Postprint of a study on the effect of statin cumulative defined daily dose on the risk of recurrent ischemic stroke

Authors: Han Yue, Bian Zhe, Gu Haochen, Wang Dali, Peng Yanbo, Peng Yanbo

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Abstract

Background In the secondary prevention of ischemic stroke (IS), statins, which lower low-density lipoprotein cholesterol (LDL-C), are listed as core medications in both domestic and international guidelines. Their clinical efficacy depends not only on treatment intensity but is also closely related to long-term patient adherence. Cumulative defined daily dose (cDDD), as an index that comprehensively evaluates both drug exposure intensity and adherence, can quantify the cumulative exposure to statins. The relationship between statin cDDD and the risk of recurrence in patients with IS remains unclear. Objective To investigate the effect of statin cDDD on the risk of IS recurrence. Methods This study included patients aged $ $18 years with first-ever acute ischemic stroke (AIS) who were admitted to the Affiliated Hospital of North China University of Science and Technology between January 2023 and March 2024. Basic information was collected within 24 h after admission. Upon discharge, all patients received standardized secondary prevention health education provided by neurologists, and they were followed up for 1 year. Patients were categorized into four groups (Group 1–Group 4) according to the quartiles of statin cDDD within 1 year, and into low-, medium-, and high-dose groups according to the total dose taken within 1 year. Kaplan–Meier survival curves were used to assess the 1-year risk of IS recurrence. Restricted cubic splines (RCS) and Cox proportional hazards regression models were applied to examine the association between cDDD and recurrence risk. Results A total of 728 patients were finally included, including 455 males (62.5%) and 273 females (37.5%); Group 1 (cDDD $\leq$ 101) included 173 cases, and Group 2 (101205) included 185 cases. During the 1-year follow-up, 100 patients (13.7%) experienced stroke recurrence. Kaplan–Meier survival analysis showed a statistically significant difference in IS recurrence rates among the cDDD quartile groups (P<0.000 1). The cumulative recurrence rates from highest to lowest were 29.5% (51/173) in Group 1, 16.2% (31/191) in Group 2, 6.7% (12/179) in Group 3, and 3.2% (6/185) in Group 4. The low-, medium-, and high-dose groups were defined as cumulative doses <2 400 mg, 2 400-3 600 mg, and >3 600 mg, respectively, with 245, 251, and 232 patients in each group. The IS recurrence rates differed significantly among the three groups ($ $2 =62.46, P<0.000 1). The cumulative IS recurrence rates from highest to lowest were 26.9% (66/245) in the low-dose group, 10.7% (27/251) in the medium-dose group, and 3.0% (7/232) in the high-dose group. RCS analysis showed a nonlinear negative correlation between cDDD and recurrence risk (PNonlinear<0.001), with a marked reduction in recurrence risk when cDDD>75. Multivariable Cox proportional hazards regression analysis demonstrated that, after adjustment for different covariates, the recurrence risk in Group 4 was reduced compared with Group 1 in Model 1 (HR=0.103, 95%CI=0.044-0.241), Model 2 (HR=0.107, 95%CI=0.046-0.251), and Model 3 (HR=0.123, 95%CI=0.052-0.289) (all P<0.05). Conclusion Statin cDDD is significantly and nonlinearly negatively associated with stroke recurrence, exhibiting a dose-dependent threshold effect.

Full Text

Impact of Cumulative Defined Daily Dose of Statins on Recurrence Risk in Ischemic Stroke Patients

Han Yue, Bian Zhe, Gu Haochen, Wang Dali, Peng Yanbo*
Department of Neurology, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei Province, China
*Corresponding author: Peng Yanbo, Chief Physician; E-mail: 15203156268@163.com

Abstract

Background: Statins are the cornerstone of secondary prevention after ischemic stroke (IS) through low-density lipoprotein cholesterol (LDL-C) reduction, as endorsed by major clinical guidelines. Their effectiveness depends on both treatment intensity and long-term adherence. The cumulative defined daily dose (cDDD) integrates exposure intensity and adherence, yet its association with recurrent IS remains unclear.

Objective: To investigate the impact of statin cDDD on recurrence risk in IS patients.

Methods: The study enrolled patients aged $ $18 years with first-ever acute ischemic stroke (AIS) admitted to the North China University of Science and Technology Affiliated Hospital between January 2023 and March 2024. Baseline data were collected within 24 hours of admission. Standardized secondary prevention education was provided at discharge, and patients were followed for 1 year. Participants were categorized into quartiles according to statin cDDD (Group 1–Group 4). Low-, medium-, and high-dose groups were defined by cumulative dose. Kaplan-Meier analysis assessed 1-year recurrence. Restricted cubic splines (RCS) and Cox proportional hazards models evaluated the association between cDDD and recurrence.

Results: The study enrolled 728 patients (males: 455, 62.5%; females: 273, 37.5%). Patients were stratified into quartiles as follows: Group 1 (cDDD $ $101, n=173), Group 2 (101<cDDD $ $152, n=191), Group 3 (152<cDDD $ 205, *n* = 179), *Group*4(*cDDD* > 205, *n* = 185).*Duringfollow* − *up*, 100*recurrentstrokesoccurred*(13.7 $^2=62.46, P<0.0001), with the highest rate in the low-dose group (26.9%, 66/245), followed by the medium-dose (10.7%, 27/251) and high-dose groups (3.0%, 7/232). RCS analysis revealed a nonlinear inverse association between cDDD and recurrence (P_{nonlinear}<0.001), with significantly reduced risk when cDDD exceeded 75. Multivariable Cox proportional hazards models consistently demonstrated a significantly lower recurrence risk in Group 4 compared to Group 1: Model 1 (HR=0.103, 95%CI=0.044-0.241), Model 2 (HR=0.107, 95%CI=0.046-0.251), and Model 3 (HR=0.123, 95%CI=0.052-0.289) (P<0.05).

Conclusion: Statin cDDD shows a significant nonlinear inverse association with IS recurrence, with evidence of a dose-dependent threshold effect.

Keywords: Ischemic stroke; Statins; Cumulative defined daily dose; Recurrence

Introduction

Statins lower low-density lipoprotein cholesterol (LDL-C) by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase and are recommended as core medications for reducing ischemic stroke (IS) recurrence by authoritative guidelines worldwide [1-4]. Clinical practice demonstrates that the secondary preventive efficacy of statins depends not only on treatment intensity but also on long-term patient adherence [5]. Previous studies have separately examined the impact of statin treatment intensity or patient adherence on IS recurrence [6-8], but comprehensive assessments integrating both factors remain scarce. The cumulative defined daily dose (cDDD) serves as a composite metric that integrates prescribed dosage and defined daily dose (DDD) parameters [9], simultaneously reflecting treatment intensity and medication adherence to enable precise quantification of long-term cumulative drug exposure. Based on this, our study systematically evaluated the impact of varying cDDD levels within one year of statin therapy on IS recurrence risk, aiming to provide evidence for precision clinical management of statins in secondary stroke prevention.

Methods

Study Design and Participants

This prospective cohort study enrolled patients with acute ischemic stroke (AIS) hospitalized at the North China University of Science and Technology Affiliated

Hospital in Tangshan, Hebei Province, between January 2023 and March 2024.

Inclusion criteria: (1) Age $ $18 years; (2) First-ever acute IS confirmed by cranial CT or diffusion-weighted imaging (DWI); (3) Within the acute phase (2 weeks) of onset.

Exclusion criteria: (1) Statin allergy; (2) Age $ $90 years; (3) Multiple statin therapies within 6 months before admission; (4) History of IS, intracerebral hemorrhage, or other severe diseases (acute coronary syndrome, renal failure, liver failure, malignant tumors, etc.) within 12 months before admission; (5) Cardioembolism, small artery occlusion, other determined etiology, or undetermined etiology according to TOAST classification; (6) NIHSS score $ $21; (7) Modified Rankin Scale (mRS) score $ $4; (8) Death during hospitalization or follow-up, or development of other severe diseases; (9) Refusal of follow-up.

The study protocol was approved by the Ethics Committee of North China University of Science and Technology Affiliated Hospital (Approval No. 20250120018), and all patients provided informed consent.

Baseline Data Collection

Basic patient data were extracted from medical records, including demographic characteristics (age, gender), lifestyle factors (smoking, alcohol consumption), medical history [hypertension, diabetes, heart disease (myocardial infarction, heart failure, revascularization, and coronary artery disease), medication use (antiplatelet drugs, antihypertensive drugs, hypoglycemic drugs)], and laboratory results [triglycerides (TG), total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C)]. All patients received standard medical care according to the *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018* [10].

In this study, **smoking** was defined as $ $1 cigarette per day on average for at least 6 months in the past year; **alcohol consumption** as $ $1 alcoholic drink per week on average in the past year, with each drink containing $ $10 g of pure alcohol; **regular medication use** as continuous adherence to prescribed medication for 3 months before data collection with treatment interruption $ $7 days [11]; **antiplatelet drugs** included aspirin, clopidogrel, ticagrelor, etc.; **antihypertensive drugs** included ACE inhibitors, ARBs, calcium channel blockers, diuretics, or beta-blockers (limited to hypertensive patients); **hypoglycemic drugs** included insulin, metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, etc. (limited to diabetic patients).

Assessment of cDDD

The DDD is defined by the WHO as the daily maintenance dose for a drug' s main indication in adult patients [12]. This study calculated the cDDD of statins during the follow-up period using the following formulas:

$$cDDD = \Sigma cDDD_i \quad \text{(Formula 1)}$$

$$cDDD_i = \Sigma\left[\left(\frac{\text{daily dose}_i}{\text{WHO DDD}_i}\right) \times \text{treatment days}_i\right] \quad \text{(Formula 2)}$$

where i represents different statin subtypes (atorvastatin, fluvastatin, etc.). Daily dose refers to the actual daily statin dose (mg/day). WHO DDD values were based on the WHO ATC/DDD Index (2025 edition) [13] (e.g., atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin 30 mg, pitavastatin 2 mg, fluvastatin 60 mg). Treatment days refer to the actual days of taking a specific statin at a constant dose. If patients switched statin types or adjusted doses during follow-up, cDDD was calculated separately for each drug or dose period and then summed. [Example: A patient took atorvastatin 40 mg/day (DDD=20 mg) for 30 days, then reduced to 20 mg/day for 20 days, and finally switched to rosuvastatin 10 mg/day (DDD=10 mg) for 10 days. The total 60-day cDDD = (40/20)$×30 + (20/20)×20 + (10/10)×$10 = 90].

Grouping method: Patients were divided into four groups based on quartiles of total statin cDDD during follow-up (Group 1–Group 4).

Follow-up and Recurrence Definition

Researchers were trained uniformly before follow-up. Patients were assessed at 3, 6, 9, and 12 months after discharge through outpatient visits or telephone calls. Follow-up ended at 12 months post-discharge or upon occurrence of an outcome event. Statin cDDD and recurrence status were recorded. Patients were also categorized into low-, medium-, and high-dose groups based on 1-year medication dosage (low-dose group: cumulative dose <2,400 mg; medium-dose group: 2,400–3,600 mg; high-dose group: >3,600 mg).

Outcome event: IS recurrence within 1 year of follow-up. **IS recurrence** was defined as new ischemic lesions on cranial CT or MRI, sudden neurological deterioration with NIHSS score increase $ $4 points, or new cerebrovascular events causing persistent (>24 hours) focal neurological deficits. Once IS recurrence occurred during follow-up, observation was terminated.

Health Education and Lifestyle Guidance

All patients received standardized secondary prevention education from neurologists at discharge. The education included: maintaining a low-salt, low-fat diet, weight control, regular physical activity (e.g., walking $ $30 minutes/day), smoking cessation and alcohol limitation, and emphasis on strict medication adherence.

Statistical Analysis

This study used R 4.4.2 and SPSS 25.0 for statistical analysis. Categorical data were expressed as frequency (percentage) and compared using χ^2 tests. Normally distributed continuous data were expressed as mean $\pm$ standard deviation and compared using ANOVA. Non-normally distributed data were expressed as median (P_{25}, P_{75}) and compared using Kruskal-Wallis tests. Patients were divided into four subgroups by cDDD quartiles (Group 1–Group 4) and into low-, medium-, and high-dose groups. Kaplan-Meier survival curves were plotted for cumulative recurrence rates. Group 1 served as the reference for univariate and multivariate Cox proportional hazards regression analyses of the association between cDDD and IS recurrence, with results expressed as hazard ratios (HR) and 95% confidence intervals (CI). Restricted cubic spline regression was used to evaluate the dose-response relationship between cDDD and IS recurrence, with likelihood ratio tests for nonlinearity. All statistical tests were two-sided, with $P<0.05$ considered statistically significant.

Results

Baseline Characteristics

Of 777 initially enrolled patients, 39 were lost to follow-up and 10 were excluded for not meeting study criteria, leaving 728 patients for analysis (male: 455, 62.5%; female: 273, 37.5%). During the 1-year follow-up, 100 recurrent strokes occurred (13.73%). By cDDD quartiles, Group 1 (cDDD $ $101) had 173 patients, Group 2 (101<cDDD $ $152) had 191, Group 3 (152<cDDD $ $205) had 179, and Group 4 (cDDD >205) had 185. Baseline characteristics showed no significant differences among groups in age, gender, heart disease history, alcohol consumption, TG, HDL-C, LDL-C, or antiplatelet drug use ($P>0.05$). However, significant differences were observed in hypertension history, diabetes history, smoking history, TC, antihypertensive drug use, and hypoglycemic drug use ($P<0.05$) .

Association Between cDDD Groups and IS Recurrence

Kaplan-Meier survival curves for IS recurrence by cDDD group are shown in [Figure 1: see original paper]. Log-rank test results demonstrated significant differences in IS recurrence rates among groups ($\chi^2=64.60$, $P<0.0001$). Cumulative recurrence rates from highest to lowest were: Group 1 at 29.5% (51/173), Group 2 at 16.2% (31/191), Group 3 at 6.7% (12/179), and Group 4 at 3.2% (6/185).

Association Between Dosage Groups and IS Recurrence

To further evaluate the relationship between statin dosage and recurrence risk, Kaplan-Meier survival curves were plotted by dosage group [Figure 2: see original paper]. The cohort included 245 patients in the low-dose group, 251 in the medium-dose group, and 232 in the high-dose group. Log-rank test results showed significant differences among groups (χ^2=62.46, P<0.0001), with cumulative recurrence rates from highest to lowest being: low-dose group 26.9% (66/245), medium-dose group 10.7% (27/251), and high-dose group 3.0% (7/232).

Nonlinear Dose-Response Relationship Between cDDD and IS Recurrence

Restricted cubic spline regression was used to evaluate the dose-response relationship between cDDD and IS recurrence risk [Figure 3: see original paper]. The results revealed a significant nonlinear association (P_{nonlinear}<0.001). When cDDD<75, although HR>1, the risk showed a dose-dependent downward trend, suggesting partial protective effects emerged gradually with prolonged exposure but had not yet crossed the risk threshold. When cDDD>75, the drug demonstrated protective effects, with risk ratios declining slowly as dose increased.

Cox Proportional Hazards Regression Model Analysis for IS Recurrence

Univariate Cox proportional hazards regression analysis was performed with IS recurrence (no=0, yes=1) as the dependent variable and age, gender, hypertension history, diabetes history, heart disease history, smoking history, alcohol consumption history, TC, TG, HDL-C, LDL-C, antiplatelet drug use, antihypertensive drug use, hypoglycemic drug use, and cDDD as independent variables. The results showed that heart disease history, smoking history, TC, antiplatelet drug use, and cDDD affected IS recurrence (P<0.05) .

After multivariable adjustment (Model 1: age and gender; Model 2: hypertension history, diabetes history, heart disease history, smoking history; Model 3: TC, LDL-C, antiplatelet drug use, antihypertensive drug use, hypoglycemic drug use), all models showed statistical significance: Model 1 (HR=0.103, 95%CI=0.044-0.241, P<0.001), Model 2 (HR=0.107, 95%CI=0.046-0.251, P<0.001), and Model 3 (HR=0.123, 95%CI=0.052-0.289, P<0.001), indicating an inverse association between cDDD and IS recurrence .

Discussion

This study found a 13.73% (100/728) cumulative recurrence rate within 1 year, slightly lower than the 17.7% reported by the China National Stroke Registry (CNSR) [14], possibly because we only included first-ever acute IS patients and excluded elderly ($ 90*years*)*andseverecases*(*NIHSS* $21), resulting in lower baseline risk.

Our prospective cohort analysis revealed a dose-response relationship between statin cDDD and recurrence risk (P_{nonlinear}<0.001). When cDDD>75, recurrence risk decreased (HR<1), suggesting cDDD may serve as a potential predictor of IS recurrence. By cDDD quartiles, the highest-dose group (>205) had a 1-year cumulative recurrence rate of only 3.2%, representing a 26.3% absolute reduction compared to the lowest-dose group ($ $101). Dosage grouping showed the high-dose group recurrence rate (3.0%) was significantly lower than the low-dose group (26.9%). Multivariable Cox regression confirmed that the highest-dose group had an 87.7%-89.7% lower recurrence risk than the lowest-dose group (Model 3: HR=0.123, 95%CI=0.052-0.289).

When cDDD<75, HR>1 indicates increased recurrence risk, potentially involving three mechanisms: (1) **Adherence deficits**: A Finnish nationwide cohort study showed 27.1% of IS patients had no statin use within 90 days post-discharge, with an average 12-month discontinuation rate of 36.0%, and early discontinuation increased recurrence risk 2.1-fold [15,16]. (2) **Delayed pharmacodynamics**: The JUPITER study [16] confirmed that clinical benefits of rosuvastatin require 6–12 months of continuous therapy, consistent with our observation of a steep risk decline after cDDD>75. (3) **Insufficient dosage intensity**: The REVERSAL trial [17] demonstrated that intensive statin therapy slowed coronary atherosclerosis progression more effectively than moderate-intensity therapy.

A dose-effect plateau was observed when cDDD>75, with risk reduction slowing (gradient change <5%). This may be explained by: (1) **Pharmacodynamic saturation**: Following the "statin efficacy 6% rule" [18-19], doubling the dose only yields an additional 6% LDL-C reduction due to nonlinear HMG-CoA reductase inhibition kinetics. (2) **Plaque stabilization**: Vessel imaging studies [19-20] showed plaque fibrous cap thickness increased to a plateau after 12 months of statin therapy ($ $0.02 mm/month increase), with lipid core volume reduction stabilizing. (3) **Individual metabolic variation**: Genome-wide association studies show that SLCO1B1*5 allele carriers (frequency 15%–20% in Asian populations) exhibit significant nonlinearity in statin plasma concentration-dose curves [21-22]. (4) **Safety boundaries**: High-dose statins may increase risks of liver enzyme abnormalities or myopathy [23], prompting conservative dosing in clinical practice.

Our findings support the moderate-intensity statin recommendation in the *Chinese Guidelines for Lipid Management* [18]. For clinical implementation of cDDD, future efforts should focus on: (1) Establishing individualized cDDD targets—while cDDD>75 appears to be a universal initial goal, high-risk patients with diabetes or heart disease may require more specific target ranges; (2) Developing dynamic monitoring and intervention mechanisms—calculate cDDD at fixed follow-up points (3, 6, 9, 12 months) and intensify adherence education or adjust treatment when cDDD falls below the theoretical cumulative progress based on prescribed dosage; (3) Implementing combined cDDD-lipid monitoring—low cDDD with achieved lipid targets suggests poor adherence, while adequate cDDD with uncontrolled lipids indicates insufficient treatment intensity. This "cDDD-lipid" dual-track assessment can identify management gaps earlier and enable precision prevention.

This study has limitations. First, despite using Cox proportional hazards models to track statin cDDD, the single-center design may introduce selection bias (e.g., excluding thrombolysis patients). Second, although all patients received uniform health education at discharge, individual adherence and execution differences were not objectively assessed. Future multicenter, long-term studies are needed to validate the predictive efficacy of cDDD.

Conclusion

Statin cDDD is inversely associated with IS recurrence risk, demonstrating a dose-dependent threshold effect. cDDD reflects both treatment intensity and adherence, serving as a potential indicator for assessing recurrence risk in IS patients.

Author Contributions

Han Yue: study design, data collection, statistical analysis, chart preparation, literature review, manuscript writing. Bian Zhe and Gu Haochen: data collection, manuscript revision, literature review. Wang Dali: project supervision, research oversight. Peng Yanbo: project supervision.

Conflict of Interest Statement

All authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.