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ORIGINAL RESEARCH

Differential Effect of Ticagrelor Versus Clopidogrel by Causative Classification of Stroke Classification and Vascular Cellular Adhesion Molecule-1 Level on the Risk of Recurrent Stroke: A Post Hoc Analysis of the CHANCE-2 Trial

Hui Li, BS*; Xue Xia, PhD*; Qin Xu, PhD; Xia Meng, MD, PhD; Yongjun Wang, MD; Anxin Wang, PhD

BACKGROUND: VCAM-1 (vascular cellular adhesion molecule-1) is an inflammatory biomarker linked to the occurrence and recurrence of stroke. However, it is uncertain if dual antiplatelet treatments may have distinct benefit for patients with varied stroke causes and VCAM-1 levels.

METHODS: This post hoc study of the CHANCE-2 (Ticagrelor or Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events II) trial included 5651 patients in total. All patients were classified using the Causative Classification of Stroke system categorization as well as the mean of baseline VCAM-1 level. The primary outcome was any stroke within 90 days. During the 90-day follow-up period, the cumulative incidence of outcomes between 2 dual antiplatelet treatments was compared using the Kaplan–Meier analysis and log-rank test. The Cox proportional hazards model was used to further assess the hazard ratios (HRs) and 95% CIs for the associations of small artery occlusion cause and VCAM-1 level with efficiency and safety outcomes.

RESULTS: The median age of 5651 patients was 64.8 years, 1908 of whom were women. Among all the subtypes, patients with nonelevated VCAM-1 (<1715.9 ng/mL) and small artery occlusion subtype (N=1252) got more benefit from aspirin-ticagrelor therapy to reduce recurrent stroke within 90 days (7.5% versus 2.9%, hazard ratio [HR], 0.37 [95% CI, 0.22–0.64], P<0.001). Regarding safety outcomes, the risk of mild bleeding was increased in the ticagrelor-aspirin group (1.4% versus 6.7%, HR, 4.85 [95% CI, 2.36–9.96]), but no significant difference was found between the 2 groups in moderate or severe bleeding (0.6% versus 0.5%, HR, 0.75 [95% CI, 0.17–3.35]).

CONCLUSIONS: VCAM-1 level combined with ischemic stroke cause classification subtypes might predict the effect of ticagrelor-aspirin or clopidogrel-aspirin dual antiplatelet therapy in preventing recurrent stroke within 90 days in patients with minor ischemic stroke or transient ischemic attack carrying *CYP2C19* loss-of-function alleles. Patients with small artery occlusion subtype and nonelevated VCAM-1 received more clinical benefit from ticagrelor-aspirin versus clopidogrel-aspirin.

REGISTRATION: URL: http://www.clinicaltrials.gov; Unique Identifier: NCT04078737.

Key Words: recurrence ■ small artery occlusion ■ stroke ■ ticagrelor ■ vascular cellular adhesion molecule-1

Correspondence to: Yongjun Wang, MD, or Anxin Wang, PhD, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 119, South 4th Ring West Road, Fengtai District, Beijing 100070, China. Email: yongjunwang@ncrcnd.org.cn; wanganxin@bjtth.org

*H. Li and X. Xia contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- We report the potential interaction between dual antiplatelet therapy type, the inflammatory biomarker VCAM-1 (vascular cellular adhesion molecule-1) level, and pathogenetic ischemic stroke subtype or transient ischemic attack.
- Patients with small artery occlusion stroke subtype and nonelevated VCAM-1 might receive more clinical benefit from ticagrelor-aspirin compared with clopidogrel-aspirin treatment for preventing stroke recurrence.

What Are the Clinical Implications?

- Our findings suggest that combining the inflammatory biomarker VCAM-1 with imaging-based pathogenetic stroke subtype might better identify a subpopulation that is more likely to benefit from a specific dual antiplatelet therapy in comparison to other antiplatelet therapy options.

Nonstandard Abbreviations and Acronyms

CCS	Causative Classification of Stroke
CHANCE-2	Ticagrelor or Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events II
IS	ischemic stroke
LOF	loss of function
SAO	small artery occlusion
VCAM-1	vascular cellular adhesion molecule-1

Globally, stroke is the third greatest cause of death and is the foremost condition contributing to disability-adjusted life years related to the nervous system.[1,2] Although immediate medical interventions and effective rehabilitation for ischemic stroke (IS) have significantly reduced recurrence rates,[3] these rates remain relatively high.[4–6] It was estimated that 30% to 50% of IS recurrences occurred despite antiplatelet therapy.[7] Previous studies have looked into more effective antiplatelet strategies. For instance, the CHANCE-2 (Ticagrelor or Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events II) trial found that aspirin-ticagrelor is a more effective dual antiplatelet strategy for minor IS or transient ischemic attack (TIA) than aspirin-clopidogrel, which can modestly reduce the risk of stroke recurrence in patients within 3 months.[8]

Based on the previous SSS-TOAST (Stop Stroke Study and the Trial of ORG 10172 in Acute Stroke Treatment), the Causative Classification of Stroke (CCS) method improved stroke subtyping into 5 major categories, akin to TOAST: large-artery atherosclerosis with ≥50% stenosis, cardiac embolism, small artery occlusion (SAO), uncommon causes, and undetermined causes.[9,10] If there were multiple potential causes, this system would assign the patient to a subtype according to the most probable mechanism. This approach addressed the high proportion of undetermined classifications in the TOAST system and demonstrated strong reliability.[11–13] SAO, caused by occlusion of deep branch arteries, accounts for approximately 25% of IS cases,[14] with this percentage increasing to 31.3% in China.[15] A large-scale study based on a Japanese registry showed that in East Asian populations, the SAO subtype had the highest early stroke risk among TIA causes and was an independent predictor of early stroke recurrence.[16] The subanalysis of the READAPT (Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or TIA) study showed an overall favorable short-term prognosis after SAO was treated with dual antiplatelet therapy.[17] Compared with other IS subtypes, SAO is associated with longer survival and less severity, suggesting a favorable risk–benefit ratio for treatment and prognosis in these patients.[18,19] The CCS system incorporates multiple aspects of current diagnostic stroke evaluation (diffusion-weighted imaging, perfusion-weighted imaging, computed tomography and magnetic resonance angiography of extracranial and intracranial arteries, transthoracic and transesophageal echocardiography, and Holter monitoring) in a regulated manner to identify both causative and phenotypic subtypes.[20]

Moreover, the role of inflammation in stroke has been extensively studied, as it contributes to stroke risk through various interconnected mechanisms.[21–23] The VCAM-1 (vascular cellular adhesion molecule-1) is a protein that belongs to the immunoglobulin superfamily that canonically participates in the adhesion and transmigration of leukocytes to the interstitium during inflammation.[24] As a predictive biomarker in inflammatory and cardiovascular diseases, VCAM-1 has been validated in several studies.[25,26]

The CHANCE-2 study was designed for 2 dual antiplatelet strategies for patients with minor stroke or TIA who are *CYP2C19* loss-of-function (LOF) allele carriers, and this study is a post hoc analysis of the CHANCE-2 trial that followed its treatment groupings and aims to explore the precision treatment population further.

Stroke cause has been proven to be an important reference for stroke treatment. However, a subgroup analysis of the CHANCE-2 trial showed no significant differences in the efficiency of dual antiplatelet therapy in patients with different TOAST subtypes.[27] The combination of imaging material and inflammatory makers may affect the efficacy of dual antiplatelet medication, as per our team's previous post hoc analyses of the CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) and CHANCE-2 research.[28,29] It remained unclear whether patients with different stroke causes and VCAM-1 levels benefit differently from antiplatelet strategies. This study aimed to explore the impact of VCAM-1 levels combined with CCS subtypes on the efficacy and safety of dual antiplatelet therapies in reducing IS recurrence.

METHODS

Study Design and Participants

This study is a post hoc subgroup and interaction analysis of the CHANCE-2 trial. The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was approved by an institutional review committee and all the subjects gave informed consent. A detailed description of the study design and methods of the CHANCE-2 trial has been published previously.[8,30] In brief, CHANCE-2 was a randomized, double-blind, double-dummy, placebo-controlled, multicenter trial conducted at 202 centers in China from September 23, 2019, to March 22, 2021, which compared 2 dual antiplatelet strategies for patients with minor IS or TIA who are *CYP2C19* LOF allele carriers. Finally, 6412 patients were enrolled in the CHANCE-2 study, and the inclusion criteria were as follows: (1) patients aged ≥40 years; (2) with acute nondisabling IS (National Institutes of Health Stroke Scale score ≤3) or high-risk TIA (ABCD^2 [age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes] score ≥4); (3) carrying the *CYP2C19* LOF alleles; (4) treated with 1 of the study drugs within 24 hours of symptom onset; and (5) signed informed consent.[30] We excluded 761 patients with missing data on CCS classification and VCAM-1 measurement (Figure 1).

The trial protocol was approved by the ethics committee of Beijing Tiantan Hospital (institutional review approval number: KY2019-035-02) and each participating center. All patients or their representatives signed a written informed consent form before enrollment. The trial was registered at ClinicalTrials.gov (Registration URL: http://www.clinicaltrials.gov), under the unique identifier NCT04078737.

Randomization and Treatment

Eligible patients were randomly assigned in a 1:1 ratio to receive placebo clopidogrel plus ticagrelor (180-mg loading dose on day 1, followed by 90 mg twice daily for days 2–90) or placebo ticagrelor plus clopidogrel (300-mg loading dose on day 1, followed by 75 mg twice daily for days 2–90). Patients were randomly assigned a number corresponding to a medication kit that was given to each patient. Both groups received a 75- to 300-mg loading dose of aspirin on day 1, followed by 75 mg daily for 21 days.

Measurement of VCAM-1 and Causative Classification of Stroke

Baseline data for the patient's demographic characteristics, medical history, physical examination findings, medical treatments, and National Institutes of Health Stroke Scale score were collected after admission through in-person interviews by trained neurologists at participating hospitals. Peripheral venous blood was drawn the first time after enrollment at each center and all samples were transported through cold chain to the central laboratory in Beijing Tiantan Hospital for analysis of VCAM-1. We performed a normality test on the VCAM-1 data collected in the CHANCE-2 trial and found that the VCAM-1 level was normally distributed in the whole population (Figure S1). We believed that the average better reflects the central trend of the data, so the patients were then classified as low VCAM-1 and high VCAM-1 groups based on the mean level of VCAM-1.

Patients completed a brain magnetic resonance imaging examination of all sequences (T1+T2+fluid-attenuated inversion recovery+diffusion weighted imaging+apparent diffusion coefficient+gradient echo sequence-T2*) within 72 hours after enrollment. All images were saved in Digital Imaging and Communications in Medicine format and transmitted to the central imaging laboratory for evaluation. All patients were classified by the CCS system classification as SAO and non-SAO type at the time of analysis. The interpretations of the clinical and imaging data, and the CCS classifications, were centralized and performed by experienced neurologists in Beijing Tiantan Hospital.

Efficacy and Safety Outcome

Patients were followed up at 90 days by trained site coordinators. The primary efficacy outcome of this study was any new stroke (IS or hemorrhagic stroke) within 3 months. Secondary efficacy outcomes were new stroke within 30 days, composite vascular events (stroke, TIA, myocardial infarction, and vascular death), IS, and disabling stroke (with a subsequent Modified

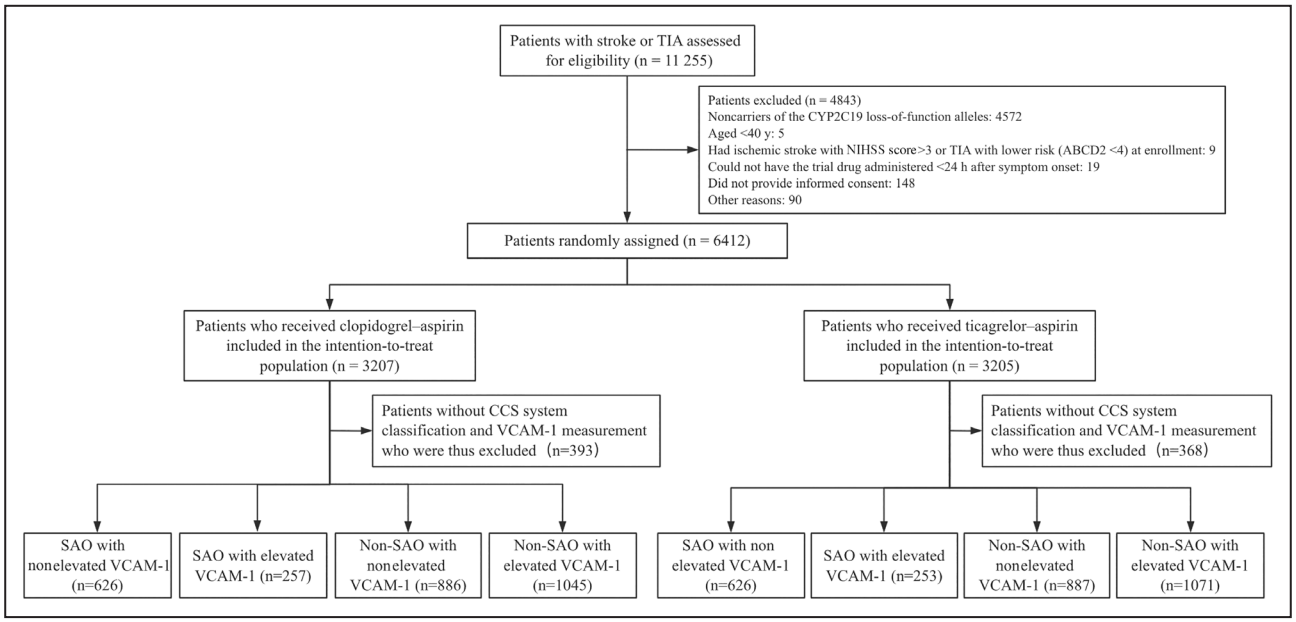

Figure 1. Diagram showing the flow of patients through the current study.
CSS indicates Causative Classification of Stroke; NIHSS, National Institutes of Health Stroke Scale; SAO, small artery occlusion; TIA, transient ischemic attack; and VCAM-1, vascular cell adhesion molecule 1.

Rankin Scale score of ≥2 and a range of 0–6, with higher scores reflecting worse outcomes) at 90 days. The primary safety outcome of this study was severe or moderate bleeding defined by the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries).[31] The secondary safety outcomes were any bleeding and mild bleeding.

Statistical Analysis

Continuous variables were expressed as medians and quartiles, and categorical variables were presented as frequency and percentage. A cutoff value of 1715.9 ng/mL (mean value) was established for VCAM-1, with levels above this indicating high inflammation. Patients in this study were categorized into 4 subgroups: the first subgroup with nonelevated VCAM-1 level and SAO cause, the second subgroup with elevated VCAM-1 level and non-SAO cause, the third subgroup with nonelevated VCAM-1 level and SAO cause, and the fourth subgroup with elevated VCAM-1 level and non-SAO cause. Data from patients with no events during the study were censored at trial termination or at the time of nonvascular death. When there were multiple events of the same type, the time to the first event was used in the model. We performed the Schoenfeld residual test before building the model and the results satisfied the proportional hazards assumption (P=0.10). Kaplan–Meier analysis was used to calculate the cumulative incidence of the primary outcome for the 2 dual antiplatelet therapies over the 90-day follow-up period, and the log-rank test was adopted to assess differences in survival curves between 2 treatment groups in each subgroup. Moreover, the multivariable Cox regression model was used to calculate hazard ratios (HRs) and 95% CIs for the associations of dual antiplatelet therapies with efficiency and safety outcomes during the 90-day follow-ups among SAO causes and VCAM-1 levels subgroups, with adjustment for sex and age. The multiplicative interaction of dual antiplatelet therapies with subgroups defined by stroke cause and VCAM-1 levels was assessed by introducing a cross-product term in the Cox model, and the P value for multiplicative interaction was calculated using the likelihood ratio test.

To ensure the robustness of the findings, 4 sensitivity analyses were conducted: (1) body mass index, medical history (hypertension, diabetes, dyslipidemia, previous ischemic stroke or TIA, myocardial infarction, angina), current smoking, type of *CYP2C19* LOF allele carrier, the median time from symptom onset to randomization, National Institutes of Health Stroke Scale score at 1 day after randomization, previous lipid-lowering therapy, previous antihypertensive therapy, previous antidiabetic therapy were further adjusted; (2) baseline VCAM-1 values was added as covariates to the primary model to avoid confounding caused by inconsistent VCAM-1 levels among participants in different groups; (3) TOAST system was adopted to

reclassify the cause of stroke or TIA, and the results of the reclassifying were incorporated into the model for analysis; and (4) the median of VCAM-1was used as the cutoff value to avoid artificially defined VCAM-1 cutoff (mean) affecting the results.

A 2-tailed *P* value of <0.05 was used to determine statistical significance. All analyses were performed using the Statistical Analysis System software V.9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics

Of the 6412 patients enrolled in the CHANCE-2 trial, 761 patients (393 in the clopidogrel-aspirin group and 368 in the ticagrelor-aspirin group) who lacked CCS system classification /or VCAM-1 measurement were excluded from this substudy. Treatment was discontinued prematurely in 527 patients due to adverse events, contraindicated medication requirements, or investigator-initiated withdrawal. All patients completed 90-day follow-up, and data from those who discontinued treatment were retained in the intention-to-treat analyses. Ultimately, 5651 patients were included in the final analysis (Figure 1).

Among the patients included in this study, the mean value of VCAM-1 was 1715.9 ng/mL; 2626 patients had high VCAM-1, 3025 patients had lower VCAM-1, 1762 patients were classified as SAO types and 3889 patients as non-SAO. In summary, there were 1252 patients in the group with SAO with nonelevated VCAM-1, 510 patients in the group with SAO with elevated VCAM-1, 1773 patients in the group with non-SAO with nonelevated VCAM-1, and 2116 patients in the group with non-SAO with elevated VCAM-1. The baseline characteristics of patients with different groups and treatment allocations are shown in Table 1.

Efficacy Outcomes

Within 90 days, 227 patients (8.1%) treated with clopidogrel-aspirin and 168 patients (5.9%) treated with ticagrelor-aspirin experienced a stroke recurrence. A significant interaction effect between stroke causes combined with VCAM-1 levels and dual antiplatelet therapies was observed on the efficacy outcome of recurrent stroke and composite vascular event ($P_{\text{for interaction}}$=0.02). Compared with clopidogrel-aspirin, ticagrelor-aspirin significantly reduced the risk of recurrent stroke in individuals with SAO and nonelevated VCAM-1 levels (2.9% versus 7.5%; HR, 0.37 [95% CI, 0.22–0.64], *P*<0.001). However, no additional benefit from ticagrelor-aspirin was found in patients in the group with SAO and elevated VCAM-1 (HR, 0.79 [95% CI0.41–1.53], *P*=0.50), group with non-SAO and non-elevated VCAM-1 (HR, 0.79 [95% CI0.55–1.15], *P*=0.23), and group with non-SAO and elevated VCAM-1 (HR, 0.83 [95% CI0.62–1.11], *P*=0.21) (Figure 2; Table 2). Similar results existed for the secondary outcomes of stroke within 30 days, composite vascular events, and IS within 90 days of follow-up (Table 2).

The results of the sensitivity analysis were consistent with those of the main analysis. With further adjustment, the HR for recurrent stroke in the patients taking ticagrelor-aspirin in the group with SAO and the nonelevated VCAM-1 was 0.34 (95% CI, 0.19–0.61) compared with clopidogrel-aspirin (Table S1). After adjusting the baseline VCAM-1 level, the HR for recurrent stroke in the patients taking ticagrelor-aspirin in the group with SAO and the nonelevated VCAM-1 was 0.37 (95% CI, 0.22–0.64) compared with clopidogrel-aspirin (Table S2). In similar, after the reclassification of stroke or TIA using the TOAST system, the HR for recurrent stroke in the ticagrelor-aspirin group compared with the clopidogrel-aspirin group was 0.38 (95% CI, 0.21–0.66) in the group with SAO and nonelevated VCAM-1 (Table S3). And after reanalyzing the model using the median of VCAM-1, the HR for recurrent stroke in the ticagrelor-aspirin group compared with the clopidogrel-aspirin group was 0.37 (95% CI, 0.21–0.65) in the group with SAO and nonelevated VCAM-1 (Table S4).

Safety Outcomes

The primary safety outcome severe or moderate bleeding was similar between patients taking clopidogrel-aspirin and ticagrelor-aspirin in all 4 groups: SAO and nonelevated VCAM-1 (0.6% versus 0.5%, HR, 0.75 [95% CI, 0.17–3.35]), SAO and elevated VCAM-1 (0.8% versus 0.8%, HR, 0.90 [95% CI, 0.13–6.41]), non-SAO and nonelevated VCAM-1 (0.2% versus 0.1%, HR, 0.52 [95% CI, 0.05–5.69]), and non-SAO and elevated VCAM-1 (0.3% versus 0.3%, HR, 0.94 [95% CI, 0.19–4.68]) (Table 2). Similar results were yielded for any bleeding. Patients in the ticagrelor-aspirin group had increased risk of mild bleeding in all 4 groups: SAO and nonelevated VCAM-1 (1.4% versus 6.7%, HR=4.85, [95% CI=2.36–9.96]), SAO and elevated VCAM-1 (1.6% versus 5.1%, HR, 3.53 [95% CI, 1.15–10.82), non-SAO and nonelevated VCAM-1 (3.1% versus 5.5%, HR, 1.82 [95% CI, 1.14–2.91]), and non-SAO and elevated VCAM-1 (2.5% versus 4.7%, HR, 1.90 [95% CI, 1.84–3.06]). Sensitivity analyses were consistent with the main analysis (Tables S1 through S4).

DISCUSSION

Post hoc analysis of the CHANCE-2 trial indicated that the combined with VCAM-1 levels and CCS subtypes

Table 1. Baseline characteristics of patients receiving different treatments, stratified according to vascular cell adhesion molecule 1 levels and small artery occlusion of causative classification of stroke system

Characteristics	SAO with nonelevated VCAM-1		SAO with elevated VCAM-1		Non-SAO with nonelevated VCAM-1		Non-SAO with elevated VCAM-1	
	(n=1252)		(n=510)		(n=1773)		(n=2116)	
	Clopidogrel-aspirin (n=626)	Ticagrelor-aspirin (n=626)	Clopidogrel-aspirin (n=257)	Ticagrelor-aspirin (n=253)	Clopidogrel-aspirin (n=886)	Ticagrelor-aspirin (n=887)	Clopidogrel-aspirin (n=1045)	Ticagrelor-aspirin (n=1071)
Median age, y (IQR)	62.9 (55.6–68.4)	62.5 (55.4–68.4)	64.8 (55.9–71.0)	65.9 (57.5–71.5)	64.5 (56.7–70.8)	64.5 (56.9–70.7)	66.3 (58.7–73.2)	66.3 (58.0–73.5)
Male sex, no. (%)	431 (68.9)	431 (68.9)	183 (71.2)	185 (73.1)	569 (64.2)	548 (61.8)	688 (65.8)	708 (66.1)
Han Chinese ethnic group, no. (%)	607 (97.0)	614 (98.1)	252 (98.1)	249 (98.4)	871 (98.3)	871 (98.2)	1027 (98.3)	1049 (98.0)
Medical history, no. (%)								
Previous ischemic stroke	106 (16.9)	102 (16.3)	43 (16.7)	43 (17.0)	213 (24.0)	198 (22.3)	246 (23.5)	262 (24.5)
Previous TIA	6 (1.0)	2 (0.3)	0 (0.0)	1 (0.4)	17 (1.92)	17 (1.92)	15 (1.4)	23 (2.2)
Myocardial infarction	6 (1.0)	3 (0.5)	2 (0.8)	5 (2.0)	10 (1.1)	18 (2.0)	19 (1.8)	14 (1.3)
Angina	13 (2.1)	14 (2.2)	5 (2.0)	6 (2.4)	30 (3.4)	32 (3.6)	31 (3.0)	21 (2.0)
Hypertension	363 (58.0)	377 (60.2)	160 (62.3)	148 (58.5)	568 (64.2)	565 (63.7)	671 (64.2)	674 (63.0)
Diabetes	130 (20.8)	160 (25.6)	54 (21.0)	57 (22.5)	208 (23.5)	199 (22.4)	269 (25.7)	298 (27.8)
Dyslipidemia	60 (9.58)	58 (9.27)	18 (7.0)	19 (7.5)	85 (9.6)	87 (9.8)	99 (9.5)	123 (11.5)
Current or previous smoker, no. (%)	264 (42.2)	253 (41.4)	111 (43.2)	123 (48.6)	319 (36.0)	335 (37.8)	388 (37.1)	389 (36.3)
Type of *CYP2C19* loss-of-function allele carrier, no. (%)								
Intermediate metabolizers	488 (78.0)	488 (78.0)	207 (80.5)	197 (77.9)	699 (78.9)	680 (76.7)	820 (78.5)	848 (79.2)
Poor metabolizers	138 (22.0)	138 (22.0)	50 (19.5)	56 (22.1)	187 (21.1)	207 (23.3)	225 (21.5)	223 (20.8)
Median time from symptom onset to randomization, hr (IQR)	16.6 (10.0–21.5)	14.6 (10.7–21.2)	16.7 (10.1–22.0)	15.4 (10.3–20.7)	13.7 (8.6–20.0)	13.5 (8.4–20.1)	13.3 (8.5–19.9)	13.0 (8.6–20.2)
Qualifying event, no. (%)								
TIA	32 (5.1)	27 (4.3)	9 (3.5)	13 (5.1)	240 (27.1)	235 (26.5)	227 (21.7)	263 (24.6)
Ischemic stroke	594 (94.9)	599 (95.7)	248 (96.5)	240 (94.9)	646 (72.9)	652 (73.5)	818 (78.3)	808 (75.4)
Median body mass index, kg/m^2 (IQR)	24.2 (22.5–26.6)	24.6 (22.8–26.7)	24.3 (22.3–26.7)	24.5 (22.9–26.6)	24.6 (22.8–26.7)	24.7 (22.9–26.7)	24.2 (22.5–26.2)	24.2 (22.5–26.6)
Median blood pressure, mm Hg (IQR)								
Systolic	151 (138–165)	151 (138–167)	152.5 (138–166)	151.5 (138–164)	149.5 (137–163)	150 (139–164)	150 (136–165)	148.5 (137–165)
Diastolic	89 (80–99)	90 (81–99)	90 (81–99)	86 (80–94)	89.5 (80–96)	88.5 (80–96)	86.5 (79–96)	86.5 (80–95)
Median NIHSS score on admission (IQR)*	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–2)	2 (1–3)	2 (1–3)
Medications, no. (%)†								
Antihypertensive	247 (39.5)	251 (40.1)	90 (35.0)	91 (36.0)	366 (41.3)	364 (41.0)	433 (41.4)	443 (41.4)
Antidiabetic	106 (16.9)	127 (20.3)	47 (18.3)	48 (19.0)	167 (18.9)	156 (17.6)	214 (20.5)	232 (21.7)
Lipid-lowering	44 (7.0)	39 (6.2)	13 (5.1)	13 (5.1)	69 (7.8)	66 (7.4)	92 (8.8)	110 (10.3)
Proton pump inhibitors	96 (15.3)	126 (20.1)	48 (18.7)	66 (26.1)	175 (19.8)	167 (18.8)	240 (23.0)	245 (22.9)
Symptomatic intracranial-artery stenosis, no. (%)	103 (16.7)	109 (17.8)	51 (20.6)	39 (15.6)	430 (50.0)	442 (51.7)	513 (51.4)	544 (52.8)
Symptomatic extracranial artery stenosis, no. (%)	24 (3.9)	32 (5.2)	10 (4.0)	8 (3.2)	97 (11.3)	94 (11.0)	88 (8.8)	125 (12.1)

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; SAO, small artery occlusion; TIA, transient ischemic attack; and VCAM-1, vascular cell adhesion molecule 1.

*Median NIHSS score in patients with qualifying ischemic stroke. NIHSS scores range from 0 to 42, with higher scores indicating more severe stroke.

†Medication within 1 mo before symptom onset.

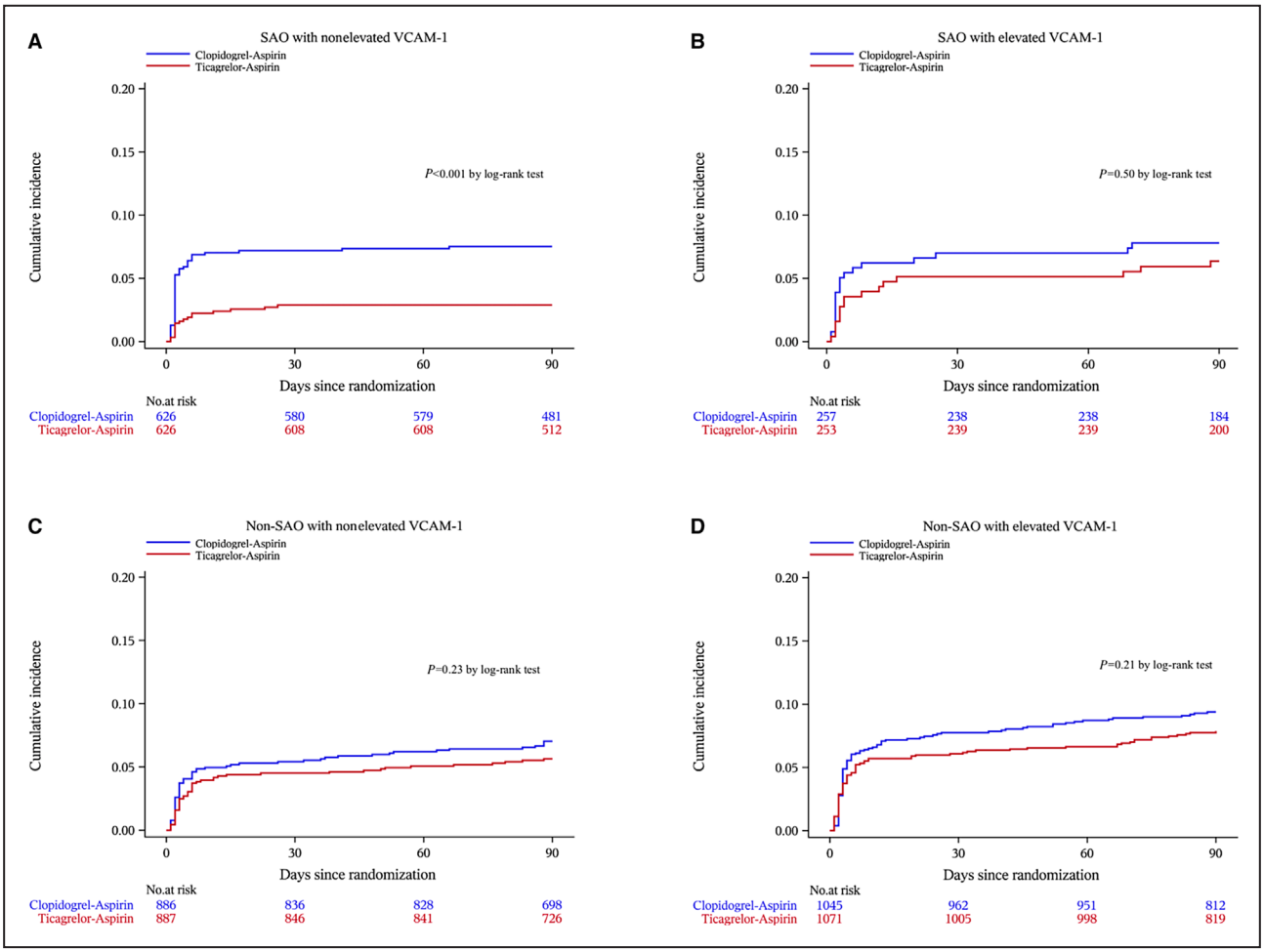

Figure 2. Cumulative incidence of stroke recurrence according to VCAM-1 levels and SAO cause of CCS system.
A, Cumulative incidence of stroke recurrence in group SAO with nonelevated VCAM-1. **B**, Cumulative incidence of stroke recurrence in group SAO with elevated VCAM-1. **C**, Cumulative incidence of stroke recurrence in group non-SAO with nonelevated VCAM-1. **D**, Cumulative incidence of stroke recurrence in group non-SAO with elevated VCAM-1. CCS indicates Causative Classification of Stroke; SAO, small artery occlusion; and VCAM-1, vascular cell adhesion molecule 1.

was linked to greater efficacy of ticagrelor-aspirin treatment compared with clopidogrel-aspirin treatment in patients with minor IS or TIA carrying *CYP2C19* LOF alleles. Ticagrelor-aspirin showed ~63% reduction in the risk of recurrent stroke for patients with SAO and nonelevated VCAM-1 levels compared with clopidogrel-aspirin, without raising the risk of moderate or severe bleeding events. However, other patient groups, such as those with elevated VCAM-1 levels or non-SAO classifications, did not benefit from this advantage. Sensitivity analyses that adjusted for multiple covariates validated these results.

The CHANCE-2 study's prespecified analysis showed that ticagrelor-aspirin's effectiveness in preventing new strokes was consistent across all TOAST subtypes,[27] despite the fact that cause classification has guided stroke treatment.[32] Evidence from the phase II PRINCE trial (Platelet Reactivity in Acute Nondisabling Cerebrovascular Events) showed significantly lower rates of stroke recurrence at 90 days in the ticagrelor-aspirin group compared with the clopidogrel-aspirin group among patients with large-artery atherosclerosis.[33] Nevertheless, studies examining the impact of different stroke subtypes on recurrence rates have yielded inconsistent results. Numerous studies have examined the role of inflammation in the pathophysiology of stroke, and inflammatory markers are acknowledged as significant risk factors for recurrent IS and TIA.[28,34,35] Thus, we assumed that the introduction of stroke causes combined with VCAM-1 levels may improve the discrimination ability of response to different dual antiplatelet therapies in patients with minor stroke or TIA. Our result indicated that ticagrelor-aspirin therapy provides greater benefit in patients with SAO combined with nonelevated VCAM-1 levels.

The precise processes that underlie these findings are yet unknown. Possible mechanisms might be as follows: Ticagrelor is the first reversible oral P2Y12

Table 2. Efficacy and safety outcomes of aspirin plus ticagrelor compared with aspirin plus clopidogrel on clinical endpoints, stratified by vascular cell adhesion molecule 1 levels and small artery occlusion cause of causative classification of stroke system

Outcome	SAO with nonelevated VCAM-1			SAO with elevated VCAM-1			Non-SAO with nonelevated VCAM-1			Non-SAO with elevated VCAM-1			$P_{\text{for interaction}}$
	Clopidogrel-aspirin no. (%)	Ticagrelor-aspirin no. (%)	HR (95% CI)*	Clopidogrel-aspirin no. (%)	Ticagrelor-aspirin no. (%)	HR (95% CI)*	Clopidogrel-aspirin no. (%)	Ticagrelor-aspirin no. (%)	HR (95% CI)*	Clopidogrel-aspirin no. (%)	Ticagrelor-aspirin no. (%)	HR (95% CI)*	
Primary outcome													
Stroke	47 (7.5)	18 (2.9)	0.37 (0.22–0.64)	20 (7.8)	16 (6.3)	0.79 (0.41–1.53)	62 (7.0)	50 (5.6)	0.79 (0.55–1.15)	98 (9.4)	84 (7.8)	0.83 (0.62–1.11)	0.02
Secondary outcome													
Stroke within 30 d	45 (7.2)	18 (2.9)	0.39 (0.23–0.67)	18 (7.0)	13 (5.1)	0.72 (0.35–1.46)	48 (5.4)	40 (4.5)	0.82 (0.54–1.25)	81 (7.8)	65 (6.1)	0.78 (0.56–1.08)	0.04
Composite vascular events	51 (8.2)	23 (3.7)	0.44 (0.27–0.72)	22 (8.6)	16 (6.3)	0.72 (0.38–1.38)	87 (9.8)	70 (7.9)	0.79 (0.57–1.08)	110 (10.5)	97 (9.1)	0.85 (0.65–1.12)	0.03
Ischemic stroke	45 (7.2)	18 (2.9)	0.39 (0.23–0.67)	19 (7.4)	15 (5.9)	0.79 (0.40–1.56)	60 (6.8)	49 (5.5)	0.80 (0.55–1.17)	98 (9.4)	84 (7.8)	0.83 (0.62–1.11)	0.03
Disabling stroke	12 (1.9)	7 (1.1)	0.57 (0.23–1.55)	8 (3.1)	6 (2.4)	0.76 (0.26–2.19)	25 (2.8)	31 (3.5)	1.22 (0.72–2.07)	37 (3.5)	46 (4.3)	1.20 (0.78–1.85)	0.15
Safety outcome													
Severe or moderate bleeding	4 (0.6)	3 (0.5)	0.75 (0.17–3.35)	2 (0.8)	2 (0.8)	0.90 (0.13–6.41)	2 (0.2)	1 (0.1)	0.52 (0.05–5.69)	3 (0.3)	3 (0.3)	0.94 (0.19–4.68)	0.89
Any bleeding	13 (2.1)	45 (7.2)	3.59 (1.94–6.66)	6 (2.3)	15 (5.9)	2.68 (1.04–6.92)	29 (3.3)	50 (5.6)	1.73 (1.10–2.74)	29 (2.8)	53 (5.0)	1.80 (1.15–2.83)	0.06
Mild bleeding	9 (1.4)	42 (6.7)	4.85 (2.36–9.96)	4 (1.6)	13 (5.1)	3.53 (1.15–10.82)	27 (3.1)	49 (5.5)	1.82 (1.14–2.91)	26 (2.5)	50 (4.7)	1.90 (1.84–3.06)	0.03

HR indicates hazard ratio; SAO, small-artery occlusion; and VCAM-1, vascular cell adhesion molecule 1.
*Adjusted for age and sex.

antagonist that directly targets the P2Y12 receptor without requiring hepatic biotransformation, resulting in a rapid onset of action. In contrast, the prodrug clopidogrel requires hepatic conversion, which results in delayed metabolite activation and significant individual variation in platelet inhibition.[36,37] Several potential mechanisms contributed to the pathogenesis of SAO, including lipohyalinosis, atherosclerotic disease, and cardioembolism.[11] The prognosis for patients with SAO is often linked to branch atherothrombosis; the diameter of the affected blood vessels is smaller than that of large arteries.[17] Consequently, patients with the SAO subtype are likely to exhibit less concurrent arteriosclerosis or smaller thrombi, making the advantages of ticagrelor as a rapid response antiplatelet agent more pronounced. Moreover, VCAM-1 plays a crucial role in mediating the adhesion between endothelial cells and leukocytes, with elevated levels indicating chronic inflammatory activation of the endothelium.[38] Such inflammatory processes can promote platelet activation through increased immune complexes, autoantibodies, and damage-associated molecular patterns.[39,40] Notably, the increased risk of thrombosis and cardiovascular disease is mostly attributed to platelet activation.[41] Patients with relatively low inflammation tend to lower platelet activation, which in turn leads to lower platelet aggregation. This makes it possible to observe ticagrelor's quick antiplatelet effects. Even while ticagrelor acts quickly, the severity of the underlying lesion may reduce its overall effectiveness in patients with elevated VCAM-1 levels.

Our study still had some limitations. First, this analysis included only 5651 patients who completed CCS system classification and blood measurement, representing only 88.1% of all patients of the CHANCE-2 trial, which may have caused selection bias. However, no significant difference in the baseline data was found between the included population and the entire CHANCE-2 study population. Second, fasting blood measurements of VCAM-1 were collected only at the time of admission but were not continuously measured during the follow-up period, and the changes in VCAM-1 levels over time and the effect of changes on efficiency of antiplatelet therapy and stroke outcomes could not be obtained. In addition, we use the mean as a cutoff value to group VCAM-1 levels, which is an artificial operation. Third, based on the grouping of patients in this study, the non-SAO group included 4 other stroke causes except the SAO cause, and further research is needed to clarify the differences between different causes. Fourth, this study was a post hoc analysis of the CHANCE-2 trial, and the exploratory nature of this analysis could increase the risk of a type I error.[42] Thus, our results need to be verified in other studies. Finally, the CHANCE-2 trial included only Chinese patients, which may limit the applicability of the findings to other populations.

CONCLUSIONS

This post hoc analysis of the CHANCE-2 trial suggested that combining VCAM-1 levels with IS causes classification subtypes that may help predict the effectiveness of ticagrelor-aspirin or clopidogrel-aspirin dual antiplatelet therapy in preventing recurrent strokes within 90 days in patients with minor IS or TIA who carried *CYP2C19* LOF alleles. In particular, patients with the SAO subtype and nonelevated VCAM-1 levels benefit more from ticagrelor-aspirin than from clopidogrel-aspirin. Further trials are needed to explore the mechanisms by which cell adhesion molecule levels and stroke cause influence the efficacy of antiplatelet therapy.

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Affiliations

Department of Neurology, Beijing Tiantan Hospital (H.L., X.X., Q.X., X.M., Y.W., A.W.), China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital (H.L., X.X., Q.X., X.M., Y.W., A.W.), and Department of Clinical Epidemiology and Clinical Trial (H.L., X.X., Q.X., X.M., Y.W., A.W.), Capital Medical University, Beijing, China; and Department of Epidemiology, Beijing Neurosurgical Institute, Beijing Tiantan Hospital, Capital Medical University, Beijing, China (X.X., Q.X., A.W.).

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Disclosures

None.

Supplemental Material

Tables S1–S4
Figure S1

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