RESEARCH ARTICLE

Dual versus mono antiplatelet therapy in mild-to-moderate stroke during hospitalization

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Abstract

Objective: Subsequent vascular events are common after acute ischemic stroke during hospitalization. This study aimed to analyze the effectiveness of combination therapy with clopidogrel and aspirin among mild-to-moderate ischemic stroke patients treated within 72 h on the basis of a high-intensity dose of statins. **Methods:** In a retrospective and multicenter cohort study, acute (within 72 h of onset) mild-to-moderate stroke patients were divided into aspirin and clopidogrel-aspirin groups on the basis of a high-intensity dose of statin therapy. The primary outcome was compound vascular events during hospitalization. Cox's proportional hazards model was used to assess differences, with the study center as a random effect. **Results:** Among the 506 patients meeting the eligibility criteria, all subjects received a high-intensity dose of statins, including 20 mg rosuvastatin or 40 mg atorvastatin while in the hospital. In an unadjusted analysis, compound vascular events occurred in 7.2% of patients in the clopidogrel-aspirin group compared with 13.7% of those in the aspirin group ($p = 0.022$). In a Cox proportional hazards regression analysis, clopidogrel-aspirin was associated with a lower risk of compound vascular events (hazard ratio [95% CI], 0.47 [0.25–0.87]; $p = 0.017$) and ischemic vascular events ($p = 0.008$). Moderate and severe hemorrhage occurred in four patients (1.07%) in the clopidogrel-aspirin group and three patients (2.30%) in the aspirin group ($p = 0.626$). **Interpretation:** In this study based on high-intensity statin therapy, clopidogrel-aspirin reduced the risk of compound vascular events and did not increase the risk of hemorrhage during patients' hospitalization after mild-to-moderate ischemic stroke within 72 h.

Introduction

More than half of patients with acute ischemic stroke have minor neurologic deficits (National Institutes of Health Stroke Scale score, NIHSS score ≤5) at presentation in China according to China National Stroke Registry III,[1] and in the acute phase of ischemic stroke, subsequent vascular events are common.[2,3] Both the CHANCE (clopidogrel in high-risk patients with acute nondisabling cerebrovascular events) trial and POINT (platelet-oriented inhibition in new TIA and minor ischemic stroke) trial showed that dual antiplatelet therapy with clopidogrel plus aspirin (DAPT) was effective in preventing recurrence of cerebrovascular diseases in patients with mild stroke (NIHSS ≤3) or a high risk of transient ischemic attack (TIA) within 24 and 12 h of symptom onset.[2,4] Therefore, combined antiplatelet therapy is a major antithrombotic method against early vascular events.

Atorvastatin at a dose of 80 mg per day was confirmed to be more effective than placebo in preventing recurrent stroke in patients with stroke and no known coronary heart disease in the stroke prevention by aggressive reduction in cholesterol level (SPARCL) trial, with a 16% decline in the incidence of recurrent stroke.[5] Therefore, high-intensity statin therapy is recommended after

atherosclerotic ischemic stroke to lower serum lipid levels. However, statins are used in all stroke patients regardless of stroke subtypes by some clinicians in real-world.

The POINT and CHANCE trials were designed and large-scale clinical trials, which included patients within 12 h and 24 h of the initial onset, respectively. Due to the subjective decisions of clinicians and individualized differences in patients, DAPT can be adopted for patients with $3 <$ NIHSS score ≤ 5 and within 24 to 72 h of symptom onset in cases of aggravation, so there is a certain distance between the practical use and the clinical trials.[6,7] However, whether dual antiplatelet therapy is effective and safe in patients who have acute, mild-to-moderate ischemic stroke within 72 h after the symptom onset on the basis of a high-intensity dose of statins is still unclear. In this study, we aimed to evaluate the comparative effectiveness of clopidogrel-aspirin versus aspirin based on a high-intensity dose of statin therapy in acute mild-to-moderate stroke patients during hospitalization by using data obtained from three advanced stroke centers in Taiyuan, Shanxi Province, China, which may help physicians select antiplatelet strategies and change clinical practice in the future.

Methods

Study subjects

Our study was based on an analysis of retrospective, multicenter data from the real world. Patients with acute cerebral infarction were admitted to the Department of Neurology in three academic hospitals in China, namely, First Hospital of Shanxi Medical University, Shanxi Bethune Hospital, and General Hospital of TISCO (Sixth Hospital of Shanxi Medical University). Among patients with minor neurological deficits, we identified those admitted to hospitals during March, June, September, December of 2012, 2014, 2016, 2018. The inclusion criteria in this study included (1) acute mild-to-moderate (defined as NIHSS score ≤ 5) ischemic stroke, (2) within 72 h after the onset of ischemic stroke, (3) features of acute ischemic stroke on cerebral computed tomography (CT) or magnetic resonance imaging (MRI) associated with the symptoms, (4) treatment with aspirin monotherapy or dual antiplatelet therapy with clopidogrel plus aspirin, and (5) medication with a high-intensity dose of statins with 40 mg of atorvastatin or 20 mg of rosuvastatin per day during hospitalization.[8] The exclusion criteria included (1) more than 72 h after symptom onset, (2) a NIHSS score >5 when symptoms appeared, and (3) a modified Rankin scale score greater than two before the index ischemic stroke appeared. According to different antiplatelet strategies during hospitalization, the patients were divided into two groups: the aspirin monotherapy group and the dual antiplatelet therapy with clopidogrel plus aspirin group. The study was approved by the ethics committee of First Hospital of Shanxi Medical University.

Study design

All the patients took aspirin at a physician-determined dose of 100 to 300 mg on the first day, followed by a dose of 100 mg per day on days 2 through the whole hospitalization period. Neither a protocol nor a prescribed approach to DAPT use was instituted at the participating hospitals. Patients in the DAPT group received clopidogrel at a loading dose of 300 mg or 75 mg on day 1, followed by a dose of 75 mg on days 2 through the hospitalization period. All enrolled patients received high-intensity doses of statins with 40 mg of atorvastatin or 20 mg of rosuvastatin per day, and statin treatment was started in the first few hours of hospital admission in the study group. The main objective was to assess the incidence of compound vascular events after minor neurological deficits during hospitalization.

Study outcomes

The primary endpoint was a composite of ischemic stroke, TIA, myocardial infarction, and moderate to severe bleeding events. The secondary efficacy endpoint was a composite of ischemic vascular events, including ischemic stroke, TIA, and myocardial infarction. Ischemic stroke included recurrent and progressive ischemic stroke. The primary safety outcome was moderate to severe bleeding events defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO).[9] Detailed definitions of the outcome events in this study are shown in Table S1 (in the Supplementary materials).

Statistical analysis

We used χ^2 tests and Student's *t*-tests to compare the baseline characteristics of the two treatment groups. Hazard ratios and 95% confidence intervals for the rates of treatment efficacy and safety during the hospitalization period were estimated by a Cox proportional hazards model. Proportions were applied for categorical variables, and the medians with interquartile ranges (IQRs) were used for continuous variables. Cumulative event rates during the hospitalization period were compared by the Kaplan–Meier method, and differences between groups were estimated with the log-rank test. We entered the variables that were considered clinically relevant or univariate with outcome into multivariate Cox proportional

hazards regression model. Baseline variables included age, sex, systolic pressure, diastolic pressure, arrival time category, baseline NIHSS score, current or previous smoking, history of hypertension, history of diabetes mellitus, history of dyslipidemia, history of atrial fibrillation, TIA history, history of stroke, history of coronary disease, history of myocardial infarction, previous antiplatelet use, and stroke cause subtypes. Stroke subtypes were categorized according to the TOAST (Trial of ORG 10172 in Acute StrokeTreatment) criteria. In subgroup analyses, we assessed the difference of medication effect among stroke subtypes using Cox models. In addition, a sensitivity analysis of those included in the analysis versus those excluded was done.

A *p* value less than 0.05 was considered statistically significant, and all tests were two-sided. The statistics were based on the intention-to-treat population. All statistical analyses were completed using the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.3.

Results

General characteristics

A total of 1494 patients with mild-to-moderate ischemic stroke treated within 72 h of symptom onset were screened. A total of 121 patients were excluded because of taking clopidogrel or other antiplatelet agents. Among the 867 patients excluded, 716 exclusions were due to therapy with a moderate-intensity dose of statins, and 151 received other hypolipidemic therapy. A total of 506 stroke patients meeting the study criteria were divided into an aspirin group (*n* = 131, 25.9%) and a clopidogrel-aspirin group (*n* = 375, 74.1%). The flow chart illustrating the inclusion and exclusion of patients is shown in Figure 1. The median age of the total study population was 61 years, and 27.5% were female. A total of 28.3% of the patients had a NIHSS score higher than 3, and 43.7% were admitted to the hospital within 24–72 h after symptom onset. The baseline characteristics of the aspirin group and clopidogrel-aspirin group are shown in Table 1. No significant differences were found between the two groups except for stroke subtype classification. In addition to aspirin therapy, 282 patients (75.2%) in the clopidogrel-aspirin group received clopidogrel at a loading dose of 300 mg on day 1, followed by a dose of 75 mg per day from day 2 to the entire hospital stay; three of them discontinued DAPT due to moderate-severe bleeding events and two due to mild bleeding events during hospitalization. Another 93 patients (24.8%) received clopidogrel at a dose of 75 mg per day after stroke hospitalization; one stopped DAPT due to

moderate-severe bleeding event and one due to mild bleeding event. Few patients who had asymptomatic intracranial artery stenosis and were still in hospitalization after 21 days discontinued DAPT. Table S2 shows the exact duration of clopidogrel-aspirin for patients with bleeding events and longer hospital stay. Compared with the excluded group, the enrolled group was more likely to to be smokers, have a relatively higher baseline NIHSS score and a large artery atherosclerosis (LAA) stroke subtype (Table S3).

Outcomes

Primary and secondary efficacy outcomes

Differences in the cumulative incidence rates of overall primary endpoint events and ischemic vascular events were statistically significant in favor of the clopidogrel-aspirin group (*p* = 0.020 and *p* = 0.043 by the log-rank test). The survival curves in Figure 2A and B were steep in the first few days and then gradually tended to be parallel. The primary endpoint event occurred in 27 patients (7.2%) receiving clopidogrel-aspirin and in 18 patients (13.7%) receiving aspirin alone (hazard ratio [95% CI], 0.47 [0.25–0.87]; *p* = 0.017) (Table 2). The secondary efficacy outcome of ischemic vascular events occurred in 23 patients (6.13%) taking clopidogrel-aspirin and in 15 patients (11.50%) taking aspirin (hazard ratio [95% CI], 0.41 [0.21–0.79]; *p* = 0.008). A Cox regression analysis model was used to analyze the results, with age, sex, NIHSS score, history of atrial fibrillation, diastolic pressure, and TOAST classification as explanatory variables for primary endpoint events and with age, sex, NIHSS score, history of hypertension, and TOAST classification as explanatory variables for ischemic vascular outcomes. No myocardial infarction cases occurred among the 506 enrolled patients during the hospitalization period. Among the 867 patients excluded, the primary endpoint events occurred in 31 patients (7.1%) receiving clopidogrel-aspirin and 30 patients (6.9%) receiving aspirin alone (hazard ratio [95% CI], 1.08 [0.64–1.83]; *p* = 0.761) (Table S4). The secondary efficacy outcome of ischemic vascular events occurred in 24 patients (5.5%) taking clopidogrel-aspirin and in 20 patients (4.6%) taking aspirin (hazard ratio [95%CI], 1.20 [0.65–2.20]; *p* = 0.564). To avoid the influence of statin therapy on the outcome events, only patients who received high-intensity statins were enrolled in the analysis. The data of 716 patients with aspirin or DAPT on the basis of moderate-intensity statins were also collected (Table S5). Compared to the moderate-intensity statin group, the incidence of primary endpoint events, and ischemic vascular events was higher in the high-intensity statin
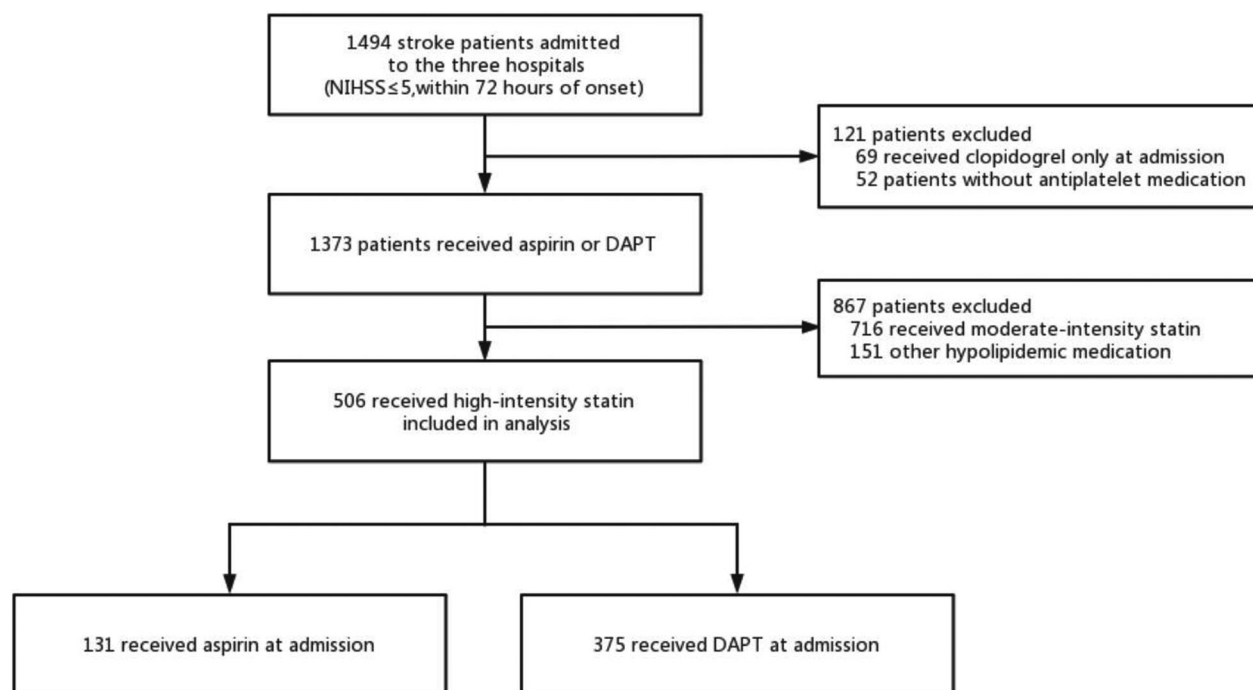
Figure 1. Flow chart illustrating the inclusion and exclusion of patients.

treatment group (Table S6). In the DAPT subgroup, no significant difference was found between high-intensity statin treatment and moderate-intensity statin treatment in preventing the outcome events, while in the aspirin subgroup, the incidence of the primary outcome and the secondary efficacy outcome in the high-dose statin treatment group was higher than that in the moderate-intensity statin treatment group (Table S7).

Safety outcomes

The cumulative incidence rate of major hemorrhage was not statistically significant ($p = 0.26$ by the log-rank test). The main hemorrhage outcome occurred in four of 375 patients (1.07%) in the clopidogrel-aspirin group and in three of 131 patients (2.30%) receiving aspirin alone (hazard ratio [95% CI], 1.84 [0.16–21.36]; $p = 0.626$). All bleeding events occurred in seven patients (1.87%) taking clopidogrel-aspirin and in six (4.58%) taking aspirin alone ($p = 0.595$) (Table 2). The incidence of bleeding events was not statistically significant between clopidogrel-aspirin and aspirin groups in excluded patients (Table S4).

Subgroups

The risk of early recurrence was higher in large artery atherosclerosis group than other subgroups. Patients with a

LAA cause in the clopidogrel-aspirin group had both a low incidence rate of primary endpoint events and ischemic vascular events, while only the risk of ischemic vascular events was statistically significant ($p = 0.023$) (Tables S8 and S9).

Discussion

In this multicenter, retrospective study based on high-intensity statin therapy, we found that among patients with mild-to-moderate stroke (NIHSS score ≤5) within 72 h of their initial onset, combination therapy with clopidogrel and aspirin was better than aspirin alone in reducing the incidence of primary endpoint events during the hospitalization period. The decrease in ischemic vascular events was more obvious in the clopidogrel-aspirin group. From a safety point of view, dual antiplatelet therapy did not increase the incidence of bleeding events. However, compared to that in the study group, clopidogrel-aspirin did not reduce the risk of compound vascular events and ischemic vascular events in the excluded patients (Table 4S). Additionally, no increase in the risk of hemorrhage was observed in this population.Therefore, combined therapy with clopidogrel-aspirin and high-intensity statins is likely to produce the greatest benefit in stroke patients with NIHSS scores ≤5 within 72 h of symptom onset during hospitalization.

In previous findings, most vascular outcomes occurred within the first 2 weeks after stroke onset,[2,3,10] as was

Table 1. Baseline characteristics of patients treated with clopidogrel-aspirin or aspirin alone within 72 h.

	Patients arrival within 72 h			
	Total (*n* = 506)	Aspirin (*n* = 131)	Clopidogrel– Aspirin (*n* = 375)	*p* value
Age, y				0.360*
Median	61	63	60	
Interquartile range	53 to 68	54 to 68	52 to 68	
Female sex, *n* (%)	139 (27.5)	35 (26.7)	104 (27.7)	0.912
Systolic pressure, mm Hg				0.424*
Median	150	151	150	
Interquartile range	134 to 164	133 to 169	134 to 162	
Diastolic pressure, mm Hg				0.514*
Median	87	87	87	
Interquartile range	80 to 97	80 to 97	80 to 97	
Medical history, *n* (%)				
Stroke	122 (24.1)	35 (26.7)	87 (23.2)	0.489
Hypertension	303 (59.9)	74 (56.5)	229 (61.1)	0.414
Diabetes mellitus	118 (23.3)	27 (20.6)	91(24.3)	0.464
Dyslipidemia	30 (5.9)	9 (6.9)	21 (5.6)	0.753
TIA	9 (1.8)	2 (1.5)	7 (1.9)	1.000
Coronary disease	29 (5.7)	5 (3.8)	24 (6.4)	0.381
Myocardial infarction	12 (2.4)	2 (1.53)	10 (2.67)	0.740
Atrial fibrillation	12 (2.4)	5 (3.82)	7 (1.87)	0.200
Antiplatelet use	59 (9.9)	11 (8.4)	39 (10.4)	0.623
Current or previous smoking	247 (48.8)	63 (48.1)	184 (49.1)	0.928
Baseline NIHSS — *n* (%)				0.739
≤3	363 (71.7)	92 (70.2)	271 (72.3)	
>3	142 (28.3)	39 (29.8)	104 (27.7)	
Arrival time categories —*n* (%)				0.198
≤24 h	285 (56.3)	67 (51.1)	218 (58.1)	
24-72 h	221 (43.7)	64 (48.9)	157 (41.9)	
TOAST — *n* (%)				0.002
LAA	247 (48.8)	54 (41.2)	193 (51.5)	
SVO	196 (38.7)	52 (39.7)	144 (38.4)	
CE	12 (2.4)	9 (6.9)	3 (0.8)	
OE	7 (1.4)	2 (1.5)	5 (1.3)	
UD	44 (8.7)	14 (10.7)	30 (8)	

CE, cardioembolic; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; OE, other etiology; SVO, small vessel occlusion; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; UD, undetermined etiology.
*By student's *t*-test, others by χ^2 tests.

shown in Kaplan–Meier cumulative incidence plots (Fig. 2A–C) in this study. The divergence trend of the curves between the two treatment groups revealed a significant difference in the incidence of endpoint events, suggesting that patients with indications should receive combination therapy with aspirin-clopidogrel as soon as possible. Our results demonstrated that the advantage of combined therapy with clopidogrel and aspirin was similar to that observed in the POINT/CHANCE trial and a registry-based study in South Korea.[11] However, unlike the CHANCE and POINT trials, the primary vascular events during hospitalization included not only ischemic stroke, myocardial infarction, hemorrhage stroke but also TIA. Ischemic vascular events in the early phase of stroke can be ascribed to unstable atherosclerotic plaques and accelerate platelet aggregation.[12] The main role of clopidogrel-aspirin in the present study may be to stabilize ischemic brain tissue by preventing platelet activation and thrombotic plaques.[13] In a nationwide, multicenter registry-based study, compared to aspirin monotherapy, clopidogrel-aspirin did not reduce the incidence of primary vascular events during the first 3 months after non-minor (NIHSS score, 4–15), noncardioembolic, ischemic stroke,[14] possibly because ischemic lesions were larger and thrombotic burdens were greater. In the TARDIS (Triple Antiplatelets for Reducing Dependency after Ischemic Stroke) trial, the time window for combination antiplatelet therapy with clopidogrel, aspirin, and dipyridamole
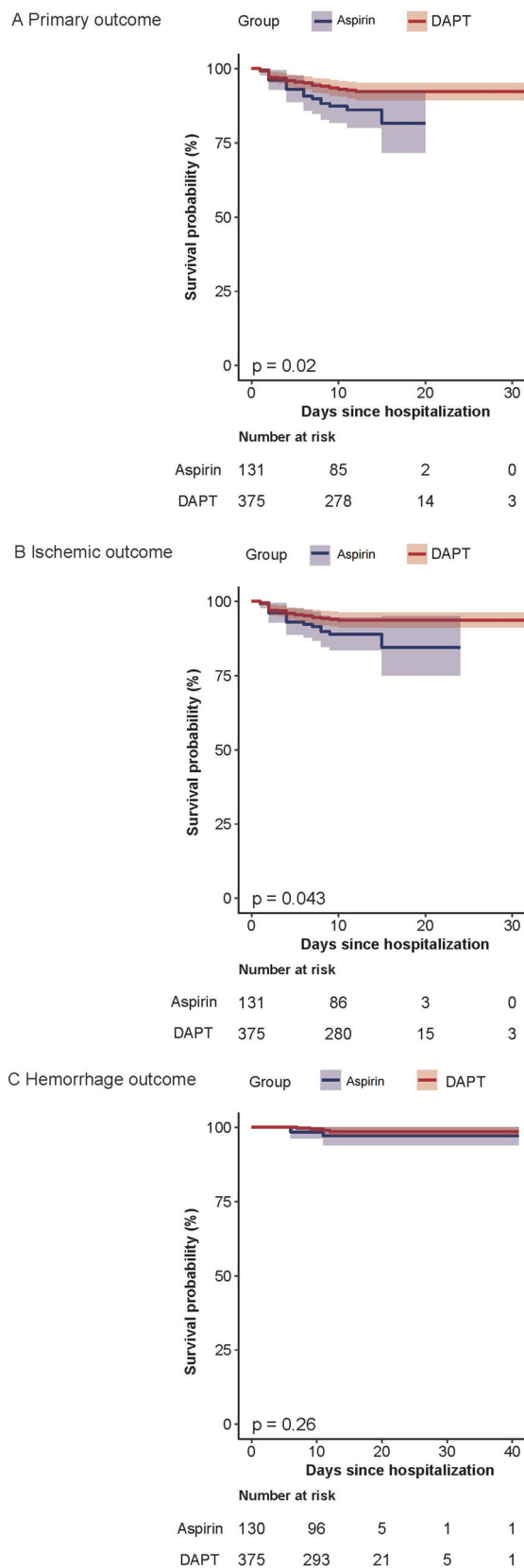
A Primary outcome

B Ischemic outcome

C Hemorrhage outcome

Figure 2. A. Kaplan–Meier incidence plot of primary outcome events B. Kaplan–Meier incidence plot of ischemic vascular events C. Kaplan–Meier incidence plot of major hemorrhage events.

was extended to 48 h after symptom onset, and no decrease in the incidence and severity of recurrent ischemic stroke was observed, but the incidence of hemorrhage was higher,[15] which may be related to excessive blockade of platelet activity in the TARDIS trial. However, the incidence of hemorrhage in our study was low, and no significant difference was found between the clopidogrel-aspirin and monotherapy groups even if the time window was extended to 72 h. One possible explanation was that the loading dose of clopidogrel was also lower in both the CHANCE trial and our study, which might have reduced the risk of hemorrhage. Furthermore, the combination therapy duration in our study was observed only during the hospitalization period, which was obviously shorter than those in the POINT trial and TARDIS trial.[4,15] In addition, gene polymorphisms encoding CYP2C19 in Asian populations are common, and the effectiveness of clopidogrel is uncertain.[16] The benefit of DAPT is mainly reflected in the first 2 weeks after symptom onset, but the risk of bleeding remained throughout the whole treatment process. A Kaplan–Meier cumulative incidence plot of major hemorrhage events in our study showed that the safety outcome event occurred mainly within the first 10 days after being hospitalized (Fig. 2C). After that, most patients were likely to be discharged from hospital.

In addition to antiplatelet therapy, statin therapy is generally an effective strategy for preventing recurrent vascular events after ischemic stroke. The LAA subtype is the main cause of stroke in patients in China (accounting for approximately 1/3–1/2), and the recurrence risk of this subtype is higher.[17] On the basis of the SPARCL trial, high-intensity statins were the recommended therapy for patients with ischemic stroke caused by atherosclerosis to prevent cardiovascular events.[8] Extensive evidences from clinical and genetic studies indicate that low-density lipoprotein (LDL) is an important cause of atherosclerotic cardiovascular disease.[18] In a trial analyzing the effect of LDL levels on the prognosis of patients with ischemic stroke or TIA from atherosclerosis, patients with a lower LDL level of less than 70 mg per deciliter had fewer cardiovascular events than those with a level ranging from 90 mg to 110 mg per deciliter, which supported the finding that a lower LDL cholesterol level was associated with a reduced cardiovascular risk.[19] The major cardiovascular events include ischemic stroke, myocardial infarction, or death from these causes. However, adjustment of the statin dose is based mainly on the LDL level, and statins are widely used in all stroke patients regardless of the stroke

Table 2. Efficacy and safety outcomes between aspirin and clopidogrel-aspirin within 72 h of symptom onset.

Outcome	Patients with event, No. (%)		Crude analysis		Multivariable analysis	
	Aspirin group, $n = 131$	Clopidogrel– aspirin group, $n = 375$	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
	Primary outcome					
Ischemic stroke, transient ischemic attack, myocardial infarction, moderate to severe bleeding	18 (13.7)	27 (7.2)	0.50 (0.27–0.91)	0.022	0.47 (0.25–0.87)	0.017*
	Secondary efficacy outcome					
Ischemic stroke, transient ischemic attack, myocardial infarction	15 (11.5)	23 (6.13)	0.52 (0.27–0.99)	0.047	0.41 (0.21–0.79)	0.008**
	Safety outcome					
Moderate to severe bleeding	3 (2.30)	4 (1.07)	0.43 (0.10–1.94)	0.273	1.84 (0.16–21.36)	0.626***
Mild bleeding	3 (2.3)	3 (0.8)	0.32 (0.06–1.59)	0.165	0.41 (0.07 ~ 2.30)	0.308***
Any bleeding	6 (4.58)	7 (1.87)	0.37 (0.12–1.10)	0.075	0.70 (0.18 ~ 2.66)	0.595***

HR for clopidogrel-aspirin vs. aspirin. p value by a Cox proportional hazards model.
*Adjusted for age, sex, NIHSS score, history of atrial fibrillation, diastolic pressure, TOAST classification.
**Adjusted for age, sex, NIHSS score, history of hypertension, TOAST classification.
***Adjusted for age, sex, history of atrial fibrillation, TOAST classification.

subtypes by some physicians in the real world.[20] The result of the subgroup analysis in our study showed that patients with LAA had a higher recurrence rate of ischemic vascular events, and this kind of patients benefited more from the clopidogrel-aspirin treatment than the aspirin therapy (Table S9). Therefore, combined therapy with clopidogrel-aspirin and high-intensity statins is necessary during hospitalization, since ischemic vascular events occur most frequently in the initial few days of symptom appearance. In our study, whether to treat patients with high-intensity statins largely depended on physicians' empirical treatment.

Obviously, our results for statin therapy are inconsistent with the current findings (Table S6 and S7). In our study, compared with the moderate-intensity group, more patients receiving high-intensity statin therapy in the study group had dyslipidemia, smoking, higher NIHSS scale, and a stroke subtype of LAA, which indicated higher risks of vascular events incidence as a matter of course (Table S5). It was observed that patients in higher NIHSS groups experienced primary events more frequently than those in lower subgroups.[14] In an analysis of comparative effectiveness of DAPT versus aspirin in mild-to-moderate (NIHSS ≤10), acute ischemic stroke using the Stroke Prognosis Instrument II score,[21] patients in the high-risk subgroup (SPI-II >7) had the highest proportion of DAPT and achieved the greatest benefits of DAPT than those in other subgroups. Patients with higher risk of vascular events were more likely to receive DAPT with

clopidogrel-aspirin than aspirin. Interestingly, in two subgroup analyses of the CHANCE trial, patients with multiple acute infarcts would benefit more from DAPT in terms of early stroke recurrence than those with no or single acute infarcts;[22] and although DAPT exhibited more advantages in reducing vascular events than aspirin, no statistical difference between DAPT and aspirin was observed in preventing stroke recurrence among the patients without intracranial arterial stenosis.[23] The treatment heterogeneity was observed in our results, consistent with those previous findings. Differences in the DAPT benefits were statistically significant in favor of the high-intensity statin use (a marker of higher risk) and LAA stroke subtype. Patients in the study group were more likely to be smokers, have a LAA stroke subtype and higher NIHSS scale than the excluded group (Table 3S). Among the excluded population, 716 patients (82.6%) received moderate-intensity statin therapy. Therefore, the lack of benefit of DAPT in the excluded population is also likely due to the lack of effect in moderate-intensity statin group. Additional studies are warranted to confirm our study.

The results of our study indicate that DAPT may be more effective than monotherapy in reducing recurrent vascular events in nondisabling ischemic stroke patients on the basis of high-intensity statins. This study provides evidence for expanding the indications for dual-antiplatelet therapy and information on which patients would obtain more benefits from DAPT, which may help clinicians select

treatment strategies in the acute stage. However, unlike previous trials, the endpoint event of antiplatelet therapy was observed only during hospitalization, and the safety and efficacy of continual treatment after discharge are still unknown. Perhaps, there is no DAPT benefit considering the entire population but one exists in high- risk subgroups based on high-intensity statin use (a marker of higher risk) and LAA stroke subtype. Therefore, further studies on the best duration and the effectiveness of DAPT as well as combined regimens with antiplatelet therapy and statins of different intensities are necessary.

Several limitations in this study should be noted. First, the antiplatelet treatment strategy was selected at clinicians' discretion rather than according to the designed distribution, and some patients with a high risk of bleeding did not receive a loading dose of clopidogrel on the first day, which was not standard for the use of DAPT. Additionally, the duration of dual antiplatelet therapy was not strictly in accordance with guidelines, and antiplatelet treatment in some patients at admission differed from that at discharge. The antiplatelet therapy strategy was based on treatment at admission rather than treatment at discharge. Therefore, some biases in the use of DAPT by clinicians could not be avoided. Second, as a limitation in design, since outcomes were not time-defined but variable based on the length of hospitalization, differential follow-up could bias the findings in favor of identifying events in those with a longer length of hospital stay (LOS) compared to a shorter LOS. Third, only a few cases in the three hospitals in provincial capital were enrolled in this study; therefore, the generalizability of the findings should be demonstrated in more studies in other regions. In addition, no evidence indicates that patients with other stroke subtypes benefit from high-intensity statin therapy, and further RCT studies are required.

In summary, on the basis of high-intensity statin therapy, patients with NIHSS score ≤5 within 72 h of DAPT initiation had a lower risk of primary vascular events and ischemic vascular events than those receiving aspirin alone. No increase in the incidence of hemorrhage events was observed in the clopidogrel-aspirin group. These findings should be confirmed in more studies.

Acknowledgments

Author Contributions

HF drafted and revised the manuscript. YW completed the picture drawing and also revised the manuscript. JR organized the data. Other authors were responsible for the data collection and manuscript revision. XN conceived and designed the study.

Conflict of Interest

The authors state that there is no conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Definitions of outcome variables used in this study.

Table S2. Characteristics of Patients Discontinuing DAPT during Hospitalization.

Table S3. Baseline Characteristics of Patients Included vs. Patients Excluded.

Table S4. Efficacy and Safety Outcomes of Patients Excluded.

Table S5. Baseline Characteristics of Patients Treated with High-intensity Statins or Moderate-intensity Statins.

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Table S7. Subgroup Analysis of Outcome Events.

Table S8. Effect of DAPT on Primary Outcome by Subtype.

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Table S10. COX Univariate Analysis for Predictors of Primary Outcome in Patients Enrolled.

Table S11. COX Univariate Analysis for Predictors of Ischemic Vascular Outcome in Patients Enrolled.

Table S12. COX Univariate Analysis for Predictors of Primary Safety Outcome in Patients Enrolled.