


RESEARCH

Open Access



A comparison of safety and efficacy between long-term DAPT and intensive statins combined with short-term DAPT for acute ischemic stroke

Ting Deng¹, Xiaomeng Liu¹, Wei He¹, Jingmian Chen¹, Xiaohua Yao¹, Lushan Liu¹, Tong Zhang^{2*}  and Haitao Lu^{2*}

Abstract

Objectives The current study compared the safety and efficacy of long-term dual antiplatelet therapy (DAPT, aspirin plus clopidogrel) and intensive rosuvastatin with short-term DAPT for acute ischemic stroke (AIS).

Methods A total of 220 patients were enrolled 72 h after the onset of mild to moderate AIS, and divided into a control group treated with 21-day DAPT and a study group treated with intensive rosuvastatin with 7-day DAPT on a voluntary basis. The primary outcome was recurrent ischemic stroke and hemorrhage during a 90-day follow-up period in an intention-to-treat analysis. The secondary outcome was clinical efficacy with respect to alleviating existing focal nerve defect symptoms. A Cox proportional-hazards model was used to evaluate treatment differences.

Results Clinical efficacy was evident in 87.3% of patients in the study group, compared with 84.3% in the control group ($p = 0.042$). Recurrent ischemic stroke occurred in 9 patients (7.6%) in the study group and in 9 (8.8%) in the control group ($p = 0.767$). Hemorrhage occurred in 6 patients (5.1%) in the study group and in 15 (14.7%) in the control group ($p = 0.023$). In comparisons of levels of ALT, AST, LDH, and CK in the two groups before and 2 weeks after therapy, only CK differed significantly ($p < 0.001$).

Conclusions Compared to long-term DAPT, intensive rosuvastatin with short-term DAPT was equivalent in reducing the risk of recurrent ischemic stroke. It alleviated symptoms more rapidly, and significantly reduced the risk of bleeding, without causing an increase in transaminase or muscle enzymes.

Clinical trial registration China Clinical Trial Registration Center (ChiCTR1800017809)

*Correspondence:

Tong Zhang
tommzhang@163.com
Haitao Lu
13051760807@163.com

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Highlights

Studies have shown that 21-day dual antiplatelet therapy (DAPT) with aspirin and clopidogrel reduced the risk of recurrent cerebral infarction in minor acute ischemic stroke (AIS) patients at the first 90 days, but also increased the risk of bleeding, especially after the 7th day of DAPT.

The results of this manuscript entitled "A comparison of safety and efficacy between long-term DAPT and intensive statins combined with short-term DAPT for acute ischemic stroke" showed that compared with 21-day DAPT, intensive rosuvastatin plus 7-day DAPT significantly reduced the risk of bleeding without increasing recurrent cerebral infarction in mild to moderate AIS patients.

Keywords Acute ischemic stroke, Double antiplatelet therapy, Intensive statin therapy, Safety and efficacy

Background

Stroke is still the leading cause of death in China [1], and its incidence has increased year by year [2]. The age standardized incidence rate of ischemic stroke in China increased by 34.7% from 1990 to 2019, and it accounted for 82.6% of strokes [3, 4]. The annual recurrence rate was approximately 18.0% [5], causing huge psychological burdens on patients, and economic burdens on families and society [6]. There is, therefore, a need to reduce the incidence and recurrence rate of ischemic stroke, and alleviate resulting nerve defect symptoms as soon as possible. Intensive statin therapy is the cornerstone of acute coronary syndrome [7, 8] and can reduce the risk of recurrent ischemic stroke [9, 10]. Abnormal platelet aggregation is the main pathogenesis of acute ischemic stroke (AIS) [11]. Double antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel can significantly reduce recurrent ischemic stroke in the first 90 days in patients with acute minor ischemic stroke or high-risk transient ischemic attack (TIA) [12–15], but also increases the incidence of bleeding events [13, 16]. To identify a more appropriate DAPT regimen for AIS, the current study compared the efficacy and safety of intensive rosuvastatin with short-term (7 days) DAPT (aspirin + clopidogrel) and long-term (21 days) DAPT in patients with mild to moderate AIS.

Materials and methods

Patients

Patients with mild to moderate AIS admitted to the Emergency Department between January 2017 and December 2019 were recruited. The study was reviewed and approved by the Medical Ethics Committee of our hospital (approval number 2016-065-1). The patients and their legal proxies were informed of the study and signed a consent form.

The inclusion criteria were (1) age ≥ 18 years; (2) onset to medication time (OMT) ≤ 72 h; (3) National

Institutes of Health Stroke Scale (NIHSS) scores at registration ≤ 7 points; and (4) head computed tomography (CT) at registration excluding intracranial hemorrhage, and brain magnetic resonance imaging (MRI) showing new infarction lesions within 3 days after registration. The exclusion criteria were (1) intravenous thrombolysis/arterial thrombectomy; (2) taking anticoagulants; (3) other brain diseases such as intracranial tumors, vascular malformations, abscesses, encephalitis, and TIA; (4) severe function disorders of the heart, liver, kidney, lung, immune system, or coagulation, or malignant tumors; and (5) pregnancy or women preparing for pregnancy within 3 months.

In total, 220 patients with focal nerve defect symptoms (excluding simple dizziness/vertigo, ataxia, and sensory or visual impairment) were confirmed via brain MRI, including 102 in the control group and 118 in the study group. There were no withdrawals or unrelated deaths except for 1 patient who died of massive gastrointestinal bleeding in the control group. She was an 84-year-old woman with a known atrial fibrillation and enrolled 70 h after the onset of AIS. During the treatment her existing nerve defect symptoms worsened, she suffered gastrointestinal bleeding on the 12th day, and she died of massive gastrointestinal bleeding on the 15th day of DAPT [17]. Because this patient did not affect efficacy evaluations at 21 days or 90 days, she was not excluded from the statistical analysis (Fig. 1).

NIHSS is the most commonly used scale for assessing stroke severity, and scores range from 0 to 43. The higher the score the greater the defect, and 0–4 is considered mild, 5–15 is considered moderate, and > 15 is considered severe [18]. Because most severe AIS patients require intravascular treatment (thrombolysis/thrombectomy), only patients with the baseline score of NIHSS (bNIHSS) ≤ 7 points were included in the study. bNIHSS ≤ 4 points and bNIHSS > 4 points (5–7 points) were used as the basis for stratification.

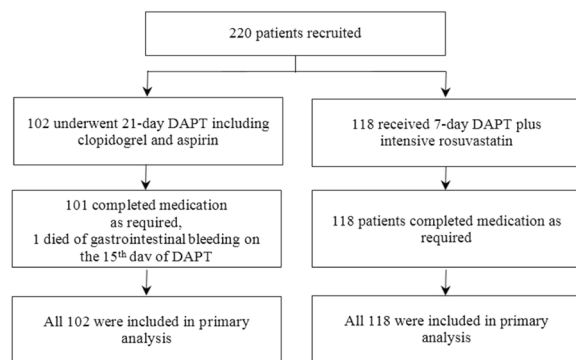


Fig. 1 Enrollment and outcomes (intention-to-treat analysis).

Therapy regimen

Due to polymorphism of the liver cytochrome P-450 isoenzyme (clopidogrel-activating enzyme) gene in Asian populations, the clinical efficacy of clopidogrel remains uncertain [19]. Therefore, the DAPT regimen in the current study included aspirin as the main body and clopidogrel as the synergy. The control group received aspirin 100 mg/day (Bayer, 100 mg per tablet, initial dose 300 mg) for 90 days, clopidogrel 75 mg/day (Sanofi, 75 mg per tablet, initial dose 75–300 mg based on clinical symptoms) for 21 days, and rosuvastatin 10 mg/day (Nanjing Chia Tai-Tianqing Pharmaceutical Co., Ltd., 10 mg per tablet) for 90 days.

The study group received aspirin 100 mg/day (100 mg per tablet, initial dose 300 mg) for 90 days, clopidogrel 75 mg/day (75 mg per tablet, initial dose 75–300 mg based on clinical symptoms) for 7 days, and rosuvastatin 20 mg/day (10 mg per tablet) for 21 days, then 10 mg/day for 69 days. The basic treatments were the same and the follow-up time was 90 days in both groups.

Measurement of biomarkers

Venous blood was collected from all patients at registration (before treatment) and after 2 weeks of treatment (14 ± 3 days), and the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK) were measured using an automatic BS-800M biochemical analyzer (Mindray, China).

Criteria used to evaluate clinical efficacy

Clinical efficacy over a 21-day period

Yoo et al. [20] reported that a change of ≥ 2 NIHSS points indicates that a patient's nerve defect symptoms have changed significantly (improvement or deterioration), and this threshold was used as the basis for judging therapeutic efficacy in the present study. NIHSS scores were determined at eight different time points; before

therapy (bNIHSS), 2, 12, 24, and 48 h after therapy, and 1, 2, and 3 weeks after therapy. When the score decreased by ≥ 2 points, one therapeutic effectiveness event and the time of the effectiveness event were recorded (each case was only recorded once). Patients with bNIHSS = 1 and those with an increase in NIHSS score within a 21-day period were treated as deletion events. All patients' NIHSS scores were jointly assessed by two emergency physicians who had received formal training.

Recurrent ischemic stroke events within 90 days

These events were defined as the appearance of a new focal nerve defect symptom within the 90-day follow-up period, or the rapid worsening of existing focal nerve defect symptoms with a duration of ≥ 24 h, as determined by brain MRI. Non-ischemic factors were excluded (i.e., intracranial infection, trauma, tumor, epilepsy, serious metabolic diseases, and degenerative neurological diseases). When a recurrent ischemic event occurred, one failure event (recurrent ischemic stroke) and the failure time were recorded.

Bleeding events within 90 days

All bleeding events in both groups were recorded over a 90-day period after initial medication. There were several bleeding sites, including intracranial, gastrointestinal, the skin, and the mucosa. All patients with bleeding, including intracranial hemorrhage confirmed by cranial CT, along with gastrointestinal bleeding with occult blood positive for vomit and stools, were recorded as one failure (bleeding) event along with the failure time. In accordance with the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria, bleeding was classified as mild, moderate, or severe, where severe bleeding referred to hemorrhage resulting in hemodynamic compromise requiring vasoactive drug support, fluid or blood replacement, or surgical intervention [17].

Statistical analysis

The study used an incomplete randomized controlled trial design, with type I error $\alpha = 0.05$ and a test power of $(1 - \beta) = 0.95$. G*Power software (Dusseldorf University, Germany) was used to estimate the required sample size. The moderate intensity effect size recommended by the software was 0.3, and the total sample size indicated was 220, with a control group to study group ratio of approximately 1:1. A total of 220 patients were recruited, including 102 in the control group and 118 in the study group.

SPSS 25.0 software (IBM Corporation, Armonk, NY, USA) was used for data analysis. Because baseline characteristics data in the two groups did not conform to a normal distribution, measurement data are expressed as

Table 1 Baseline characteristics of the patients

Characteristic	All cases (n = 220)	Control group (n = 102)	Study group (n = 118)	Z/ χ^2	P-Value
Age (IQR)/year	65.50 (58.00, 76.00)	65.00 (57.75–76.00)	66.00 (58.00–76.00)	−0.082	0.935
Female (n, %)	53 (24.09)	25 (24.51)	28 (23.73)	0.018	0.893
SBP (IQR)/mmHg	154.00 (140.00, 172.0)	155.50 (138.00–176.00)	154.00 (142.75–170.50)	−0.398	0.690
DBP (IQR)/mmHg	90.00 (80.00, 103.00)	89.00 (77.50–103.00)	90.00 (81.00–103.00)	−1.113	0.266
OMT (IQR)/h	16.00 (5.00, 36.00)	13.00 (4.75–27.00)	18.00 (5.00–48.00)	−0.761	0.447
bNIHSS (IQR)	4.00 (3.00, 5.00)	4.00 (3.00–5.00)	4.00 (3.00–4.25)	−1.223	0.221
Medical history (n, %)					
Hypertension	184 (83.64)	85 (83.33)	99 (83.90)	0.013	0.910
Diabetes	93 (42.27)	45 (44.12)	48 (40.68)	0.265	0.607
Hyperlipidemia	38 (17.27)	19 (18.63)	19 (16.10)	0.244	0.621
Atrial fibrillation	31 (14.09)	16 (15.69)	15 (12.71)	0.400	0.527
Prior ischemic stroke	69 (31.36)	32 (31.37)	37 (31.36)	0.000	0.998
Prior antiplatelet	72 (32.73)	37 (36.27)	35 (29.66)	1.087	0.297
Median baseline of various enzymology before medication (IQR) – U/L					
ALT	16.80 (12.20, 23.40)	17.55 (11.95–25.08)	16.45 (12.73–22.30)	−0.238	0.812
AST	16.60 (12.80, 21.65)	15.95 (11.78–20.93)	17.15 (13.55–22.00)	−1.494	0.135
LDH	171.00 (149.00, 200.00)	173.50 (150.00–200.00)	170.00 (147.50–200.25)	−0.713	0.476
CK	74.50 (54.25, 105.50)	75.50 (58.75–113.25)	74.50 (52.00–101.25)	−0.825	0.409
Median of various enzymology in 2 weeks (14 ± 3 d) after medication (IQR) – U/L					
ALT	17.35 (12.03, 27.18)	18.15 (12.00–27.70)	16.85 (12.00–25.68)	−0.832	0.406
AST	16.40 (13.20, 21.78)	16.10 (13.00–21.25)	16.85 (13.28–22.03)	−0.658	0.510
LDH	168.00 (151.00, 187.00)	168.00 (152.75–187.00)	168.00 (147.50–188.25)	−0.219	0.827
CK	71.00 (46.25, 100.00)	66.00 (46.00–95.25)	72.00 (49.00–102.25)	−1.165	0.244

There were no significant differences between study group and control group for any characteristic

SBP systolic blood pressure, DBP diastolic blood pressure, OMT onset to medication time, bNIHSS the baseline score of National Institutes of Health Stroke Scale, ALT alanine aminotransferase, AST aspartate aminotransferase, LDH lactate dehydrogenase, CK creatine kinase

median and interquartile range and were analyzed via the Mann–Whitney *U* test, and frequency data are expressed as percentages and were analyzed via the chi square test. The log-rank survival function model was used to compare clinical efficacy in the two groups within a 21-day period. A Cox proportional hazards model was used to evaluate recurrent ischemic stroke and hemorrhage within 90 days in the two groups. Age, gender, OMT, systolic blood pressure at registration, bNIHSS, and other factors were stratified to analyze associations with recurrent ischemic stroke in the two groups. $P < 0.05$ was considered statistically significant.

Results

Baseline patient characteristics

A total of 220 patients with mild to moderate AIS were enrolled, their median age was 65.5 years, and 24.1% were women. There was a history of hypertension in 83.6% of patients, 42.2% had diabetes, 17.3% had hyperlipidemia, 31.4% had prior ischemic stroke, and 32.7% were current or former recipients of antiplatelet therapy. There

were no significant differences in baseline characteristics between the two groups (all $p > 0.05$) (Table 1).

Clinical efficacy in the two groups

Within a 21-day period, there were 86 (84.31%) therapeutic effectiveness events in patients in the control group and 103 (87.29%) in patients in the study group. A log-rank survival function model revealed a significant difference between the two groups ($\chi^2 = 4.149$, $p = 0.042$). The effectiveness events mainly occurred within the 1 week after initial medication (75 patients in the control group and 94 in the study group) and were more prevalent in the study group within 1.5 days (34 patients in the control group and 61 in the study group), suggesting that intensive statins combined with short-term (7-day) DAPT was more effective in terms of relieving existing nerve defect symptoms in patients with mild to moderate AIS (Table 2 and Fig. 2).

Recurrent ischemic stroke in the two groups

Within a 90-day follow-up period there were 9 (8.8%) recurrent ischemic stroke events in the control group and

Table 2 Therapeutic efficacy within a 21-day period*

Outcomes	Effective—no (%)		Log Rank (Mantel-Cox)	
	Cases with events	Incidence of events (%)	Chi-Square	p value
Control group (n = 102)	86	84.3	4.149	0.042
Study group (n = 118)	103	87.3		

Therapeutic efficacy events were recorded when NIHSS score decreased by ≥ 2 points, in accordance with Yoo et al. [20]

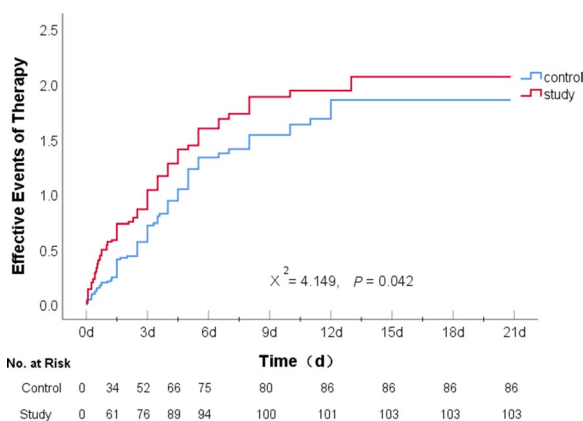


Fig. 2 Probability of therapeutic efficacy events at 21 days

9 (7.6%) in the study group. In a Cox proportional hazards model there was no significant difference between the two groups ($p = 0.767$), although the risk of recurrent ischemic stroke was reduced by 13% in the study group compared to the control group (hazard ratio [HR] 0.870; 95% confidence interval [CI] 0.345–2.191). The recurrent ischemic stroke events in the two groups mainly occurred within 3 days of initial medication (8 cases in the control group and 8 cases in the study group; Table 3 and Fig. 3). This suggested that the two regimens of the intensive statins with short-term DAPT and long-term DAPT had equivalent effects on reducing the risk of recurrent stroke in AIS patients at 90 days. Intensive statin therapy with

short-term DAPT was slightly better than the long-term DAPT regimen.

To ensure the accuracy of evaluation of the risk of recurrent ischemic stroke, the baseline characteristics of patients in the two groups were analyzed with respect to interaction between subgroups and their respective therapy regimen. According to the DAWN trial [21] and Epidemiological data in China, the OMT cut-off value is 24 h (< 24 h and ≥ 24 h), and the age cut-off value is 65 years (< 65 years and ≥ 65 years) [22]. There was no significant interaction between therapy regimen and any subgroup (all $p > 0.20$), indicating that the two regimens had the same effects on reducing the risk of recurrent cerebral infarction (Fig. 4).

Bleeding events in the two groups

With respect to patients with bleeding events within 90 days, there were 15 (14.7%) in the control group including the patient with massive gastrointestinal bleeding, and there were 6 (5.1%) in the study group. In a Cox proportional hazards model there was a significant difference between the two groups ($p = 0.023$). The risk of bleeding in the control group was threefold higher than that in the study group (HR 3.008; 95% CI 1.167–7.753). Bleeding events mainly occurred from the 5th to the 15th day after initial medication (12 patients in the control group and 4 in the study group) (Table 3 and Fig. 5), suggesting that DAPT was the main cause of bleeding events. The risk of bleeding in the long-term DAPT group was significantly higher than that in the intensive statins plus short-term DAPT group.

Levels of transaminase and muscle enzymes before and 2 weeks after initial medication

No patients exhibited a threefold increase in levels of transaminase or muscle enzymes in either group within 21 days after the initiation of medication. There were no significant differences in levels of ALT, AST, or LDH before and 2 weeks (14 ± 3 days) after treatment in either group ($p > 0.05$). In the control group, CK levels after medication initiation were significantly lower than pre-medication levels ($p = 0.001$) (Table 4). These results

Table 3 Efficacy and safety outcomes

Outcomes	Control group		Study group		Hazard ratio (95% CI)	p-value
	Cases with events	Incidence of events (%)	Cases with events	Incidence of events (%)		
Stroke	9	8.8	9	7.6	0.870 (0.35–2.19)	0.767
Bleeding	15	14.7	6	5.1	3.008 (1.17–7.75)	0.023
Severe ^a	1	1.0	0	0.0		
Mild	14	13.9	6	5.1	3.039 (1.18–7.84)	0.021

^a One patient in the control group died of massive gastrointestinal bleeding

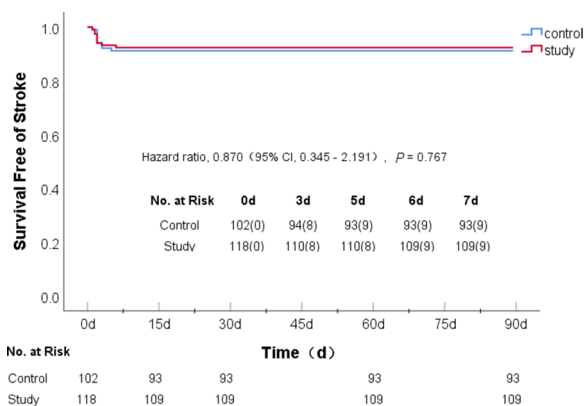


Fig. 3 Probability of survival free of recurrent ischemic stroke within 90 days

showed that the two regimens did not increase levels of transaminase or muscle enzymes.

Discussion

The current study compared the safety and efficacy of a 21-day DAPT regimen and intensive rosuvastatin plus a 7-day DAPT regimen in patients with mild to moderate

AIS. The two regimens had the same effectiveness with respect to reducing the risk of recurrent ischemic stroke within 90 days. Compared to the 21-day DAPT regimen, the regimen of intensive rosuvastatin plus 7-day DAPT alleviated existing focal nerve defect symptoms more effectively, and significantly reduced the risk of bleeding without causing an increase in transaminase or muscle enzymes.

The equivalence of the two regimens in reducing the risk of recurrent ischemic stroke within 90 days suggests that an intensive statins plus short-term (7-day) DAPT regimen could replace long-term (21-day) DAPT regimens in patients with mild to moderate AIS. It is possible that there is a material basis for the role of intensive statins in the early stages of AIS. Non-cardiogenic AIS is a form of atherosclerotic cardiovascular disease (ASCVD) [23]. Increased levels of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) in circulation are the root cause of arterial atherosclerosis and central to the occurrence of ASCVD events [24, 25]. Intensive statin therapy can effectively reduce the levels of LDL-C and non-HDL-C in circulation, inhibit the formation of thrombus, and promote thrombolysis and plaque stability [26, 27],

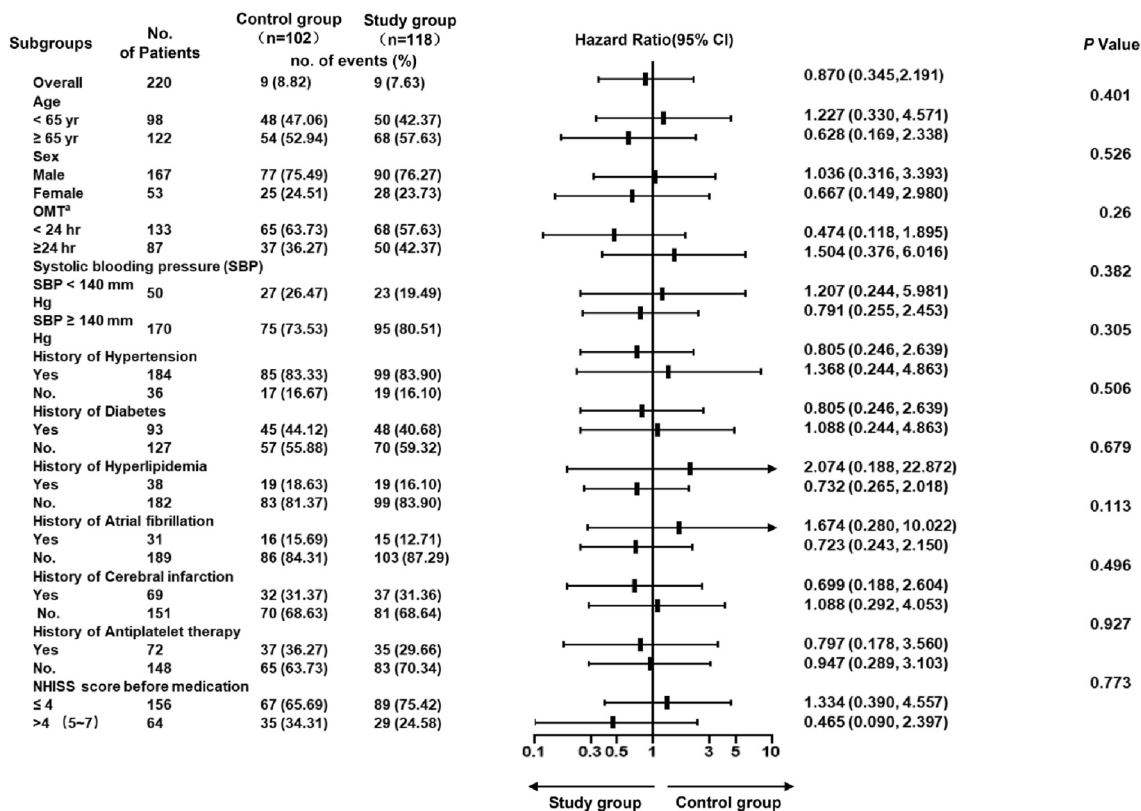


Fig. 4 Hazard ratio for recurrent ischemic stroke in subgroups within 90 days.

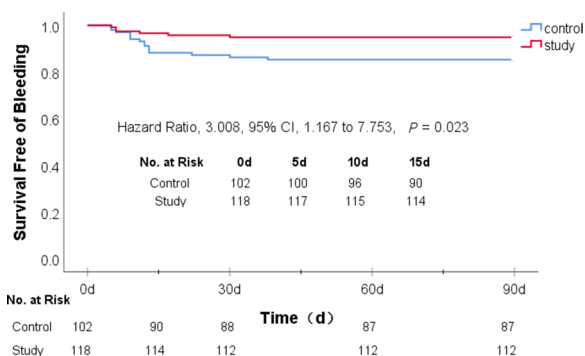


Fig. 5 Probability of survival free of bleeding within 90 days.

thereby reducing the occurrence of acute events related to ASCVD [28, 29] and significantly reducing the risk of recurrent ischemic stroke [9, 10]. Moderate intensity statin therapy can significantly reduce the risk of cardiovascular and cerebrovascular diseases by reducing LDL-C levels, especially in elderly patients [30]. For every 1 mmol/L decrease in LDL-C, the risk of major cardiovascular events decreases by 15% in people aged under 75 years, and by 26% in those aged over 75 years [31]. Compared to conventional doses, intensive statins can significantly reduce the risk of recurrent stroke within 90 days [32].

The intensive statins plus short-term (7-day) DAPT regimen administered in the current study could effectively alleviate clinical symptoms. This is because DAPT including aspirin and clopidogrel effectively inhibited platelet aggregation and reduced thrombosis, and the multiple effects of intensive statin therapy also played a key role. Studies have shown that statins exhibit strong anti-inflammatory and antioxidant functions [33] and can improve atherosclerosis, reduce vascular plaques, and prevent the formation of thrombosis [26, 27]. Statins can increase nitric oxide levels, expand cerebral vessels, increase cerebral blood flow, and reduce the area of infarction by

upregulating levels of endothelial nitric oxide synthase, thereby relieving nerve defect symptoms [34, 35]. Moreover, these effects are dose dependent [26, 29].

AIS is associated with multiple factors, including hypertension, diabetes, hyperlipidemia, smoking, and drinking alcohol. Most patients usually have accompanying gastric mucosal erosion or gastroduodenal ulcers, and cannot tolerate long-term high-dose DAPT. Previous studies have shown that bleeding events mainly occur after the 7th day of DAPT [13], which is consistent with our findings indicating that DAPT was a major factor in bleeding events. The intensive rosuvastatin combined with a 7-day DAPT regimen exhibited clinical efficacy while effectively reducing the risk of bleeding.

The intensive rosuvastatin plus short-term DAPT regimen in the study group did not result in adverse events such as significant increases in transaminase or muscle enzyme levels. This is because rosuvastatin is a water-soluble statin that can only enter liver cells via specific carrier proteins located in the liver cell membrane, to inhibit cholesterol synthesis. Rosuvastatin rarely leads to serious side effects such as rhabdomyolysis [36, 37], and rarely inhibits cholesterol synthesis in the adrenal glands, heart, brain, or other tissues [36].

The results of the current study are objective, reliable, and highly replicable in clinical practice. However, due to the single center, small sample size, incompletely randomized and controlled design of the study, and the lack of hierarchical analysis based on different stroke types, it is inevitable that there are some deviations that need to be addressed in future studies with larger sample sizes.

Conclusion

Compared to a long-term (21-day) DAPT regimen, an intensive rosuvastatin with short-term (7-day) DAPT regimen was equally effective for reducing the risk of recurrent ischemic stroke within 90 days and alleviated

Table 4 Comparison of levels of ALT, AST, LDH, and CK before and 2 weeks after therapy

		Control group				Study group			
		ALT	AST	LDH	CK	ALT	AST	LDH	CK
Before	25%	12.18	10.58	152.00	54.00	12.75	13.55	147.50	52.00
	Median	18.55	14.80	171.00	69.00	16.45	17.15	170.00	74.50
	75%	26.38	20.68	197.75	104.00	22.30	22.00	200.25	101.25
After	25%	12.00	13.00	152.75	46.00	12.00	13.28	147.50	49.00
	Median	18.15	16.10	168.00	66.00	16.85	16.85	168.00	72.00
	75%	27.70	21.25	187.00	95.25	25.68	22.03	188.25	102.00
P Value(2-tailed)		0.217	0.520	0.292	0.000	0.498	0.357	0.973	0.601

ALT alanine aminotransferase, AST aspartate aminotransferase, LDH lactate dehydrogenase, CK creatine kinase

existing focal nerve defect symptoms more rapidly, and it significantly reduced the risk of bleeding without increasing levels of transaminase or muscle enzymes.

Abbreviations

AIS	Acute ischemic stroke
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
bNIHSS	The baseline score of NIHSS
CK	Creatine kinase
CT	Computed tomography
DAPT	Dual antiplatelet therapy
DBP	Diastolic blood pressure
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
OMT	Onset to medication time
TIA	Transient ischemic attack

Acknowledgements

We thank Wang Yunlei (Ph. D) for careful reading of the manuscript.

Author contributions

Study conception and design, TZ and HTL. Data acquisition, TD, JMC, XML, XHY, and LSL. Data analysis and interpretation, TD, WH, and XML. Drafting and revising the article, TZ and HTL. All authors read and approved the final manuscript.

Funding

This study was funded by the Beijing Municipal Commission of Science and Technology (Grant number Z181100001718066).

Data Availability

The data used to support the findings of this study are available from the corresponding author upon requests.

Declarations

Ethics approval and consent to participate

Ethics approval for the study was granted by the Medical Ethics Committee of China Rehabilitation Research Center (approval number 2016-065-1). Written informed consent was obtained from all participants.

Competing interests

The authors declare that they have no conflicts of interests.

Author details

¹Emergency Department of Beijing Bo'ai Hospital, School of Rehabilitation Medicine, Capital Medical University, Beijing 100068, China. ²Neurology Department of Beijing Bo'ai Hospital, School of Rehabilitation Medicine, Capital Medical University, Beijing 100068, China.

Received: 11 October 2022 Accepted: 4 April 2023

Published online: 21 April 2023

References

- Wu S, Wu B, Liu M, Chen Z, Wang W, Anderson CS, et al. Stroke in China: advances and challenges in epidemiology, prevention, and management. *Lancet Neurol.* 2019;18(4):394–405. [https://doi.org/10.1016/S1474-4422\(18\)30500-3](https://doi.org/10.1016/S1474-4422(18)30500-3).
- Tu WJ, Hua Y, Yan F, Bian H, Yang Y, Lou M, et al. Prevalence of stroke in China, 2013–2019: a population-based study. *Lancet Reg Health West Pac.* 2022;28:100550. <https://doi.org/10.1016/j.lanwpc.2022.100550>.
- Sun T, Chen S, Wu K, et al. Trends in incidence and mortality of stroke in China from 1990 to 2019. *Front Neurol.* 2021;12:e759221. <https://doi.org/10.3389/fneur.2021.759221>.
- Wang YJ, Li ZX, Gu HQ, et al. China stroke report 2020 (Chinese version) (1). *Chin J Stroke.* 2022;17(5):433–47. <https://doi.org/10.3969/j.issn.1673-5765.2022.05.001>.
- Wang YL, Xu J, Zhao XQ, et al. Association of hypertension with stroke recurrence depends on ischemic stroke subtype. *Stroke.* 2013;44(5):1232–7. <https://doi.org/10.1161/STROKEAHA.111.000302>.
- Tu WJ, Zhao Z, Yin P, Cao L, Zeng J, Chen H, Fan D, Fang Q, Gao P, Gu Y, Tan G, Han J, et al. Estimated burden of stroke in China in 2020. *JAMA Netw Open.* 2023;6(3):e231455. <https://doi.org/10.1001/jamanetworkopen.2023.1455>.
- Jeong HY, Lee SY, Kim SH, Kim J. Long-term benefit and withdrawal effect of statins after percutaneous coronary intervention: a nationwide population-based cohort study. *Patient Prefer Adherence.* 2020;14:717–24. <https://doi.org/10.2147/PPA.S245324>.
- Xie JX, Gunzburger EC, Kaun L, et al. Medical therapy utilization and long-term outcomes following percutaneous coronary intervention: five-year results from the veterans affairs clinical assessment, reporting, and tracking system program. *Circ Cardiovasc Qual Outcomes.* 2019;12(11):e005455. <https://doi.org/10.1161/CIRCOUTCOMES.118.005455>.
- Rodriguez F, Maron DJ, Knowles JW, et al. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol.* 2017;2(1):47–54. <https://doi.org/10.1001/jamacardio.2016.4052>.
- Amarenco P, Bogousslavsky J, Callahan A, et al. Stroke prevention by aggressive reduction in cholesterol levels (SPARCL) investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355(6):549–59. <https://doi.org/10.1056/NEJMoa061894>.
- Koupenova M, Kehrel BE, Corkrey HA, et al. Thrombosis and platelets: an update. *Eur Heart J.* 2017;38(11):785–91. <https://doi.org/10.1093/eurheartj/ehw550>.
- Wang Y, Wang Y, Zhao X, et al. CHANCE investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* 2013;369(1):11–9. <https://doi.org/10.1056/NEJMoa1215340>.
- Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N End J Med.* 2018;379(3):215–25. <https://doi.org/10.1056/NEJMoa1800410>.
- Condello F, Liccardo G, Ferrante G. Clinical effects of dual antiplatelet therapy or aspirin monotherapy after acute minor ischemic stroke or transient ischemic attack, a meta-analysis. *Curr Pharm Des.* 2021;27(40):4140–6. <https://doi.org/10.2174/1381612827666210728102459>.
- Ringler J, Steck M, Shah SP, Chester KW. Indications and evidence for dual antiplatelet therapy after acute ischemic stroke. *Crit Care Nurs Q.* 2020;43(2):122–37. <https://doi.org/10.1097/CNQ.0000000000000298>.
- Wang D, Gui L, Dong Y, et al. Dual antiplatelet therapy may increase the risk of non-intracranial haemorrhage in patients with minor strokes: a subgroup analysis of the CHANCE trial. *Stroke Vasc Neurol.* 2016;1(2):29–36. <https://doi.org/10.1136/svn-2016-000008>.
- The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329(10):673–82. <https://doi.org/10.1056/NEJM199309023291001>.
- Ghandehari K. Challenging comparison of stroke scales. *J Res Med Sci.* 2013;18(10):906–10.
- Scott SA, Sangkuhl K, Stein CM, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther.* 2013;94(3):317–23. <https://doi.org/10.1038/clpt.2013.105>.
- Yoo AJ, Romero J, Hakimelahi R, et al. Predictors of functional outcome vary by the hemisphere of involvement in major ischemic stroke treated with intra-arterial therapy: a retrospective cohort study. *BMC Neurol.* 2010;10(1):1–11. <https://doi.org/10.1186/1471-2377-10-25>.
- Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* 2018;378(1):11–21. <https://doi.org/10.1056/NEJMoa1706442>.

22. Yang SH, Zhao Y, Lin J. Some thoughts on the definition standard of China's elderly population. *Northwest Popul.* 2017;38(2):77–83.
23. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation.* 2014;129(25):S1–45. <https://doi.org/10.1161/01.cir.0000437738.63853.7a>.
24. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. evidence from genetic, epidemiologic, and clinical studies. a consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J.* 2017;38(32):2459–72. <https://doi.org/10.1093/eurheartj/ehx144>.
25. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: Pathophysiological, genetic, and therapeutic insights: a consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J.* 2020;41(24):2313–30. <https://doi.org/10.1093/eurheartj/ehz962>.
26. Räber L, Taniwaki M, Zaugg S, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. *Eur Heart J.* 2015;36(8):490–500. <https://doi.org/10.1093/eurheartj/ehu373>.
27. Mollazadeh H, Tavana E, Fanni G, et al. Effects of statins on mitochondrial pathways. *J Cachexia Sarcopenia Muscle.* 2021;12(2):237–51. <https://doi.org/10.1002/jcsm.12654>.
28. Liu M, Li GW. Clinical observation of intensive rosuvastatin therapy in the treatment of acute coronary syndrome. *China Pharmacy.* 2017;28(11):1510–3. <https://doi.org/10.6039/j.issn.1001-0408.2017.11.20>.
29. Kilit C, Koçak FE, Kilit TP. Comparison of the effects of high-dose atorvastatin and high-dose rosuvastatin on oxidative stress in patients with acute myocardial infarction: a pilot study. *Turk Kardiyol Dern Ars.* 2017;45(3):235–43. <https://doi.org/10.5543/TKDA.2017.22792>.
30. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. *Lancet.* 2020;396(10263):1644–52. [https://doi.org/10.1016/S0140-6736\(20\)32233-9](https://doi.org/10.1016/S0140-6736(20)32233-9).
31. Gencer B, Marston NA, Im K, Cannon CP, Sever P, Keech A, Braunwald E, Giugliano RP, Sabatine MS, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet.* 2020;396(10263):1637–43. [https://doi.org/10.1016/S0140-6736\(20\)32332-1](https://doi.org/10.1016/S0140-6736(20)32332-1).
32. Deng T, He W, Yao X, Chen J, Liu X, Liu L, Zhang T, Lu HT. Safety and efficacy of short-term dual antiplatelet therapy combined with intensive rosuvastatin in acute ischemic stroke. *Clinics.* 2023;78:100171. <https://doi.org/10.1016/j.clinsp.2023.100171>.
33. Nenna A, Nappi F, Lusini M, et al. Effect of statins on platelet activation and function: from molecular pathways to clinical effects. *Biomed Res Int.* 2021;2021:6661847. <https://doi.org/10.1155/2021/6661847>.
34. Cheng ZJ, Dai TM, Shen YY, et al. Atorvastatin pretreatment attenuates ischemic brain edema by suppressing aquaporin 4. *J Stroke Cerebrovasc Dis.* 2018;27(11):3247–55. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.07.011>.
35. Christophe B, Karatela M, Sanchez J, Pucci J, Connolly ES. Statin therapy in ischemic stroke models: a meta-analysis. *Transl Stroke Res.* 2020;11(4):590–600. <https://doi.org/10.1007/s12975-019-00750-7>.
36. Li YF. Research and development of statins and their fat solubility and water solubility. *Chin J Geriatr Heart Brain Vessel Dis.* 2018;20(9):1008–1008. <https://doi.org/10.3969/j.issn.1009-0126.2018.09.030>.
37. Petry NJ, Baye JF, Frear S, et al. Progression of precision statin prescribing for reduction of statin-associated muscle symptoms. *Pharmacogenomics.* 2022;23(10):585–96. <https://doi.org/10.2217/pgs-2022-0055>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

