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ORIGINAL RESEARCH

Effect of dual antiplatelet on recurrent stroke in minor stroke or TIA depends on bodyweight

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Objective: To assess whether bodyweight influences the efficacy and safety of dual antiplatelet therapy (DAT) in male patients with minor stroke or transient ischemic attack patients.

Materials and methods: All 3,420 male participants coming from the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events trial were divided into 3 groups based on bodyweight (<65 kg, 65–75 kg, and ≥75 kg). The stroke outcomes included stroke recurrence, combined vascular events, and bleeding events during 90 days of follow-up. The interaction of the treatment effects of DAT among patients with different bodyweight was assessed by Cox proportional hazards models.

Results: DAT is superior to mono antiplatelet therapy (MAT) for reducing stroke recurrence among patients with weight <65 kg (5.0% vs 11.7%; hazard ratio [HR], 0.41; 95% CI: 0.22–0.76) and 65–75 kg (6.7% vs 10.8%, HR, 0.62; 95% CI: 0.43–0.89). However, no significant difference was found in stroke recurrence between DAT and MAT in patients with weight ≥75 kg (9.4% vs 11.6%; HR, 0.80; 95% CI: 0.58–1.10). A significant interaction was observed between weight and antiplatelet therapy on stroke recurrence ($p<0.05$). Similar result was found for combined vascular events. More bleeding events were found in DAT group among patients with weight <65 kg (3.7% vs 2.2%), but with no significant difference.

Conclusion: DAT does not show benefit in patients with higher weight, compared with MAT. Bleeding events found in the DAT group were not more than the MAT group among patients with lower weight.

Clinical trial registration: URL: http://www.ClinicalTrials.gov. Unique identifier: NCT00979589.

Keywords: bodyweight, dual antiplatelet therapy, ischemic stroke, outcomes, TIA

Introduction

Dual antiplatelet therapy (DAT) is an effective way in reducing the risk of early stroke recurrence and other vascular events as compared with mono antiplatelet therapy (MAT) in patients with acute ischemic stroke or transient ischemic attack (TIA).[1–3] After Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) study reported that DAT was superior to MAT for reducing the risk of stroke in the first 90 days, the American Heart Association/American Stroke Association recommended that the combination of aspirin and clopidogrel can be initiated within 24 h for a minor ischemic stroke or TIA and be continued for 90 days in 2014.[4] It is not clear which subgroup can benefit from the DAT.[5] We can find an interesting phenomenon that DAT seemed superior to MAT in Eastern population but not in Western.[1,3,6,7] This discrepancy might be attributed to the different demographic characteristics between 2 populations, bodyweight was an obvious disparity.[8] Some studies showed that higher weight was associated with more vascular recurrence

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after stroke.[9] Whether bodyweight may influence the effect of antiplatelet therapy on stroke recurrence in patients with ischemic stroke or TIA is unreported. We sought to assess whether bodyweight would influence the efficacy and safety of DAT in minor stroke and TIA patients in the cohort of the CHANCE trial.

Materials and methods

Data sources

We used data from CHANCE trial. Details on the rationale, design, and early results have been published previously.[1,10] The study was approved by medical ethics committee of Beijing Tiantan Hospital. The CHANCE trial was a randomized, double-blind, placebo-controlled clinical trial conducted at 114 centers in China between October 2009 and July 2012. The complete list of investigators and institutions participating in the CHANCE trial is provided in the Supplementary material. Patients were recruited if they met the following criteria: ≥40 years of age, had a diagnosis of an acute minor stroke or high-risk TIA, and were able to start the study drug within 24 h after onset of symptom. All eligible patients were randomly assigned to the following therapy arms: a placebo version of Plavix (clopidogrel bisulfate; Sanofi Pharmaceuticals Partnership, Bridgewater, NJ, USA) on days 1 through 90, plus aspirin at a dose of 75 mg per day on days 2 through 90; or 300 mg of clopidogrel on day 1, followed by a dose of 75 mg per day on days 2 through 90, plus Aspirin (Friedrich Bayer & Co., Elberfeld, Germany) at a dose of 75 mg per day on days 2 through 21, and placebo aspirin on days 22 through 90. Acute minor stroke was defined by a score of 3 or less on the National Institutes of Health Stroke Scale (NIHSS) upon randomization. TIA was defined as focal brain ischemia with resolution of symptoms within 24 h after onset, and with a score of ≥4 on the ABCD2 when randomized. Study visits were planned on the day of randomization, 21, and 90 days after randomization and at hospital discharge. Details of the information about patients' clinical status, interim occurrence of any adverse events, and medication compliance were collected.

Study population

Bodyweight is a gender-specific variable. Gender-related differences in pharmacokinetics have frequently been considered as potentially important determinants for the clinical effectiveness of drug therapy.[11] Thus, in this subgroup we only investigate the effect of bodyweight on DAT in one gender. Males were a majority in the CHANCE trial. Bigger sample size can give us greater power to detect differences, so we analyzed 3,420 male patients in this subgroup.

Bodyweight measurement and classification

The bodyweight was measured by the study coordinator at the initial randomization visit. Each participant was weighed in lightweight clothing, with the measurement taken on a calibrated beam scale, and the weight recorded to the nearest 1 kg. Average weight of an adult male in China was 66.2 kg in 2012 according to a Chinese government report.[12] We classified bodyweight as low bodyweight (weight <65 kg), middle bodyweight (65 kg ≤ weight <75 kg), and high bodyweight (weight ≥75 kg).

Efficacy and safety outcome

Written informed consent was obtained from all participants or their legal proxies. CHANCE protocol was approved by the ethics committee at each study center. The primary efficacy outcome was recurrent stroke (ischemic or hemorrhagic) within 90 days.[1] The secondary efficacy outcome included combined vascular events (CVEs) (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death). The primary safety outcome was any bleeding event, as per the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.[13] All reported efficacy and safety outcomes were confirmed by a central adjudication committee that was blinded to the study group assignments.

Statistical analysis

Continuous and categorical variables were reported as mean ± SD or percentages and compared by use of Student's *t*-test, Fisher's exact test or χ^2 test (2 tailed), respectively. Furthermore, we performed survival analysis and present Kaplan–Meier curves by different groups of bodyweight for stroke and CVE. Multivariate Cox regressions were performed to assess the associations between bodyweight and clinical outcome variables. Interaction effect between bodyweight and antiplatelet was also tested in Cox model.

The adjusted variables, including age, gender, current or previous smoking, current or previous drinking, history of ischemic stroke or TIA, myocardial infarction, hypertension and hyperlipidemia, final diagnosis of an acute minor ischemic stroke or TIA, the use of lipid-lowering agents and antihypertension agents during 90-day follow-up period. All *p*-values were 2-sided, with values of $p<0.05$ considered

statistically significant. All statistical analyses were performed using SAS Version 9.4 software (SAS Institute, Cary, NC, USA). As this was a post hoc analysis, we considered these analyses to be hypothesis generating.

Search terms

[12] Stroke prevention; [13] Other cerebrovascular disease/stroke.

Results

Patient demographics and baseline characteristics

Among the 5,170 patients recruited in CHANCE, all the 3,420 (66.2%) male patients were included in this subgroup analysis. Participant demographics and characteristics are presented in Table 1. Patients with higher bodyweight were younger, more likely to be current or previous smokers and drinkers. They tended to have a history of TIA or ischemic stroke, myocardial infarction, hypertension, diabetes mellitus, and hypercholesterolemia, and most of them had TIA as a qualifying event. In addition, the rates of using antihypertensive at baseline were higher in patients included in the high-weight group, but the rates of using lipid-lowering-medicine were highest in the low-weight group. In each group, no significant difference was found with previous baseline information between DAT and MAT patients.

Efficacy outcomes

Overall, 320 patients (9.4%) in the current subgroup analysis had a primary efficacy outcome of recurrent stroke at 90 days. The relative proportion of patients with stroke recurrence was different between DAT and MAT in low bodyweight group (p=0.003) and middle bodyweight group (p=0.007), but no significant difference was found in high bodyweight group (p=0.172) (Figure 1). A similar result was found for CVE. In low and middle bodyweight groups, the risks with CVE in DAT and MAT were different (p=0.003 and p=0.007, respectively) but not in high bodyweight group (p=0.173) (Figure 2). As shown in Figure 3, significant interactions were found between bodyweight and randomized antiplatelet therapy in their effects on both stroke and CVE in low and middle bodyweight groups. In patients with low and middle bodyweight, combination therapy of clopidogrel and aspirin obviously reduced the occurrence of stroke and CVE compared with aspirin alone. The crude hazard ratio (HR) for clopidogrel plus aspirin vs aspirin alone on the primary outcome of any stroke in patients with low bodyweight was 0.41 (95% CI: 0.22–0.76) and the adjusted HR 0.41 (95% CI: 0.22–0.76). As in middle bodyweight group, the crude HR of total stroke for clopidogrel plus aspirin vs aspirin alone in patients with low bodyweight was 0.61 (95% CI: 0.42–0.88) and the adjusted HR 0.41 (95% CI: 0.43–0.89). However, in the patients with high bodyweight, no difference was found

Table 1 Demographic and clinical characteristics of patients according to the bodyweight in the current subgroup analysis of the CHANCE trial

Variables	Weight <65 kg		p-value	65 kg ≤ weight <75 kg		p-value	Weight ≥75 kg		p-value
	Clopidogrel-aspirin (n=301)	Aspirin (n=274)		Clopidogrel-aspirin (n=706)	Aspirin (n=688)		Clopidogrel-aspirin (n=725)	Aspirin (n=726)	
Age (years), mean ± SD	65.9±10.8	64.6±10.8	0.14	62.0±10.5	61.9±10.4	0.87	60.3±10.8	59.6±10.8	0.21
Medical history-no. (%)									
TIA or ischemic stroke	61 (20.3)	60 (21.9)	0.63	169 (23.9)	164 (23.8)	0.96	204 (28.1)	177 (24.4)	0.1
Myocardial infarction	8 (2.7)	3 (52.2)	0.17	14 (2.0)	20 (2.9)	0.26	14 (1.9)	18 (2.5)	0.48
Hypertension	164 (54.5)	143 (52.2)	0.58	433 (61.3)	417 (60.6)	0.78	517 (71.3)	501 (69.0)	0.34
Diabetes mellitus	40 (13.3)	39 (14.2)	0.74	108 (15.3)	133 (19.3)	0.05	166 (22.9)	158 (21.8)	0.6
Hypercholesterolemia	18 (6.0)	22 (8.0)	0.33	69 (9.8)	71 (10.3)	0.73	105 (14.5)	94 (13.0)	0.4
Current or previous smoking-no. (%)	183 (60.8)	163 (59.5)	0.75	433 (61.3)	413 (60.0)	0.62	459 (63.3)	471 (64.9)	0.53
Current or previous drinking-no. (%)	128 (42.5)	118 (43.1)	0.9	312 (44.2)	302 (43.9)	0.91	356 (49.1)	356 (49.0)	0.98
Qualifying event-no. (%)									
TIA	74 (24.6)	68 (24.8)	0.95	188 (26.6)	182 (26.5)	0.94	209 (28.8)	203 (28.0)	0.71
Minor stroke	227 (75.4)	206 (75.2)		518 (73.4)	506 (73.5)		516 (71.2)	523 (72.0)	
Secondary prevention-no./total (%)									
Anti-hypertension	91/277 (30.6)	87/271 (32.1)	0.71	247/701 (35.2)	217/681 (31.9)	0.18	258/725 (35.8)	256/720 (35.3)	0.84
Lowering-lipid	132/277 (44.4)	121/271 (44.7)	0.96	310/701 (44.2)	274/681 (40.2)	0.13	307/725 (42.6)	315/720 (43.5)	0.76

Abbreviations: CHANCE, Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events; TIA, transient ischemic attack.

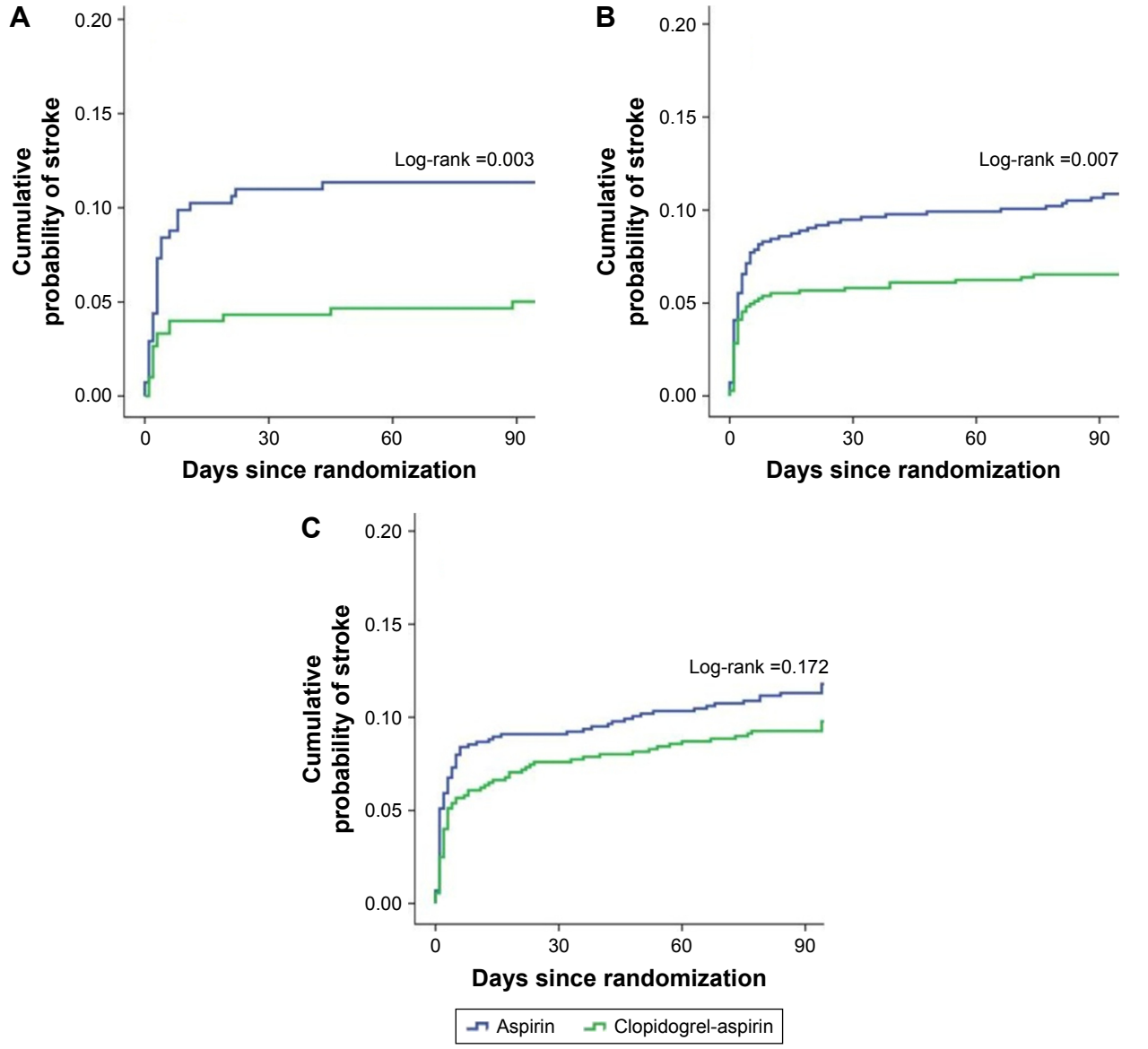

Figure 1 Kaplan–Meier curves for the primary efficacy outcome of any stroke.
Notes: Kaplan–Meier curves showing the time to the primary efficacy outcome event (any stroke) in patients with different bodyweight, treated with placebo plus aspirin, or clopidogrel plus aspirin. (**A**) Low bodyweight (weight <65 kg); (**B**) middle bodyweight (65 kg ≤ weight <75 kg); (**C**) high bodyweight (weight ≥75 kg).

in the rate of stroke or CVE between DAT and MAT. The crude HR of stroke was 0.80 (95% CI: 0.58–1.10) and the adjusted HR 0.80 (95% CI: 0.58–1.10).

Safety outcomes

The rates of the primary safety outcome of moderate-to-severe bleeding events at 90 days were both extremely low in the patients of 3 different weight groups as shown in Table 2. Moderate or severe hemorrhage, as defined by means of the GUSTO criteria, occurred in 2 patients with DAT and 1 patient with MAT in low bodyweight group. The rate of any bleeding event was 3.7% with DAT and 2.2% with MAT in low bodyweight group. No statistically significant evidence was found for the interaction on the effect of clopidogrel plus aspirin vs aspirin alone on bleeding events among patients with different bodyweight (Figure 3).

Discussion

In this subgroup analysis of the CHANCE trial, a better therapeutic response with DAT than MAT was found in male patients with low and middle bodyweight. Compared with MAT, DAT did not show superior benefit in high bodyweight patients. A significant interaction of bodyweight with randomized antiplatelet therapy was observed. DAT was not associated with an increase in incidence of bleeding events in all 3 bodyweight groups.

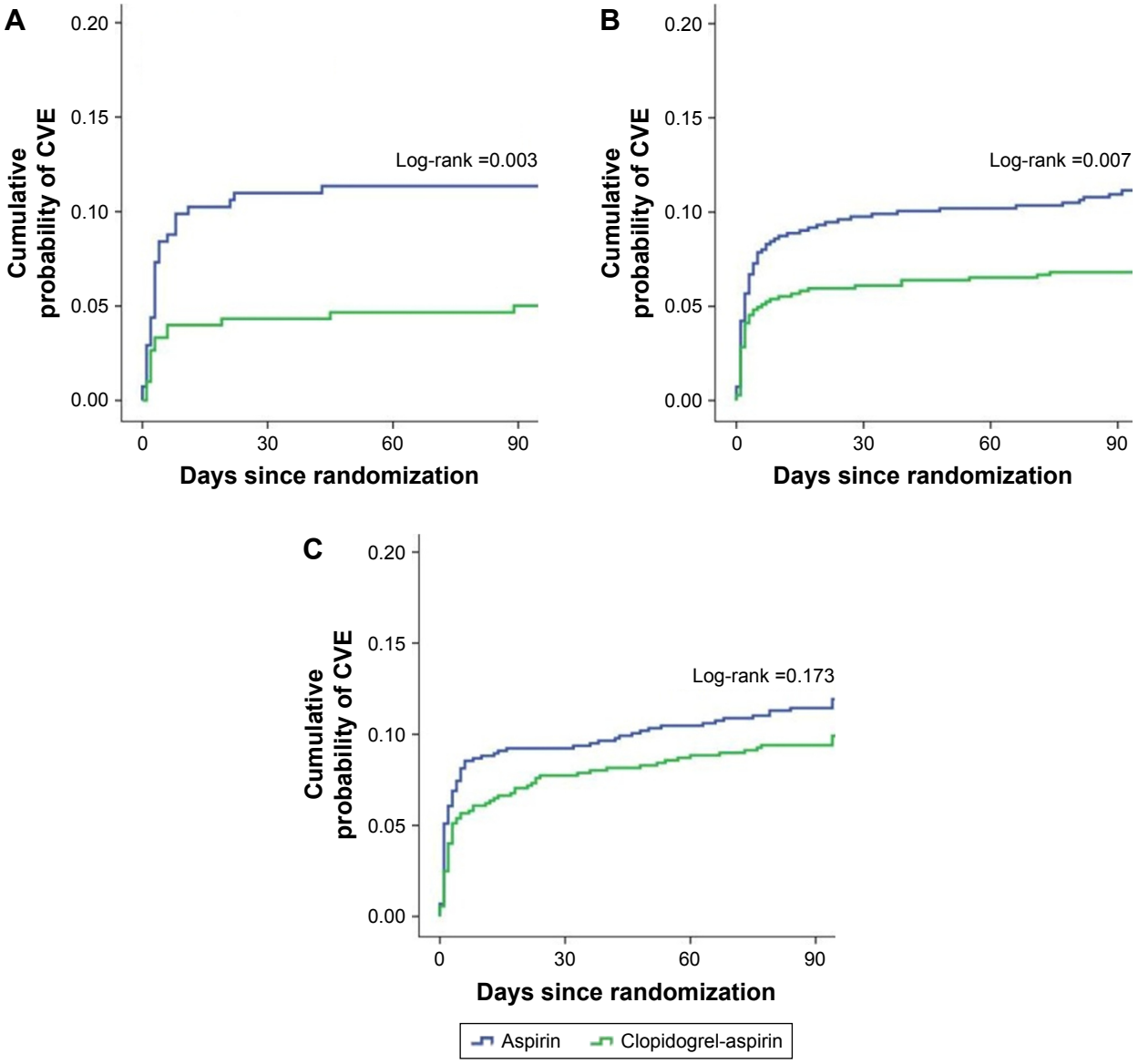

Figure 2 Kaplan–Meier curves for the secondary efficacy outcome of CVE.
Notes: Kaplan–Meier curves showing the time to the secondary efficacy outcome event (CVE) in patients with different bodyweight treated with placebo plus aspirin, or clopidogrel plus aspirin. (**A**) Low bodyweight (weight <65 kg); (**B**) middle bodyweight (65 kg ≤ weight <75 kg); (**C**) high bodyweight (weight ≥75 kg).
Abbreviation: CVE, combined vascular event.

DAT as the secondary prevention of stroke has been studied in many randomized controlled trials (RCTs). These RCTs were distinct from each other in design. Ongoing POINT trial is assessing a higher loading dose of clopidogrel (600 mg) than CHANCE.[14] The higher loading dose may be partly due to the bigger body size of the included population. The CHANCE and CLAIR trials which were conducted in Eastern populations preferred DAT, while CHARISMA and FASTER trials carried out in Western populations reported no advantage of DAT vs MAT.[1,3,6,7,14] No more benefits of DAT documented in Western population may be partly attributable to their higher bodyweight than Eastern populations. DAT using aspirin and clopidogrel is of great importance after acute non-disabling cerebrovascular events nowadays. But 1 antiplatelet therapy algorithm does not fit all. To identify patients with the risk of inadequate DAT is of significant clinical practice. Recently, as obesity and overweight are increasing, more and more researchers show interest in the effect of bodyweight on the effectiveness of antiplatelet therapy.[15–19]

The mechanisms responsible for the no superior effect with DAT in the high bodyweight population may be elucidated as follows. First, DAT is still not sufficient to prevent stroke events in heavier patients. So one underlying explanation for no difference between DAT vs MAT in high bodyweight group

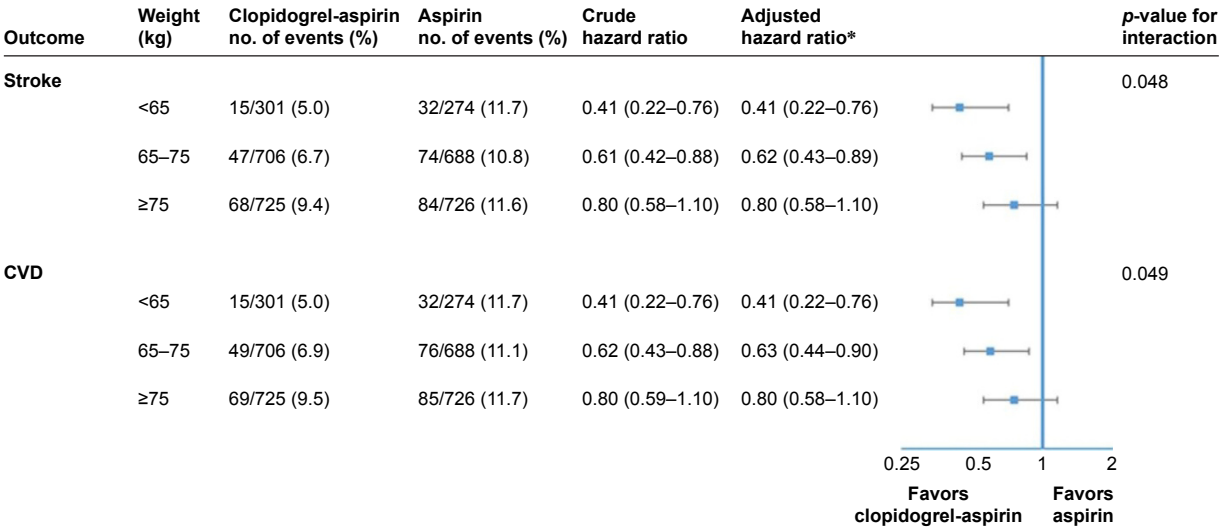

Figure 3 Hazard ratios for the primary and secondary end point.
Notes: Associations between antiplatelet treatment regime and efficacy outcomes in patients stratified by bodyweight. *Adjusted for age, gender, current or previous smoking, current or previous drinking, history of ischemic stroke or TIA, myocardial infarction, hypertension and hyperlipidaemia, final diagnosis of an acute minor ischemic stroke or TIA, the use of lipid lowering agents and antihypertension agents during 90-day follow-up period.
Abbreviations: CVD, cardiovascular disease; TIA, transient ischemic attack.

is the ceiling effect. Compared with some other pharmaceuticals in the market, antiplatelet agents are always prescribed in a uniform dosage, without conventional dose adjustments. From the practical standpoint, we should consider about dose modification for antiplatelet agents in different bodyweight patients. For the higher weight population, higher loading dose or triple therapy should be taken into account. Triple antiplatelet therapy vs DAT has been tested in several ongoing clinical trials.[5,20] There are few trials focussing on the effect of bodyweight on antiplatelet therapy. This study provides clues for the research in this direction. Second, the incidence of clopidogrel resistance may be higher in patients with high bodyweight. Clinical trials have reported that high residual platelet activation after clopidogrel administration increases the risk of recurrent vascular events.[21,22] The antiplatelet effect of $P2Y_{12}$-antagonists clopidogrel may depend on bodyweight in patients after ischemic stroke or TIA. In consideration of this potential mechanism, we may assess the effect of platelet function monitoring with treatment adjustment in overweight patients. And higher dose clopidogrel or novel $P2Y_{12}$-antagonists are needed to achieve sufficient platelet inhibition.

Table 2 Safety outcomes between clopidogrel-aspirin and aspirin alone treatment in patients stratified by bodyweight

Safety outcome[a]	Weight (kg)	Clopidogrel-aspirin no. of events (%)	Aspirin no. of events (%)
Any bleeding	<65	11/301 (3.7)	6/274 (2.2)
	65–75	9/706 (1.3)	9/688 (1.3)
	≥75	12/725 (1.7)	9/726 (1.2)
Severe bleeding	<65	1/301 (0.3)	1/274 (0.4)
	65–75	0/706 (0.0)	2/688 (0.3)
	≥75	1/725 (0.1)	1/726 (0.1)
Moderate bleeding	<65	1/301 (0.3)	0/274 (0.0)
	65–75	0/706 (0.0)	1/688 (0.2)
	≥75	1/725 (0.1)	1/726 (0.1)
Mild bleeding	<65	4/301 (1.3)	3/274 (1.1)
	65–75	5/706 (0.7)	3/688 (0.4)
	≥75	7/725 (1.0)	3/726 (0.4)

Note: [a]Safety outcomes was based on the GUSTO definition.
Abbreviation: GUSTO, global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

In present study, compared with MAT, DAT reduced the risk of stroke recurrence in low and middle bodyweight patients with minor stroke and TIA. The potential additional bleeding risk by DAT should also be assessed. The result showed that there was no significant difference in severe or mild bleeding among 3 groups. It indicates that DAT does not increase bleeding risk compared with MAT even in low bodyweight patients with minor stroke or TIA.

Limitations

This subgroup study has several limitations. First of all, the whole sample merely consisted of males, limiting broad applicability of findings. In addition, this was a subgroup analysis and may lack enough power to detect heterogeneities of treatment effects of DAT vs MAT among high weight patients. Furthermore, a large randomized and controlled clinical trial testing the effect of DAT on high weight population is needed to confirm this finding.

Conclusion

In summary, to compare the effects of clopidogrel plus aspirin vs aspirin alone in secondary prevention of ischemic stroke or TIA patients with different bodyweight is rarely reported out of practical significance. And the result of this subgroup study showed that there were no statistically significant effects of clopidogrel plus aspirin vs aspirin single in those bodyweight ≥75 kg. However, subgroup analyses can only generate hypotheses that should be tested in sufficiently powered RCTs. Therefore, our findings should be further validated in other populations because of this limitation.

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Disclosure

The authors report no conflicts of interest in this work.

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. Wong KS, Wang Y, Leng X, et al. Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis. *Circulation*. 2013;128(15):1656–1666.
3. Wong KS, Chen C, Fu J, et al; CLAIR study investigators. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol*. 2010;9(5):489–497.
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(7):2160–2236.
5. Bath PM, Appleton JP, Beridze M, et al. Baseline characteristics of the 3096 patients recruited into the 'Triple Antiplatelets for Reducing Dependency after Ischemic Stroke' trial. *Int J Stroke*. 2017;12(5):524–538.
6. Bhatt DL, Fox KA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354(16):1706–1717.
7. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007;6(11):961–969.
8. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9945):766–781.
9. Serena J, Segura T, Roquer J, Garcia-Gil M, Castillo J, Study A. The ARTICO study: identification of patients at high risk of vascular recurrence after a first non-cardioembolic stroke. *BMC Neurol*. 2015;15:28.
10. 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(3):380–386. e381.
11. Harris RZ, Benet LZ, Schwartz JB. Gender effects in pharmacokinetics and pharmacodynamics. *Drugs*. 1995;50(2):222–239.
12. The Nutrition and Chronic Desease Status of Chinese People (2015) [online]. Available from: http://www.nhfpc.gov.cn. Accessed November 01, 2016.
13. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med*. 1993;329:673–682.
14. Johnston SC, Easton JD, Farrant M, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. *Int J Stroke*. 2013;8(6):479–483.
15. Pankert M, Quilici J, Loundou AD, et al. Impact of obesity and the metabolic syndrome on response to clopidogrel or prasugrel and bleeding risk in patients treated after coronary stenting. *Am J Cardiol*. 2014;113(1):54–59.
16. Haberka M, Mizia-Stec K, Lasota B, Kyrcz-Krzemien S, Gasior Z. Obesity and antiplatelet effects of acetylsalicylic acid and clopidogrel in patients with stable angina pectoris after percutaneous coronary intervention. *Pol Arch Med Wewn*. 2015;125(9):620–630.
17. Garcia-Labbe D, Ruka E, Bertrand OF, Voisine P, Costerousse O, Poirier P. Obesity and coronary artery disease: evaluation and treatment. *Can J Cardiol*. 2015;31(2):184–194.
18. Badimon L, Hernandez Vera R, Padro T, Vilahur G. Antithrombotic therapy in obesity. *Thromb Haemost*. 2013;110(4):681–688.
19. Serebruany VL, Fortmann SD, Kim MH. Should the dose of antiplatelet drugs be adjusted for body weight? The example of vorapaxar. *Cardiology*. 2016;133(2):69–72.
20. TARDIS Trial Investigators, Krishnan K, Beridze M, et al. Safety and efficacy of intensive vs. guideline antiplatelet therapy in high-risk patients with recent ischemic stroke or transient ischemic attack: rationale and design of the Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial (ISRCTN47823388). *Int J Stroke*. 2015;10(7):1159–1165.
21. Sibbing D, von Beckerath O, Schomig A, Kastrati A, von Beckerath N. Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. *Am J Cardiol*. 2007;100(2):203–205.
22. Cuisset T, Frere C, Quilici J, et al. Relationship between aspirin and clopidogrel responses in acute coronary syndrome and clinical predictors of non response. *Thromb Res*. 2009;123(4):597–603.

Supplementary material

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