L) were measured at admission and collected from medical records at each site. Primary study outcomes were all-cause mortality and stroke severity (moderate-to-severe stroke, NIHSS score ≥16) recorded during hospitalization. The NIHSS score ranges from 0 to 42, with higher scores indicating greater stroke severity. Secondary study outcomes included new-onset ischemic stroke, hemorrhagic stroke, and myocardial infarction during hospitalization, which are the major cardiovascular events influenced by statin therapy. Study outcomes were confirmed based on clinical symptoms, electrocardiography, and laboratory and radiographic findings. Detailed definitions of the study outcomes are presented in Table S1.

Matching between statin users and non-users according to the LDL-C levels

Patients with and without preceding statin treatment were matched in a 1:1 ratio. A statin user was randomly selected and then matched to a non-user whose LDL-C level was closest to that of the statin user (±0.05 mmol/L). The two LDL-C-matched patients were included in the LDL-C-matched cohort and excluded from the subsequent matching process of the

A

The overall effect	Events/Patients	Adjusted OR (95% CI)
All-cause mortality		
Without preceding statin and LDL-C ≥2.6	1413/388 707 (0.36)	1 [reference]
With preceding statin and LDL-C ≥2.6	248/59 224 (0.42)	0.73 (0.63, 0.84)
Without preceding statin and LDL-C <2.6	1451/311 516 (0.47)	1.06 (0.99, 1.15)
With preceding statin and LDL-C <2.6	340/66 427 (0.51)	0.75 (0.66, 0.85)
Moderate-to-severe stroke		
Without preceding statin and LDL-C ≥2.6	14 673/311 070 (4.72)	1 [reference]
With preceding statin and LDL-C ≥2.6	2879/46 013 (6.26)	1.04 (1.00, 1.09)
Without preceding statin and LDL-C <2.6	13 319/249 224 (5.34)	1.00 (0.98, 1.03)
With preceding statin and LDL-C <2.6	3059/53 108 (5.76)	0.85 (0.81, 0.88)



B

The overall effect	Events/Patients	Adjusted OR (95% CI)	*P* for interaction
All-cause mortality			
Without preceding statin and LDL-C ≥2.6	1413/388 707 (0.36)	1 [reference]	
With preceding statin and LDL-C ≥2.6	248/59 224 (0.42)	0.71 (0.61, 0.82)	0.708
Without preceding statin and LDL-C <2.6	1451/311 516 (0.47)	1 [reference]	
With preceding statin and LDL-C <2.6	340/66 427 (0.51)	0.72 (0.64, 0.83)	
Moderate-to-severe stroke			
Without preceding statin and LDL-C ≥2.6	14 673/311 070 (4.72)	1 [reference]	
With preceding statin and LDL-C ≥2.6	2879/46 013 (6.26)	1.01 (0.96, 1.05)	<.0001
Without preceding statin and LDL-C <2.6	13 319/249 224 (5.34)	1 [reference]	
With preceding statin and LDL-C <2.6	3059/53 108 (5.76)	0.87 (0.83, 0.91)	

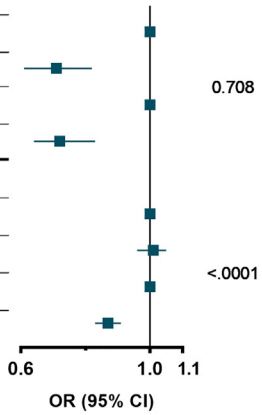


Figure 5. Significance of low LDL-C levels in the overall efficacy of preceding statin treatment (A) The overall effect of preceding statin treatment on all-cause mortality and moderate-to-severe stroke, at different LDL-C levels. (B) Interaction effects between preceding statin treatment and LDL-C levels on all-cause mortality and moderate-to-severe stroke. All analyses were performed in the overall cohort using logistic regression models after adjusting for age, sex, body mass index, smoking status, alcohol intake, history of hypertension, diabetes mellitus, ischemic stroke, myocardial infarction, atrial fibrillation and heart failure, IV thrombolytic therapy, and antithrombotic treatment. LDL-C, low-density lipoprotein cholesterol; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.

other patients. Among the statin users, one patient who could not be matched with a statin non-user was excluded from the LDL-C-matched cohort.

Sensitivity analyses

Details are provided in the supplemental information.

Subgroup analyses

Subgroup analyses were conducted in the overall and LDL-C-matched cohorts to assess the interaction effect and determine whether the overall effect and the effect beyond the LDL-C level varied among different populations. The patients were grouped by age (<65 years vs. ≥65 years), where age was still adjusted; sex (male vs. female); history of atrial fibrillation (yes vs. no); ischemic stroke (yes vs. no); hemorrhagic stroke (intracerebral hemorrhage or subarachnoid hemorrhage) (yes vs. no); diabetes mellitus (yes vs. no); and hyperlipidemia (yes vs. no).

Effect beyond the LDL-C level and the significance of low LDL-C level in the overall statin efficacy

The effects of statin treatment beyond LDL-C levels and the clinical significance of low LDL-C levels were investigated by examining the following three key aspects.

(1) Whether effects beyond LDL-C levels occurred alongside LDL-C reduction.
(2) The mediating effect of LDL-C reduction on the overall efficacy of statins assessed using mediation analyses to identify the relative contributions of LDL-C reduction and its effects beyond LDL-C level.
(3) Significance of low LDL-C levels on the overall efficacy of statins.

The details of these analyses are provided in the supplemental information.

Statistical analysis

Multivariate and conditional logistic regression models were used to estimate the associations between statin treatment, mortality, stroke severity, and secondary outcomes in the overall and LDL-C-matched cohorts. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA), with $p < 0.05$ considered significant, except for interaction effects in subgroup analyses ($p < 0.1$). The details are provided in the supplemental information.

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AUTHOR CONTRIBUTIONS

Z.L. and H.G. contributed to the conception and design of the study; Z.C. and J.M. contributed to manuscript drafting; K.Y. and Y.J. conducted the mediation and other statistical analyses; and J.C., X.Y., J.X., X.M., Y.J., H.L., L.L., Y.W., X.Z., and Y.W. contributed to data acquisition.

DECLARATION OF INTERESTS

The authors have nothing to declare.

SUPPLEMENTAL INFORMATION

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LEAD CONTACT WEBSITE

https://www.bjtth.org/Html/Doctors/Main/Index_1032321.html.