ORIGINAL RESEARCH

Treatment Effect of Clopidogrel Plus Aspirin Within 12 Hours of Acute Minor Stroke or Transient Ischemic Attack

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***Background*—**The aim of this study was to analyze the benefits and safety associated with the combination therapy of clopidogrel and aspirin among minor stroke or transient ischemic attack patients treated within 12 hours.

***Methods and Results*—**This was a subanalysis of the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) trial, mainly limited to the prespecified group of patients randomized within 12 hours to either the combination of clopidogrel plus aspirin or aspirin alone. The primary outcome was ischemic stroke during 90-day follow-up. Recurrent ischemic stroke and progressive ischemic stroke were analyzed. Multivariable Cox modeling showed that randomization within 12 hours was an independent predictor of ischemic stroke events (hazard ratio [95% CI] 1.25 [1.04–1.49], P=0.02). Among 2573 patients randomized within 12 hours, 282 (10.96%) patients had ischemic stroke events. Among them, 158 (12.34%) of 1280 patients taking aspirin experienced ischemic stroke compared with 124 (9.59%) of 1293 patients taking clopidogrel–aspirin (P=0.02). The dual antiplatelet was more effective than aspirin alone in reducing the risk of recurrent ischemic stroke (6.57% versus 8.91%, P=0.03) but not progressive ischemic stroke (3.02% versus 3.43%, P=0.28). There was no significant difference in hemorrhagic events (P=0.39).

***Conclusions*—**Among patients treated within 12 hours, the combination of clopidogrel and aspirin was more effective than aspirin alone in reducing the risk of recurrent ischemic stroke during the 90-day follow-up and did not increase the hemorrhagic risk.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov/. Unique identifier: NCT00979589. **(*J Am Heart Assoc*. 2016;5: e003038 doi: 10.1161/JAHA.115.003038)**

Key Words: acute cerebral infarction • antiplatelets • transient ischemic attacks • trials

It is crucial to treat stroke patients during the acute phase. Acute minor stroke or transient ischemic attack (TIA) events often are warning signs of a possible pending disabling ischemic stroke and increase the risk of new stroke events, most of which occur within the initial hours and days after symptom onset.[1–4] Given the short therapeutic time window, treatment should be started immediately to reduce the risk of new stroke events.[5,6] It remains controversial whether intravenous alteplase should be given to patients with minor or rapidly improving stroke symptoms within 3 hours of symptom onset.[7,8] Antiplatelet therapy initiated within 48 hours of symptom onset in ischemic stroke patients

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*An accompanying Appendix S1, which lists the CHANCE Investigators, is available at http://jaha.ahajournals.org/content/5/3/e003038/suppl/DC1

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decreased their risk of new stroke events.[9,10] The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial and another trial demonstrated that patients with high-risk acute minor stroke or TIA who were treated with clopidogrel and aspirin within 24 hours of symptom onset had fewer subsequent stroke events than did those taking aspirin alone.[11,12] Given that there is a high recurrence rate within the initial hours and days after stroke, whether dual-antithrombotic therapy could significantly reduce the risk of ischemic stroke if the treatment is initiated within 12 hours of symptom onset is worth studying. The types of symptomatic ischemic events after stroke are divided into stroke progression and recurrence, which likely have different pathophysiologies, such as perfusion failure and recurrence of emboli.[13] Whether the dual-antiplatelet treatment is more effective in reducing recurrent ischemic stroke or progressive ischemic stroke is also unclear. We therefore examined the benefits and risk of starting combination therapy with clopidogrel and aspirin within 12 hours of onset in patients with acute minor stroke or TIA compared with those treated with aspirin alone in the CHANCE trial.

Methods

Details of the CHANCE trial have been published elsewhere.[11,14] Briefly, CHANCE was a prospective multicenter double-blind randomized placebo-controlled trial conducted at 114 centers in China. The trial compared the combination therapy of clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg/d for 90 days, plus aspirin at a dosage of 75 mg/d for the first 21 days) versus placebo plus aspirin (75 mg/d for 90 days) in 5170 patients who were 40 years or older and able to start the study drug within 24 hours after the onset of minor ischemic stroke (defined by a score of ≤3 at the time of randomization on the National Institutes of Health Stroke Scale [NIHSS]) or high-risk TIA (defined as a score of ≥4 at the time of randomization on the ABCD^2 scale). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on the first day. A stratified randomization was performed according to clinical center and interval between symptom onset and enrollment (within 12 hours versus 12–24 hours). According to prespecified randomization time, patients were divided into 2 groups—one was within 12 hours and the other was from 12 to 24 hours after the symptom onset in this subgroup analysis. Clinical follow-up was obtained in the first 90 days after acute minor stroke or high-risk TIA. All the participants or their legal proxies provided written informed consent. The CHANCE protocol was approved by the ethics committee at each study center.

Study Outcomes

The primary end point event of efficacy for this subanalysis was a new symptomatic ischemic stroke event in the first 90 days. The symptomatic ischemic stroke events were divided into 2 types:

1. Recurrent ischemic stroke: (a) sudden onset of a new focal neurologic deficit, with clinical or imaging evidence of infarction lasting ≥24 hours and not attributable to a nonischemic cause (ie, not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurologic disease), and (b) a new focal neurologic deficit lasting <24 hours and not attributable to a nonischemic cause but accompanied by neuroimaging evidence of new brain infarction. Imaging indicated that the new infarct should be geographically distinct from the original infarct.[13]
2. Progressive ischemic stroke: rapid worsening of an existing focal neurologic deficit (NIHSS increasing ≥4, excluding hemorrhagic transformation after infarction or symptomatic intracranial hemorrhage) lasting >24 hours and not attributable to a nonischemic cause, accompanied by new ischemic changes from the initial infarct on baseline magnetic resonance imaging or computed tomography of the brain. For example, initial mild hemiparesis (NIHSS 2) evolving to hemiplegia (NIHSS 6) was considered stroke progression rather than recurrent stroke, unless imaging clearly demonstrated a distinct second event remote from the presenting event.[13]

Secondary end point event of efficacy was a new clinical vascular event (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), and analyzed as a composite end point and an individual outcome. Vascular death was defined as death resulting from stroke (ischemic or hemorrhagic), systemic hemorrhage, pulmonary embolism, congestive heart failure, myocardial infarction, arrhythmia, or sudden death.

The primary end point event of safety was a moderate to severe bleeding event, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.[15]

All reported efficacy and safety end point events were verified by a central adjudication committee blinded to the assignments of study groups through review of all clinical and imaging information.

Statistical Methods

The baseline characteristics of all patients in the 2 treatment groups within 12 hours after acute minor stroke or TIA were

compared with the use of χ^2 tests for categorical variables and Student *t* test for continuous variables. Proportions were used for categorical variables, and medians with IQR values were used for continuous variables. Differences between treatment groups within 12 hours in the rate of treatment effect and safety during the 90-day follow-up period were assessed by the hazard ratio (relative risk), and their associated 95% CIs were estimated by using Cox's proportional-hazards model, with pooled study centers (≥20 patients) as a random effect. To assess the role of time, multivariable Cox proportional hazards modeling was used on the entire cohort (<12 hours and 12–24 hours randomization from onset) with a stepwise approach to identify potential independent predictors of new ischemic stroke event including randomization within 12 hours and other risk factors, such as age, sex, treatment allocation, body mass index, prior ischemic stroke, TIA, hypertension, diabetes mellitus, hyperlipidemia, myocardial infarction, angina pectoris, cardiac dysfunction, atrial fibrillation, valvular heart disease, and smoking (*P* value for a variable entering the model <0.10; *P* value for a variable removed from the model >0.05).

All data analyses were performed on the intention-to-treat population. All tests were 2-sided, and a *P* value of 0.05 was considered of statistical significance. All statistical analyses were performed with the use of SAS software, version 9.0 (SAS Institute).

Results

Baseline Demographic Characteristics

Among 5170 patients enrolled in CHANCE, 2573 (49.8%) patients were randomized within 12 hours (including 1293 [25.0%] to the clopidogrel–aspirin group and 1280 [24.8%] to aspirin group). Table 1 shows the baseline demographic characteristics of the subsets of 2573 patients enrolled within 12 hours after symptom onset. There were no significance differences in the prevalence and baseline demographic characteristics among patients randomized within 12 hours regardless of the treatment types.

Time Distribution of Ischemic Stroke Events During 90-Day Follow-up

Among 5170 patients enrolled in CHANCE trial, 499 (9.65%) patients experienced ischemic stroke events during 90-day follow-up. The timeline of these ischemic strokes during the 90-day follow-up demonstrated that 184 (36.87%) events occurred within 24 hours since randomization and 259 (51.90%) within 48 hours. Among these ischemic events within the first 48 hours, 156 (60.20%) were presenters within 12 hours since randomization.

Table 1. Baseline Characteristics of Patients Treated With Clopidogrel–Aspirin or Aspirin Alone Within 12 Hours

	Time to Randomization Within 12 Hours (N=2573)		
	Aspirin (n=1280)	Clopidogrel–Aspirin (n=1293)	*P* Value
Age, y			
Median	62	63	0.05
Interquartile range	54 to 71	55 to 72	
Female sex, n (%)	441 (34.5)	439 (34.0)	0.79
Systolic pressure, mm Hg			0.54
Median	150	150	
Interquartile range	135 to 160	136 to 161	
Diastolic pressure, mm Hg			0.58
Median	90	90	
Interquartile range	80 to 100	80 to 98	
Body-mass index*			0.57
Median	24.5	24.5	
IQR	22.9–26.6	22.7–26.5	
Medical history, n (%)			
Ischemic stroke	273 (21.3)	295 (22.8)	0.36
TIA	47 (3.7)	45 (3.5)	0.79
Myocardial infarction	31 (2.4)	27 (2.1)	0.57
Angina	48 (3.8)	44 (3.4)	0.64
Congestive heart failure	18 (1.4)	20 (1.6)	0.77
Known atrial fibrillation or flutter	29 (2.3)	24 (1.9)	0.46
Valvular heart disease	3 (0.2)	1 (0.1)	0.61
Hypertension	831 (64.9)	867 (67.1)	0.25
Diabetes mellitus	256 (20.0)	299 (23.1)	0.05
Hypercholesterolemia	139 (10.9)	140 (10.8)	0.98
Pulmonary embolism	1 (0.1)	0 (0.0)	0.50
Current or previous smoking, n (%)	536 (41.9)	524 (40.5)	0.49
$ABCD^2$ score†			0.57
Median	4	4	
IQR	4 to 5	4 to 5	

TIA indicates transient ischemic attack.

*The bodyvmass index is the weight in kilograms divided by the square of the height in meters.

†Data are only for patients who had a TIA. The $ABCD^2$ score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes, with scores ranging from 0 to 7 and higher scores indicating greater short-term risk.

Using the whole study cohort (<12 and 12–24 hours patients), multivariable Cox proportional hazards modeling showed that the randomization within 12 hours was an independent predictor of ischemic stroke events

Table 2. Independent Factors Associated With 90-Day Ischemic Stroke Events

	Hazard Ratio (95% CI)	*P* Value
Randomization within 12 h	1.25 (1.04–1.49)	0.02
Allocation of treatment (clopidogrel–aspirin group)	0.68 (0.57–0.81)	<0.001
Age	1.01 (1.01–1.02)	0.003
Body mass index	1.03 (1.00–1.06)	0.04
Prior hypertension	1.45 (1.19–1.78)	<0.001
Prior diabetes mellitus	1.23 (1.00–1.51)	0.05

(hazard ratio 1.25, 95% CI 1.04–1.49, *P*=0.02). Other independent predictors included treatment allocation, age, body mass index, prior hypertension, and diabetes mellitus (Table 2).

Outcomes During 3-Month Follow-up of All Patients Randomized Within 12 Hours of TIA or Minor Ischemic Stroke

Efficacy

Within 12 hours of the initial acute minor ischemic stroke or TIA, 282 (10.96%) of the 2573 patients experienced ischemic stroke events during the 3-month follow-up period, including 199 (7.73%) recurrent ischemic stroke and 83 (3.23%) progressive ischemic stroke (Table 3).

Among patients in the clopidogrel–aspirin group, 124 (9.59%) experienced an ischemic stroke compared with 158 (12.34%) patients in the aspirin group (hazard ratio 0.75, 95% CI 0.59–0.95, *P*=0.02) (Figure). As for the 2 types of ischemic stroke events, the clopidogrel–aspirin treatment was more likely than the aspirin alone to reduce the risk of recurrent ischemic stroke (6.57% versus 8.91%, hazard ratio 0.73, 95% CI 0.55–0.96, *P*=0.03) but not progressive ischemic stroke (3.02% versus 3.43%, hazard ratio 0.79, 95% CI 0.51–1.22, *P*=0.28).

The composite outcome of vascular events occurred in 127 (9.82%) patients in the clopidogrel–aspirin group and 165 (12.89%) patients in the aspirin group (hazard ratio 0.72, 95% CI 0.57–0.91, *P*=0.01). One (0.08%) cardiovascular death occurred in the clopidogrel–aspirin group and 2 (0.16%) occurred in the aspirin group (hazard ratio 0.49, 95% CI 0.04–5.49, *P*=0.57) (Table 3).

Safety

Four (0.16%) of 2573 patients treated within 12 hours of symptoms onset had moderate or severe bleeding events during the 3-month follow-up period (Table 3). Among

Table 3. Efficacy and Safety Outcomes Between Aspirin and Clopidogrel With Aspirin Within 12 Hours of Time to Randomization

Outcome	Time to Randomization Within 12 h		Hazard Ratio (95% CI)	*P* Value
	Aspirin Patients With Event, No. (%) (n=1280)	Clopidogrel–Aspirin Patients With Event, No. (%) (n=1293)		
Primary outcomes				
Ischemic stroke	158 (12.34)	124 (9.59)	0.75 (0.59–0.95)	0.02
Recurrent ischemic stroke	114 (8.91)	85 (6.57)	0.73 (0.55–0.96)	0.03
Progressive ischemic stroke	44 (3.43)	39 (3.02)	0.79 (0.51–1.22)	0.28
Secondary outcomes				
Stroke, myocardial infarction, or death from cardiovascular causes	165 (12.89)	127 (9.82)	0.72 (0.57–0.91)	0.01
Ischemic stroke	158 (12.34)	124 (9.59)	0.75 (0.59–0.95)	0.02
Hemorrhagic stroke	4 (0.31)	1 (0.08)	—	—
Myocardial infarction	1 (0.08)	1 (0.08)	—	—
Death from cardiovascular causes	2 (0.16)	1 (0.08)	—	—
Death from any cause	4 (0.31)	4 (0.31)	0.98 (0.24–3.95)	0.98
Transient ischemic attack	28 (2.19)	22 (1.70)	0.71 (0.40–1.25)	0.24
Safety outcomes				
Bleeding				
Severe	1 (0.08)	0 (0.00)	—	—
Moderate	2 (0.16)	1 (0.08)	—	—
Mild	8 (0.63)	13 (1.01)	1.62 (0.67–3.91)	0.29
Any bleeding	18 (1.41)	26 (2.01)	1.31 (0.71–2.40)	0.39

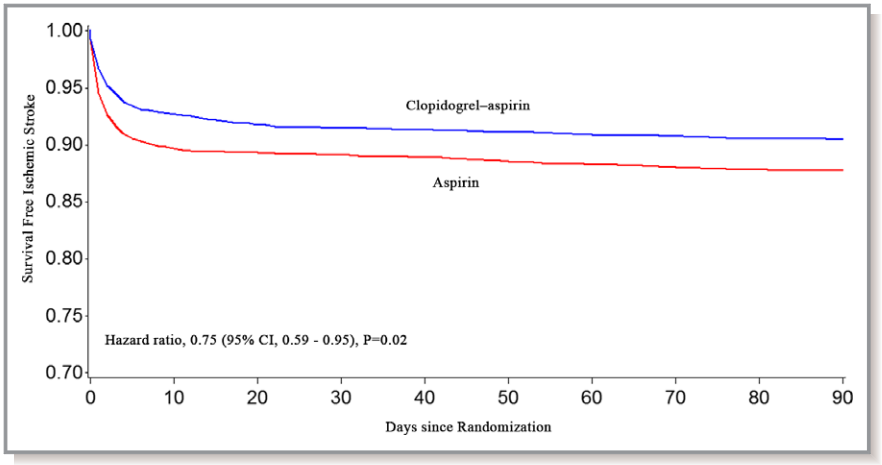

Figure. Probability of survival free of ischemic stroke among the group randomized within 0 to 12 hours.

patients randomized to the clopidogrel–aspirin group, 0 (0.00%) experienced a severe bleeding event compared with 1 (0.08%) randomized to the aspirin group. For any bleeding event, it occurred in 26 (2.01%) in the clopidogrel–aspirin group and 18 (1.41%) in the aspirin group (hazard ratio 1.31, 95% CI 0.71–2.40, *P*=0.39).

Discussions

From this subgroup analysis of the CHANCE trial, we have found that among those patients who started antiplatelet therapy within 12 hours of their initial acute minor stroke or TIA, the combination of clopidogrel and aspirin was superior to aspirin alone in reducing the risk of ischemic stroke during the 3-month follow-up period, with a 2.7% absolute risk reduction rate (the number needed to treat is 34). The dual-antiplatelet therapy was more effective than aspirin alone in reducing the risk of recurrent ischemic stroke but not progressive ischemic stroke. From the safety point of view, dual-antiplatelet therapy initiated within 12 hours of symptom onset was not associated with an increased incidence of hemorrhage.

CHANCE was a randomized double-blind placebo-controlled trial, and randomization was stratified according to the interval between symptom onset and enrollment (<12 hours versus 12–24 hours) and participating center. The prevalence or level of potential prognostic factors between the treatment groups was balanced and reliable for this subgroup analysis so that systematic bias in allocation and attrition were avoided. Consequentially, our study identified a statistically significant positive effect of clopidogrel plus aspirin within 12 hours of symptom onset compared with aspirin alone.

Similar to the previous findings, >50% of such risk occurs in the first 2 days after the initial acute minor stroke or TIA.[1,5,12] These data suggested that the highest risk period for ischemic stroke event is during the early hours and days following the initial ischemic event. In the multivariable analysis, the randomization within 12 hours after the symptom onset is an independent predictor of ischemic stroke event, besides age, history of hypertension, and diabetes, as mentioned in previous studies.[2,16] This high risk of developing new ischemic stroke events might be attributed to a patient's unstable atherosclerotic plaque and accelerated platelet aggregation in the early phase of the disease.[17–19] We observed that the curves for cumulative rate of stroke event were particularly steep within the first few days, during which the different treatment groups' curve diverged significantly. After that, the rates of ischemic stroke were similar. This suggests that the main benefit of the early combination therapy of clopidogrel and aspirin was to prevent the early stroke occurrence. Even without a demonstrated relative benefit for early treatment, this finding implies that patients with acute minor stroke or TIA should be given dual-antiplatelet treatment as early as possible.

Ischemic stroke progression and recurrence likely have different pathophysiologies, such as perfusion failure and recurrence of emboli. Recurrent ischemic stroke is likely caused by unstable atherosclerotic plaque and accelerated platelet aggregation. Patients can benefit from more aggressive antithrombotic therapy.[17–20] Ischemic stroke progression may be attributed to the collateral failure in the setting of an intracranial occlusion or stenosis or, less commonly, to recurrent embolus.[13,21] Coutts et al implied that, like for the patient with progression of the infarct, antithrombotic agents might be less effective than drugs targeting reduction of final infarct volume in reducing the risk of stroke recurrence.[13] In

our study, patients with acute symptomatic atherothrombosis were recruited, and early dual-antiplatelet therapy of 75 mg of aspirin and a 300-mg bolus loading dose of clopidogrel rapidly produced a stronger effect of inhibition of platelet aggregation.[22] And, we observed that dual-antiplatelet therapy reduced the risk of recurrent ischemic stroke but not progressive ischemic stroke.

In our study, there was the low incidence of hemorrhage and no difference between the 2 treatment groups. One possible explanation is that our trial included TIA patients and patients with less severe strokes than in previous trials.[23] Patients with more severe stroke are at a relatively high risk of hemorrhage.[24] In addition, in our trial, the combination therapy with clopidogrel and aspirin just lasted 21 days, shorter than previous trials that continued treatment for ≥3 months.[12,23]

There are several limitations in this subanalysis. First, there was no baseline perfusion imaging, which would have been helpful to distinguish recurrent and progressive stroke.[13] However, in a large-scale multicenter trial, the implementation of baseline perfusion imaging is extremely hard. We used structural magnetic resonance imaging or computed tomography to distinguish between the 2, which was also used in a previous study.[13] Second, we observed that the dual-antiplatelet treatment mainly reduced the risk of recurrent ischemic stroke. However, because of the lack of initial stroke etiology and vascular imaging data, we could not determine the substantial mechanism; further research based on etiology and imaging is needed. Additionally, in this subgroup analysis, although the efficacy among patients treated with dual-antiplatelet therapy within 12 hours showed statistically significant benefit, the results came from Chinese participants with predominant intracranial disease and hence may not be generalizable to other populations.[25] The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) study (ClinicalTrials.gov number, NCT00991029) is enrolling subjects at sites primarily in the United States within 12 hours after symptom onset.[26] Compared with the CHANCE trial, the POINT trial is assessing a higher loading dose and longer-lasting clopidogrel (600-mg loading dose then 75 mg/d from day 2 to day 90), which will be expected to provide robust evidence of earlier and more aggressive antiplatelet treatment.

In summary, dual-antiplatelet therapy was more effective in reducing ischemic stroke than aspirin alone in patients with minor acute ischemic stroke or high-risk TIA within 12 hours of the initial onset but did not increase the risk of hemorrhage. In addition, the majority of reduced ischemic events were newly recurrent ischemic stroke events rather than progressive ischemic stroke events. Also, because the highest risk period for new stroke events was during the early hours and days after the initial ischemic event, aggressive antiplatelet therapy among patients with minor stroke or TIA should be administrated as early as possible.

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Disclosures

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