Risks and benefits of clopidogrel–aspirin in minor stroke or TIA

Time course analysis of CHANCE

Yuesong Pan, MD*
Jing Jing, MD, PhD*
Weiqi Chen, MD
Xia Meng, MD, PhD
Hao Li, PhD
Xingquan Zhao, MD, PhD
Liping Liu, MD, PhD
David Wang, DO
S. Claiborne Johnston, MD, PhD
Yilong Wang, MD, PhD
Yongjun Wang, MD
On behalf of the CHANCE investigators

Correspondence to Dr. Yongjun Wang: yongjunwang1962@gmail.com or Dr. Yilong Wang: yilong528@gmail.com

ABSTRACT

Objective: To investigate the short-term time course risks and benefits of clopidogrel with aspirin in minor ischemic stroke or TIA.

Methods: Data were derived from the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial. The primary outcome was a new ischemic stroke. Safety outcomes included any bleeding and moderate to severe bleeding. Time course analyses were performed for the outcomes of both stroke and bleeding.

Results: A total of 145 (71.1%), 13 (6.4%), and 12 (5.9%) of 204 new ischemic strokes in the clopidogrel–aspirin group vs 223 (75.6%), 19 (6.4%), and 8 (2.7%) of 295 in the aspirin alone group occurred at the first, second, and third week, respectively. A total of 23 (38.3%), 15 (25.0%), and 9 (15.0%) of 60 bleeding cases in the clopidogrel–aspirin group vs 15 (36.6%), 8 (19.5%), and 3 (7.3%) of 41 in the aspirin alone group occurred at the first, second, and third week, respectively. Clopidogrel–aspirin treatment numerically reduced the risk of ischemic stroke within the first 2 weeks. From the 10th day, the number of any bleeding cases caused by dual antiplatelets outweighed that of new stroke reduced by dual antiplatelets.

Conclusions: Clopidogrel–aspirin treatment may have a benefit of reducing stroke risk outweighing the potential risk of increased bleeding especially within the first 2 weeks compared with aspirin alone in patients with minor stroke or TIA.

Clinicaltrials.gov identifier: NCT00979589.

Classification of evidence: This study provides Class II evidence that for patients with minor stroke or TIA, the reduction of stroke risk from clopidogrel plus aspirin within the first 2 weeks outweighs the risk of bleeding compared with aspirin alone. *Neurology*® 2017;88:1906–1911

GLOSSARY

CHANCE = Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events; **CI** = confidence interval; **FASTER** = Fast Assessment of Stroke and TIA to Prevent Early Recurrence; **GUSTO** = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; **HR** = hazard ratio; **MATCH** = Management of Atherothrombosis with Clopidogrel in High-Risk Patients.

Combination treatment of clopidogrel and aspirin taken soon after a minor ischemic stroke or TIA was showed to reduce the early risk of new stroke without increasing the risk of bleeding.[1,2] In current guidelines for the early management of patients with acute ischemic stroke published by both Chinese Medical Association and by the American Heart Association/American Stroke Association,[3,4] combination of clopidogrel and aspirin is recommended for initiation within 24 hours of a minor stroke or TIA and continuation for 21 days based on the results of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial.[1] However, the duration of dual antiplatelet therapy for 21 days in the

Supplemental data at Neurology.org

*These authors equally to this work.

From the Department of Neurology (Y.P., J.J., W.C., X.M., H.L., X.Z., L.L., Yilong Wang, Yongjun Wang), Beijing Tiantan Hospital, Capital Medical University; China National Clinical Research Center for Neurological Diseases (Y.P., J.J., W.C., X.M., H.L., X.Z., L.L., Yilong Wang, Yongjun Wang); Center of Stroke, Beijing Institute for Brain Disorders (Y.P., J.J., W.C., X.M., H.L., X.Z., L.L., Yilong Wang, Yongjun Wang); Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease (Y.P., J.J., W.C., X.M., H.L., X.Z., L.L., Yilong Wang, Yongjun Wang); Department of Epidemiology and Health Statistics (Y.P.), School of Public Health, Capital Medical University, Beijing, China; INI Stroke Network (D.W.), OSF Healthcare System, University of Illinois College of Medicine, Peoria; and Dell Medical School (S.C.J.), University of Texas at Austin.

Coinvestigators are listed at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

CHANCE trial was somewhat arbitrary. As acknowledged, the risk of bleeding increased as the duration of dual antiplatelet therapy became prolonged.[5] Therefore, the optimal duration of dual antiplatelet therapy for minor stroke or TIA is controversial. A concern for increase in bleeding risk on dual antiplatelet therapy remains in clinical practice.[5,6]

To evaluate the optimal duration of dual antiplatelet therapy, we aimed to investigate the short-term time course risks and benefits of clopidogrel with aspirin in minor stroke or TIA using data from the CHANCE trial.

METHODS

Study participants. We derived data from the CHANCE trial. Details on the design and major results of the CHANCE trial have been published elsewhere.[1,2,7] In brief, the CHANCE trial is a randomized, double-blind, controlled trial enrolling 5,170 patients from 114 hospitals in China between October 2009 and July 2012 to assess the efficacy and safety of combined treatment of clopidogrel and aspirin vs aspirin alone in minor ischemic stroke and TIA. Patients included in the trial were diagnosed with an acute minor ischemic stroke (NIH Stroke Scale ≤ 3) or high-risk TIA (ABCD^2 ≥ 4) within 24 hours after onset with an age 40 years or older.

Standard protocol approvals, registrations, and patient consents. The CHANCE trial is registered at clinicaltrials.gov (registration number NCT00979589). The protocol of the trial was approved by the ethics committee of Beijing Tiantan Hospital and all the participating hospitals. All participants or their representatives provided written informed consent before data collection.

Randomization and treatments. We randomly assigned patients to the clopidogrel–aspirin group or aspirin alone group by using a double-blind, double-dummy design. After a patient was enrolled, the site investigator called into an automated system. The system randomly assigned a number that corresponded to a medication kit stored at the research site. Then the patient was administered the medication in the kit. Clopidogrel and the placebo were purchased from Sanofi-Aventis (Gentilly, France).

The clopidogrel–aspirin group was treated as follows: day 1: randomized-blind clopidogrel 300 mg and open-label aspirin 75–300 mg. Days 2 through 21: randomized-blind clopidogrel 75 mg and aspirin 75 mg per day. Days 22 through 90: randomized-blind clopidogrel 75 mg/d and placebo aspirin daily.

The aspirin alone group was treated as follows: day 1: randomized-blind placebo clopidogrel and open-label aspirin 75–300 mg. Days 2 through 90: randomized-blind aspirin 75 mg/d and placebo clopidogrel daily.

Outcome assessment. We collected outcomes through face-to-face interviews by trained neurologists from participating sites. The primary efficacy outcome was a new ischemic stroke during the 90-day follow-up period.[1] Safety outcomes included any bleeding and moderate to severe bleeding defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.[8] Severe bleeding was defined as fatal or intracranial or other hemorrhage causing substantial hemodynamic compromise that required intervention. Moderate bleeding was defined as bleeding that did not lead to hemodynamic compromise requiring intervention but required transfusion of blood.[8] The definition of the outcomes in the current analysis was consistent with those in the trial.[1] All reported events were verified by an independent central adjudication committee that was blinded to the study treatment assignments.

Statistical analysis. All analyses were performed by intention-to-treat based on the randomized treatment assignment. To determine the time course of effect of clopidogrel–aspirin at the acute stage, we presented the number of events and calculated the effects of clopidogrel–aspirin vs aspirin alone with stratification by time since randomization (each week for the first 5 weeks and 6th week–day 90). This analysis covered the full period of randomized treatment allocation in the trial (90 days), and detailed the first 5 weeks (in the clopidogrel–aspirin arm, 3 weeks with dual antiplatelet therapy and 2 weeks after dual antiplatelet therapy) in both arms. For the outcomes of new ischemic stroke and any bleeding, we presented the time to the first event by Kaplan-Meier curves (1 − proportion free of event) and determined the effect of treatment allocation using the log-rank test. We then calculated hazard ratios (HRs) with their 95% confidence intervals (CIs) using Cox proportional hazard models for each time period stratified.

To estimate the short-term time course of relative risks and benefits of dual antiplatelet therapy at the acute stage (the first 3 weeks), we generated absolute numbers and HRs of new ischemic stroke and any bleeding in patients with clopidogrel–aspirin for each stratified time period from randomization. To improve the robustness of the estimation, this analysis was performed for the stratified time period of each week, each 6 days, each 5 days, each 4 days, and each 3 days, respectively. Numbers of events at the median day of each stratified time period were estimated by total numbers of events divided by days in the time period. Data of the fourth week since randomization (without dual antiplatelet treatment) were included in the estimation but estimated events for the fourth week were not presented. Then, curves representing time course of risks and benefits of dual antiplatelet therapy at the acute stage were fitted for these estimated absolute numbers and HRs in each stratified time period using quadratic or quartic function.

In sensitivity analysis, we also calculated the net clinical benefit of dual antiplatelet therapy. The number of any bleeding events attributable to dual antiplatelet therapy was subtracted from the number of new ischemic strokes avoided by dual antiplatelet therapy with the weight of 0.1–1.2: net benefit = (ischemic stroke$_{\text{aspirin group}}$ − ischemic stroke$_{\text{clopidogrel – aspirin group}}$) − weight × (bleeding$_{\text{clopidogrel – aspirin group}}$ − bleeding$_{\text{aspirin group}}$). The weight accounts for the effects of a bleeding compared with a new ischemic stroke.[9]

Two-sided $p < 0.05$ were considered to be statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Classification of evidence. The primary research question was whether the reduction of stroke risk from clopidogrel plus aspirin outweighs the risk of bleeding at the early stage compared with aspirin alone in patients with minor stroke or TIA. This study provides Class II evidence that for patients with minor stroke or TIA, the reduction of stroke risk from clopidogrel plus aspirin within the first 2 weeks outweighs the risk of bleeding compared with aspirin alone.

RESULTS

Study participants and characteristics. A total of 5,170 patients with a minor ischemic stroke

Table 1 Time course distribution of ischemic stroke and bleeding by treatment assignment

			No. of events					
Outcome	Group	Total	1st week	2nd week	3rd week	4th week	5th week	6th week–day 90
Ischemic stroke	ASA (n = 2,586)	295	223 (75.59)	19 (6.44)	8 (2.71)	6 (2.03)	2 (0.68)	37 (12.54)
	CLP + ASA (n = 2,584)	204	145 (71.08)	13 (6.37)	12 (5.88)	6 (2.94)	3 (1.47)	25 (12.25)
Any bleeding	ASA (n = 2,586)	41	15 (36.59)	8 (19.51)	3 (7.32)	2 (4.88)	2 (4.88)	11 (26.83)
	CLP + ASA (n = 2,584)	60	23 (38.33)	15 (25.00)	9 (15.00)	3 (5.00)	1 (1.67)	9 (15.00)
Moderate to severe bleeding	ASA (n = 2,586)	4	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (100.00)
	CLP + ASA (n = 2,584)	4	1 (25.00)	2 (50.00)	1 (25.00)	0 (0.00)	0 (0.00)	0 (0.00)
Mild bleeding	ASA (n = 2,586)	19	3 (15.79)	7 (36.84)	2 (10.53)	1 (5.26)	1 (5.26)	5 (26.32)
	CLP + ASA (n = 2,584)	30	8 (26.67)	9 (30.00)	8 (26.67)	1 (3.33)	0 (0.00)	4 (13.33)

Abbreviations: ASA = aspirin; CLP = clopidogrel.

or TIA, including 2,584 patients in the clopidogrel–aspirin arm and 2,586 patients in the aspirin alone arm, were enrolled in the CHANCE trial.

Table 1 shows the time course distribution of stroke and bleeding by treatment assignment. In the clopidogrel–aspirin group, a total of 204 (7.9%) new ischemic strokes occurred within 90 days, 145 (71.1%), 13 (6.4%), and 12 (5.9%) of which occurred at the first, second, and third week, respectively (table 1). In the aspirin alone group, 223 (75.6%), 19 (6.4%), and 8 (2.7%) of 295 (11.4%) new ischemic strokes occurred at the first, second, and third week, respectively. At the first week, clopidogrel–aspirin treatment reduced the 1-week risk of new ischemic stroke by approximately 35% (HR 0.64, 95% CI 0.52–0.79, $p < 0.001$) (table 2). The effect decreased during the second week and numerically increased the risk of new stroke during the third week ($p = 0.25$, $p = 0.41$). Cumulative risk of new ischemic stroke by treatment assignment at the acute stage is shown in figure 1A.

In the clopidogrel–aspirin group, a total of 60 (2.3%) bleedings occurred within 90 days, 23 (38.3%), 15 (25.0%), and 9 (15.0%) of which occurred at the first, second, and third week, respectively (table 1). In the aspirin alone group, 15 (36.6%), 8 (19.5%), and 3 (7.3%) of 41 (1.6%) bleedings occurred at the first, second, and third week, respectively. Although not reaching statistical significance, clopidogrel–aspirin treatment numerically increased the risk of any bleeding during the first 4 weeks (table 2). Cumulative risk of any bleeding by treatment assignment at the acute stage is shown in figure 1B. A total of 4 moderate to severe bleedings occurred within the first month in the clopidogrel–aspirin group with 1 during the first week, 2 during the second week, and 1 during the third week, respectively. No moderate to severe bleeding occurred within the first month in the aspirin alone group. Analyses of specific bleeding events as well as the measures needed to be taken and the outcome are shown in table e-1 at Neurology.org. The most frequent type of bleeding in the dual antiplatelet group was intracranial hemorrhage (n = 20), skin bruises (n = 17), gastrointestinal bleeding (n = 8), intraocular hemorrhage (n = 5), epistaxis (n = 4), and gum bleeding (n = 4).

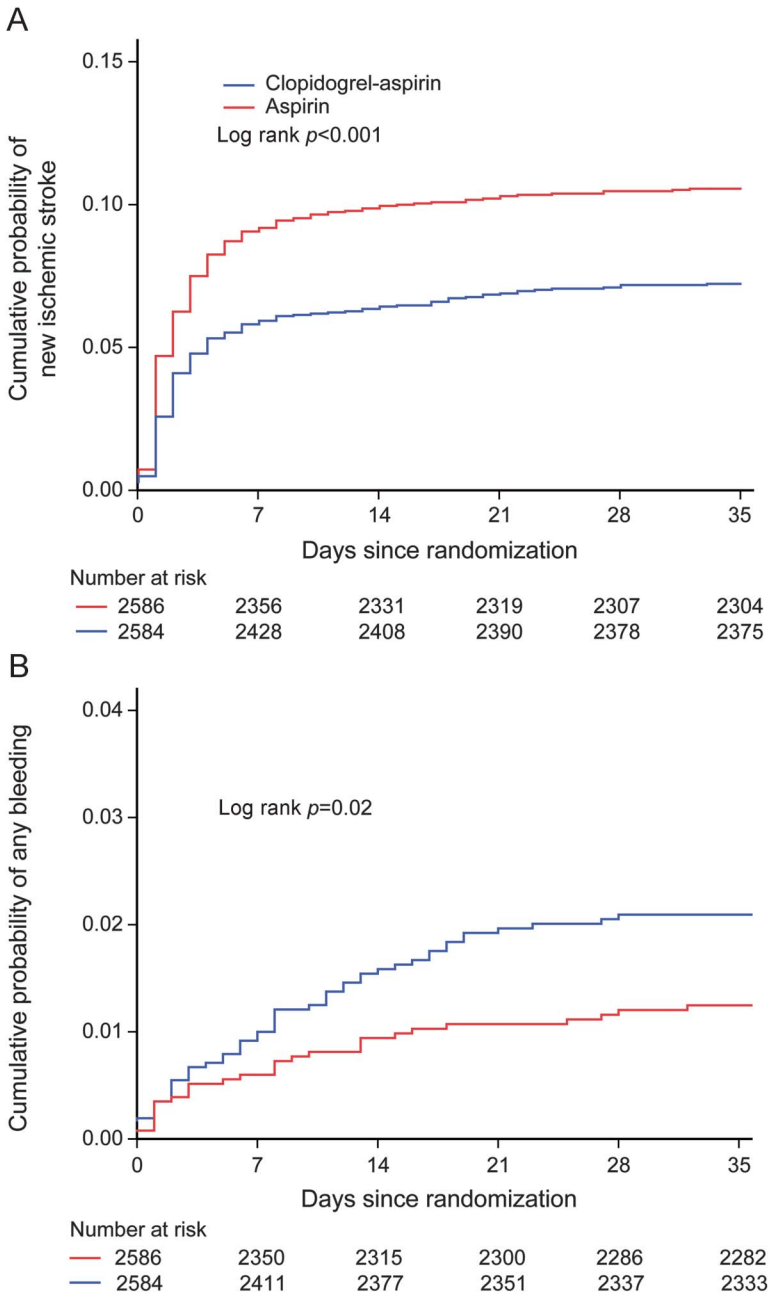
Figure 2 shows the time course of estimated HR of new ischemic stroke and any bleeding in patients with clopidogrel–aspirin vs aspirin alone. Within 21 days since randomization, HRs of both new ischemic stroke and any bleeding numerically increased with the duration of dual antiplatelet therapy prolongation. Clopidogrel–aspirin therapy numerically reduced the risk of new ischemic stroke within the first 2 weeks, but numerically increased the risk of new stroke during the third week. Estimated absolute numbers of new ischemic stroke avoided by dual antiplatelet therapy outweighed that of any bleeding caused at the early stage (figure 3). The discrepancy attenuated with the duration of dual antiplatelet therapy prolongation and curves of new ischemic stroke and any bleeding crossover at the 10th day.

Table 2 Effect of clopidogrel-aspirin vs aspirin alone by time since randomization

	Ischemic stroke		Bleeding	
Time period	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
1st week	0.64 (0.52-0.79)	<0.001	1.53 (0.80-2.93)	0.20
2nd week	0.66 (0.33-1.34)	0.25	1.83 (0.78-4.31)	0.17
3rd week	1.45 (0.59-3.55)	0.41	2.92 (0.79-10.79)	0.11
4th week	0.97 (0.31-3.01)	0.96	1.47 (0.25-8.79)	0.67
5th week	1.46 (0.24-8.71)	0.68	0.49 (0.04-5.40)	0.56
6th week–day 90	0.70 (0.42-1.19)	0.19	0.49 (0.17-1.43)	0.19

Abbreviations: CI = confidence interval; HR = hazard ratio.

Figure 1 Cumulative probability of events by treatment assignment at the acute stage



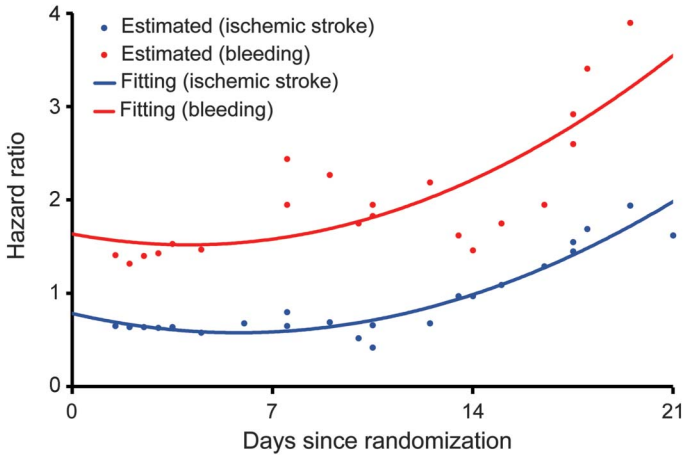
(A) New ischemic stroke. (B) Any bleeding.

Sensitivity analysis regarding net clinical benefit showed that dual antiplatelet therapy may have a positive net benefit within the first 2 weeks if the weight of a bleeding compared with a new ischemic stroke was 0.8 or less (table e-2).

DISCUSSION In this post hoc analysis of the CHANCE trial, we found that clopidogrel–aspirin treatment numerically reduced the risk of new ischemic stroke within the first 2 weeks, but numerically increased the risk of new ischemic stroke during the third week in patients with minor ischemic stroke or TIA, whereas the risk of any bleeding was constant within the 3 weeks. Within 3 weeks' treatment, estimated absolute numbers of new ischemic stroke avoided by dual antiplatelet therapy exceeded that of any bleeding caused at the early stage but risk outweighed benefit after the 10th day.

Antiplatelet therapy was a double-edged sword: high platelet inhibition decreased the risk of recurrent ischemic events but increased the risk of bleeding.[10] The risk of bleeding was the major concern when combination treatment of clopidogrel and aspirin were administrated in clinical practice. Besides older age, history of antiplatelet agents use and presentation of stroke as qualifying event (vs TIA)[11] and dose and duration of antiplatelet treatment could be other important indicators of increased risk of bleeding for dual antiplatelet therapy. The results of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial indicated that bleeding complications of clopidogrel–aspirin were constant over time and a time margin (approximately 3 months) existed at which risk outweighed benefit in high-risk patients with ischemic stroke or TIA.[6] However, the participants in the MATCH trial (ischemic stroke or TIA within 3 months after onset of the event) were different from those of our study (minor ischemic stroke or TIA within 24 hours after onset of the event). The Fast Assessment of Stroke and TIA to Prevent Early Recurrence (FASTER) trial indicated that patients with 90 days' combination treatment of clopidogrel and aspirin seem to be at an increased risk of bleeding in patients with minor stroke or TIA within 24 hours of symptom onset compared with those with aspirin alone.[12] Although having similar participants to our study, the FASTER trial had a duration of dual antiplatelet therapy of 90 days (21 days in the CHANCE trial) and did not report the time course risks and benefits at the early stage. In addition to the overall efficacy and safety of clopidogrel–aspirin vs aspirin alone at 90-day follow-up presented in the main results of the CHANCE trial,[1] this study described the time course of risk and benefit of dual antiplatelet therapy in patients with minor stroke or TIA with 3 weeks of clopidogrel–aspirin treatment and indicated that the net benefit of dual antiplatelet therapy might exist primarily within the first 2 weeks. There were several potential explanations for the numeric increase in the risk of new ischemic stroke in the 3rd week in the clopidogrel–aspirin group. First, patients in the aspirin alone group may have had a stroke recurrence mainly at the early stage (within the first 2 weeks), while clopidogrel–aspirin treatment may have delayed the stroke recurrence in some patients. Second, this may be caused by randomized error. This study may provide a reference for the clinical administration of

Figure 2 Time course of estimated hazard ratio of events in patients with clopidogrel-aspirin vs aspirin alone



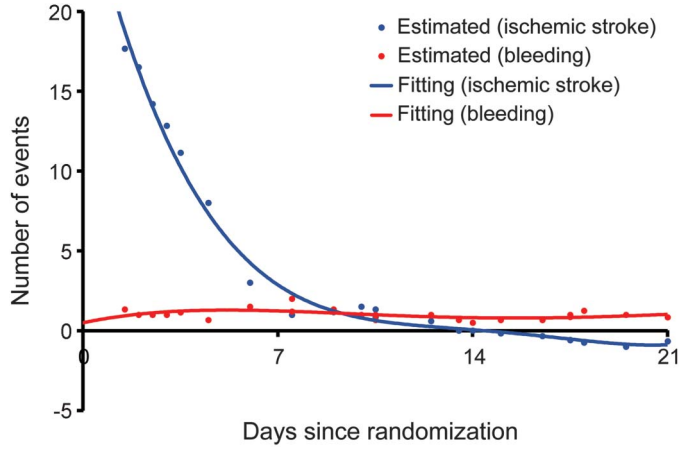
dual antiplatelet therapy and design of future research on antiplatelet agents.

It should be acknowledged that the primary safety outcome in this study is any bleeding. Concerns may arise that most mild bleeding was reversible and our results could be more clinically significant if major or severe bleeding were used as a safety outcome. However, the assessment of clinical significance of bleeding events classified by GUSTO criteria could be subjective.[11] A minor or moderate bleeding event, such as gastrointestinal bleeding, can evolve into a severe event if there is a large amount of blood loss. Intraocular bleeding could be disabling although not classified as severe bleeding. Events such as hemoptysis and epistaxis could be clinically important, although they were likely mild according to GUSTO classification. Even mild bleeding, such as skin bruises and gum bleeding, could have a substantial influence on clinical compliance with antiplatelet administration. Furthermore, although the sample size of events was small, results from the endpoints of moderate to severe bleeding also showed a similar trend that 4 moderate to severe bleeding events occurred within 3 weeks in the dual antiplatelet group compared with 0 within 3 weeks in the aspirin alone group.

This study had several limitations. First, the sample size of patients in each stratified time period, especially for the event of bleeding, was small. The results found in this study need further validation in studies with larger sample size. Second, the generalizability of these results was limited to patients with an acute minor ischemic stroke or high-risk TIA within 24 hours after onset, and cannot be generalized to patients with major stroke who may be more at risk for hemorrhagic transformation. Third, the CHANCE trial enrolled only Chinese patients, and hence the external generalizability of these findings needs further validation in non-Asian populations having different demographics and disease patterns. Asian patients, with lower body weight than white patients, are more susceptible to bleeding.[13] Furthermore, the prevalence of intracranial atherosclerosis in Asian patients with ischemic stroke (30%–50%) was higher than that in non-Asian patients (8%),[14,15] suggesting that clopidogrel may be more effective in Asian than non-Asian patients. Finally, although sensitivity analysis of net clinical benefit was performed under assumption of different weights, there was no definite weight of a bleeding compared with a new ischemic stroke. However, this study mainly focused on the early time course of risks and benefits of clopidogrel with aspirin in minor stroke or TIA.

This time course analysis showed that clopidogrel–aspirin treatment may have a benefit of reducing ischemic stroke risk outweighing the potential risk of increased bleeding primarily within the first 2 weeks compared with aspirin alone in patients with minor ischemic stroke or TIA.

Figure 3 Time course of estimated absolute numbers of events



The numbers indicate new ischemic stroke avoided and any bleeding caused daily by clopidogrel-aspirin vs aspirin alone.

AUTHOR CONTRIBUTIONS

Dr. Pan: study concept and design, analysis and interpretation of data, drafting of the manuscript. Dr. Jing: acquisition of data, analysis and interpretation of data. Dr. Chen: acquisition of data. Dr. Meng: acquisition of data. Dr. Li: analysis and interpretation of data. Dr. Zhao: acquisition of data, study supervision or coordination. Dr. Liu: acquisition of data. David Wang: revision of the drafting of the manuscript. S. Claiborne Johnston: revision of the drafting of the manuscript. Yilong Wang: study concept and design, acquisition of data, analysis and interpretation of data. Yongjun Wang: study concept and design, obtaining funding, study supervision or coordination.

STUDY FUNDING

This study is supported by grants from the Ministry of Science and Technology of the People's Republic of China (2013BAI09B03, 2013BAI09B14, 2015BAI12B04, 2015BAI12B02), a grant from the Beijing Biobank of Cerebral Vascular Disease (D131100005313003), a grant from Beijing Institute for Brain Disorders (1152130306), a grant

from the National Natural Science Foundation of China (81322019), grants from Beijing Municipal Science and Technology Commission (D131100002313002, D151100002015001, D151100002015002, D151100002015003, Z15110200390000, Z151100003915117), and grants from Beijing Municipal Commission of Health and Family Planning (2016-1-2041, SML20150502). The funding agencies played no role in the design of the study, in the collection, analysis, and interpretation of the data, or in the preparation and review of the manuscript.

DISCLOSURE

Y. Pan, J. Jing, W. Chen, X. Meng, H. Li, X. Zhao, L. Liu, and D. Wang report no disclosures relevant to the manuscript. S. Claiborne Johnston is the principal investigator of the POINT trial, a NIH-sponsored trial with clopidogrel and placebo donated by Sanofi. Yilong Wang and Yongjun Wang report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received November 9, 2016. Accepted in final form February 15, 2017.

REFERENCES

1. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11–19.
2. Wang Y, Pan Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial: one-year outcomes. Circulation 2015;132:40–46.
3. The Cerebrovascular Disease Group of Chinese Medical Association. Chinese guidelines for the secondary prevention of ischemic stroke and transient ischemic attack 2014 [in Chinese]. Clin J Neurol 2015;48:258–273.
4. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160–2236.
5. Ge F, Lin H, Liu Y, et al. Dual antiplatelet therapy after stroke or transient ischaemic attack: how long to treat? The duration of aspirin plus clopidogrel in stroke or transient ischaemic attack: a systematic review and meta-analysis. Eur J Neurol 2016;23:1051–1057.
6. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331–337.
7. Wang Y, Johnston SC; CHANCE Investigators. Rationale and design of a randomized, double-blind trial comparing the effects of a 3-month clopidogrel-aspirin regimen versus aspirin alone for the treatment of high-risk patients with acute nondisabling cerebrovascular event. Am Heart J 2010;160:380–386.
8. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–682.
9. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 2012;125:2298–2307.
10. Ferreiro JL, Sibbing D, Angiolillo DJ. Platelet function testing and risk of bleeding complications. Thromb Haemost 2010;103:1128–1135.
11. 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;1:29–36.
12. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol 2007;6:961–969.
13. Kang HJ, Clare RM, Gao R, et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: a retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Am Heart J 2015;169:899–905 e891.
14. Wong LK. Global burden of intracranial atherosclerosis. Int J Stroke 2006;1:158–159.
15. Wang Y, Zhao X, Liu L, et al. Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) study. Stroke 2014;45:663–669.

Risks and benefits of clopidogrel–aspirin in minor stroke or TIA: Time course analysis of CHANCE

Yuesong Pan, Jing Jing, Weiqi Chen, et al.

Neurology 2017;88;1906-1911 Published Online before print April 19, 2017
DOI 10.1212/WNL.0000000000003941