JoS JOURNAL OF STROKE

Journal of Stroke 2024;26(2):231-241
https://doi.org/10.5853/jos.2024.00367

Original Article

The Influence of Non–High-Density Lipoprotein Cholesterol on the Efficacy of Genotype-Guided Dual Antiplatelet Therapy in Preventing Stroke Recurrence

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Background and Purpose Non-high-density lipoprotein cholesterol (non-HDL-C), which represents the total cholesterol content of all pro-atherogenic lipoproteins, has recently been included as a new target for lipid-lowering therapy in high-risk atherosclerotic patients in multiple guidelines. Herein, we aimed to explore the relationship between non-HDL-C level and the efficacy and safety of ticagrelor-aspirin versus clopidogrel-aspirin in preventing stroke recurrence.

Methods This study comprised a *post hoc* analysis of the CHANCE-2 (Ticagrelor or Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II) trial, from which 5,901 patients with complete data on non-HDL-C were included and categorized by median non-HDL-C levels, using a cutoff of 3.5 mmol/L. The primary efficacy and safety outcomes were recurrent stroke and severe or moderate bleeding within 90 days.

Results Ticagrelor-aspirin significantly reduced the risk of recurrent stroke in patients with low non-HDL-C (71 [4.8%] vs. 119 [7.7%]; adjusted hazard ratio [HR] 0.54; 95% confidence interval [CI], 0.40–0.74), but not in those with high non-HDL-C (107 [7.3%] vs. 108 [7.6%]; adjusted HR, 0.88; 95% CI, 0.67–1.16), compared with clopidogrel-aspirin (*P* for interaction=0.010). When analyzed as a continuous variable, the benefit of ticagrelor-aspirin for recurrent stroke decreased as non-HDL-C levels increased. No significant differences in the treatment assignments across the non-HDL-C groups were observed in terms of the rate of severe or moderate bleeding (5 [0.3%] vs. 8 [0.5%] in the low non-HDL-C group; 4 [0.3%] vs. 2 [0.1%] in the high non-HDL-C group; *P* for interaction=0.425).

Conclusion CHANCE-2 participants with low non-HDL-C levels received more clinical benefit from ticagrelor-aspirin versus clopidogrel-aspirin compared to those with high non-HDL-C, following minor ischemic stroke or transient ischemic attack.

Keywords CHANCE-2; Stroke; Ticagrelor; Clopidogrel; Non–high-density lipoprotein cholesterol

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Received: January 22, 2024
Revised: March 7, 2024
Accepted: March 8, 2024

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Introduction

Even when administered sustained dual antiplatelet therapy, patients with minor ischemic stroke or transient ischemic attack (TIA) still display a high risk of subsequent stroke within 3 months of initial symptom onset. Evidence from the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events),[1-3] POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke),[4,5] and CHANCE-2 (Ticagrelor or Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II) trials[6,7] have suggested that this treatment failure may be caused by patients' variable responses to antiplatelet therapies. As such, identifying effect modifiers and exploring optimal treatment strategies are of utmost importance in this patient population.

Non-high-density lipoprotein cholesterol (non-HDL-C) is defined as a measure of the cholesterol content of all proatherogenic lipoproteins containing apolipoprotein B, including low-density lipoprotein (LDL), lipoprotein(a), and triglyceride-rich lipoproteins (very-low-density lipoproteins and intermediate density lipoprotein). This measure has been shown to be a more accurate predictive marker of cardiovascular risk than LDL cholesterol (LDL-C), and can better capture the contribution of apolipoprotein B-containing particles to atherogenesis.[8-13] Therefore, non-HDL-C level has been included as a new therapeutic target for lipid-lowering therapy in high-risk atherosclerotic patients by multiple guidelines.[14-16] Previous studies have further indicated that atherogenic lipoproteins enhance platelet responsiveness, while elevated cholesterol concentrations can increase platelet production, activation, and aggregation.[17-19] Furthermore, studies have reported that non-HDL-C is an independent risk factor for aspirin resistance in type 2 diabetes patients.[20] Accordingly, non-HDL-C could be considered as a valuable biomarker to predict patients' response to antiplatelet therapy. However, no study has yet addressed the association of non-HDL-C with the effectiveness of different dual antiplatelet regimens in patients following stroke.

The CHANCE-2 trial found that early and intensive antiplatelet treatment with ticagrelor-aspirin was superior to clopidogrel-aspirin in reducing the risk of recurrent stroke in patients with minor ischemic stroke or high-risk TIA carrying *CYP2C19* loss-of-function (LOF) alleles. Herein, we conducted a *post hoc* analysis of the CHANCE-2 trial to explore the relationship between non-HDL-C and the efficacy and safety of ticagrelor-aspirin and clopidogrel-aspirin therapy in *CYP2C19* LOF carriers with minor ischemic stroke or TIA.

Methods

Data availability

Data will be made available to researchers upon request to reproduce the results or replicate the procedure by directly contacting the corresponding author.

Study design and participants

A detailed description of the study design and methods of the CHANCE-2 trial have been provided elsewhere.[21,22] Briefly, this study was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial conducted at 202 centers in China from September 23, 2019, to March 22, 2021. The inclusion criteria were: patients aged 40 years or older, with acute nondisabling ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score ≤3) or high-risk TIA ($ABCD^2$ [age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus] score ≥4), carrying the *CYP2C19* LOF alleles, who were treated with one of the study drugs within 24 hours of symptom onset.

The trial adhered to the guidelines outlined by the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. The trial protocol was approved by the Ethics Committee of Beijing Tiantan Hospital (approval number: KY2019-035-02) and each participating center. Written informed consent was obtained from all patients or their representatives before enrollment. The trial was registered at ClinicalTrials.gov (Registration URL: http://www.clinicaltrials.gov), under the unique identifier NCT04078737.

Randomization and treatment

A total of 6,412 eligible patients were randomly assigned in a 1:1 ratio to either 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). All patients in both arms received a 75–300 mg loading dose of aspirin, followed by doses of 75 mg administered daily for 21 days.

Measurement of non-HDL-C

Venous blood samples were obtained from fasting patients after randomization and were subsequently sent for routine laboratory tests. Serum total cholesterol (TC), HDL-C, and LDL-C levels were measured by laboratory personnel blinded to the trial group assignments. Non-HDL-C was calculated by subtracting the HDL-C value from the TC value.[14] The collection, preservation, and processing of blood samples were performed in accordance with the laboratory's policies and procedures in each study center.

https://doi.org/10.5853/jos.2024.00367

Efficacy and safety outcomes

The efficacy and safety outcomes of this analysis are consistent with those of the CHANCE-2 trial. The primary efficacy outcome was new stroke (ischemic or hemorrhagic) within 90 days. Secondary outcomes included new stroke within 30 days, composite vascular events (stroke, TIA, myocardial infarction, or vascular death), and ischemic stroke within 90 days, as well as disabling stroke (with a subsequent modified Rankin Scale score of ≥2) at day 90. The primary safety outcome was severe or moderate bleeding, as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria, within 90 days.[23] The secondary safety outcomes included any bleeding and death within 90 days of follow-up. All efficacy and safety outcomes were confirmed by an independent clinical event adjudication committee, whose members were unaware of the trial group assignments.[21]

Statistical analyses

Patients included in this *post hoc* analysis of the CHANCE-2 trial were classified into low and high non-HDL-C groups, according to the median non-HDL-C value. In each subgroup, the baseline characteristics were compared according to the treatment assignments. Medians with interquartile ranges were used for continuous variables because of their skewed distributions. Frequencies and percentages were used as categorical variables. Baseline characteristics were compared using the nonparametric Wilcoxon test for continuous variables, and the chi-square test for categorical variables.

The main analyses were performed in the intention-to-treat population. The cumulative risks of the primary outcome of any ischemic or hemorrhagic event during the 90-day follow-up period for each non-HDL-C group were estimated using the Kaplan–Meier method. Differences in the rates of efficacy and safety outcomes between trial groups were assessed using a Cox proportional hazards regression model, with study centers set as a random effect after adjusting for age, sex, body mass index (BMI; weight in kilograms divided by the square of the height in meters), Han ethnicity, medical history (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, prior TIA), *CYP2C19* LOF allele carriers, previous antiplatelet therapy, previous lipid-lowering therapy, and symptomatic intracranial artery stenosis. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were further calculated. The time to the first event was used in the model when multiple events of the same type occurred. Patient data were censored at the last follow-up assessment if a clinical event had occurred, at the end of the trial, at the time of withdrawal from the trial, or at the last visit if the primary outcome data were missing. For each model, the proportionality assumption was assessed by testing the interaction of treatment with time, and we found no violation of the assumptions. The interactions between non-HDL-C levels and treatment assignments were investigated with the addition of treatment by non-HDL-C groups using multivariable Cox proportional hazards regression models. Sensitivity analyses were performed in the per-protocol population, or among patients with no history of previous lipid-lowering therapy, or according to baseline LDL-C levels (<2.6 mmol/L or ≥2.6 mmol/L).

All statistical analyses were performed using the SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). A two-sided *P* value <0.05 indicated statistical significance.

Results

Baseline characteristics

Of the 6,412 patients who underwent randomization in the CHANCE-2 trial, 511 without TC or HDL-C measurements were excluded. Thus, 5,901 patients were included in the final analysis (Figure 1). The baseline characteristics of the included and excluded patients were well-balanced, except that the included patients had a higher proportion of dyslipidemia, previous ischemic stroke, current smokers, and symptomatic intracranial artery stenosis (Supplementary Table 1).

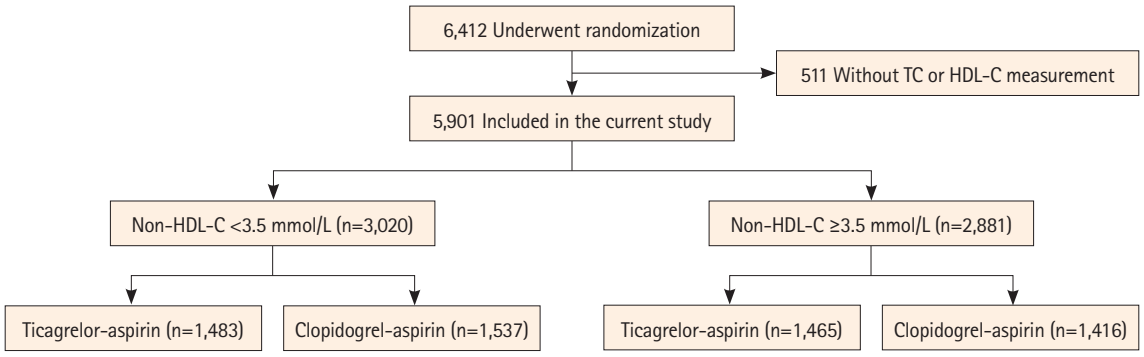

Figure 1. Flowchart of the study design. HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

Among the patients included in this analysis, the median concentration of non-HDL-C was 3.5 mmol/L (interquartile range: 2.8 to 4.2 mmol/L); 2,881 (48.8%) had high non-HDL-C levels (≥3.5 mmol/L), and 3,020 (51.2%) did not (<3.5 mmol/L). The detailed characteristics of the patients with low and high non-HDL-C levels and the two treatment groups are presented in Table 1. Patients with high non-HDL-C were more likely to be younger, female, and of Han ethnicity, with a higher BMI, higher proportion of hypertension, diabetes mellitus, dyslipidemia, symptomatic intracranial-artery stenosis, and lower proportion of previous ischemic stroke, previous TIA, previous antiplatelet therapy, and previous lipid-lowering therapy, compared with those with low non-HDL-C. The baseline characteristics between the two treatment groups were well balanced, except that, among patients with high non-HDL-C, the ticagrelor-aspirin group had a slightly higher proportion of previous lipid-lowering therapy compared with the clopidogrel-aspirin group.

Efficacy outcomes

Recurrent stroke within 90 days (the primary efficacy) was observed in 405 (6.9%) patients in the current analysis. The cumulative risk of stroke recurrence among patients with low or high non-HDL-C levels by treatment assignment is shown in Figure 2. Those with low non-HDL-C who were treated with ticagrelor-aspirin experienced the lowest risk of stroke recurrence (P<0.001, log-rank test). Overall, there was a significant interaction between non-HDL-C levels and the two antiplatelet therapy groups in terms of the treatment effects on recurrent stroke after adjusting for other confounding factors (P=0.010 for interaction) (Table 2). Furthermore, ticagrelor-aspirin was found to significantly reduce the risk of recurrent stroke (adjusted HR, 0.54; 95% CI, 0.40–0.74; P<0.001) compared with clopidogrel-aspirin in patients with low non-HDL-C. However, this additional benefit of ticagrelor-aspirin dual antiplatelet treatment was not observed in patients with high non-HDL-C levels (adjusted HR, 0.88; 95% CI, 0.67–1.16; P=0.374). Further, when non-HDL-C was treated as a continuous variable, non-HDL-C levels also influenced the effect of ticagrelor-aspirin on the primary outcome. As non-HDL-C levels increased, the risk of stroke recurrence within 90 days also increased in patients receiving ticagrelor-aspirin compared with those receiving clopidogrel-aspirin (Figure 3). Similar results were observed for secondary outcomes of stroke within 30 days, composite vascular events, and ischemic stroke within 90 days of follow-up (Table 2). Per-protocol analysis yielded results similar to those identified in the intention-to-treat analysis (Supplementary Table 2). Furthermore, when an analysis was performed restricted to patients without previous lipid-lowering therapy, or with baseline LDL-C <2.6 mmol/L or ≥2.6 mmol/L, all the results were consistent with those of the main analysis (Supplementary Tables 3-5).

The absent extra benefit of ticagrelor-aspirin therapy in patients with high non-HDL-C may be related to the predominant efficacy of clopidogrel-aspirin on reducing vascular events, or the weak efficacy of ticagrelor-aspirin therapy. We performed additional analyses to further illustrate this finding, finding that the rate of stroke recurrence tended to be higher in patients with high non-HDL-C levels than in those with low non-HDL-C levels (7.5% vs. 6.3%) (Figure 2). As shown in Table 3, patients with high non-HDL-C showed increased risks of recurrent stroke (adjusted HR, 1.27; 95% CI, 1.01–1.58), ischemic stroke (adjusted HR, 1.29; 95% CI, 1.03–1.62), and disabling stroke (adjusted HR, 1.44; 95% CI, 1.02–2.04), after adjusting for confounding factors. Furthermore, subgroup analysis of patients stratified by the dual antiplatelet therapy revealed that high non-HDL-C was associated with a higher rate of recurrent stroke, stroke within 30 days, composite vascular events, ischemic stroke, and disabling stroke in patients receiving ticagrelor-aspirin, but not in patients receiving clopidogrel-aspirin.

Safety outcomes

There was no interaction between non-HDL-C levels and antiplatelet assignment for the risk of severe or moderate bleeding (P=0.425 for interaction) (Table 2). The rate in ticagrelor-aspirin group and clopidogrel-aspirin group was similar in patients with low non-HDL-C (0.3% vs. 0.5%; HR, 0.72; 95% CI, 0.23–2.28), and high non-HDL-C (0.3% vs. 0.1%; HR, 2.32; 95% CI, 0.42–12.76). Ticagrelor-aspirin increased the rate of bleeding compared to clopidogrel-aspirin among patients with low and high non-HDL-C levels (Table 2). The results of the per-protocol and other sensitivity analyses were consistent with those of the intention-to-treat analysis (Supplementary Tables 2-5).

Discussion

This *post hoc* analysis of the CHANCE-2 trial indicated that non-HDL-C could be used to efficiently stratify patients with minor ischemic stroke or high-risk TIA carrying *CYP2C19* LOF alleles according to the efficacy of ticagrelor-aspirin compared with clopidogrel-aspirin. Patients with low non-HDL-C administrated ticagrelor-aspirin achieved approximately 46% of risk reduction for recurrent stroke compared with those treated with clopidogrel-aspirin, without any increase in the risk of severe or moderate bleeding events. However, this benefit was not observed in patients with high non-HDL-C levels.

Lipids play an essential role in platelet function. Lipids can affect platelet count and characteristics, and modulate athero-

https://doi.org/10.5853/jos.2024.00367

Table 1. Baseline characteristics of patients receiving different treatments stratified, by non-HDL-C levels

Characteristics	Non-HDL-C <3.5 mmol/L				Non-HDL-C ≥3.5 mmol/L				$P^{\S}$
	Total (n=3,020)	Ticagrelor-aspirin (n=1,483)	Clopidogrel-aspirin (n=1,537)	*P*	Total (n=2,881)	Ticagrelor-aspirin (n=1,465)	Clopidogrel-aspirin (n=1,416)	*P*	
Age (yr)	65.4 (57.4–72.2)	65.5 (57.5–72.1)	65.3 (57.3–72.2)	0.620	63.9 (56.6–70.4)	63.9 (56.5–70.6)	63.9 (56.6–70.3)	0.683	<0.001
Female sex	853 (28.3)	397 (26.8)	456 (29.7)	0.077	1,126 (39.1)	587 (40.1)	539 (38.1)	0.271	<0.001
Han ethnicity	2,944 (97.5)	1,445 (97.4)	1,499 (97.5)	0.874	2,840 (98.6)	1,449 (98.9)	1,391 (98.2)	0.127	0.003
BMI (kg/m^2)	24.2 (22.5–26.4)	24.2 (22.5–26.6)	24.2 (22.5–26.2)	0.306	24.7 (22.9–26.7)	24.8 (22.9–26.8)	24.5 (22.9–26.7)	0.093	<0.001
Medical history									
Hypertension	2,187 (72.4)	1,058 (71.3)	1,129 (73.5)	0.194	2,170 (75.3)	1,105 (75.4)	1,065 (75.2)	0.894	0.011
Diabetes mellitus	897 (29.7)	443 (29.9)	454 (29.5)	0.841	980 (34.0)	506 (34.5)	474 (33.5)	0.547	<0.001
Dyslipidemia	469 (15.5)	216 (14.6)	253 (16.5)	0.151	1,223 (42.5)	631 (43.1)	592 (41.8)	0.493	<0.001
Previous ischemic stroke	786 (26.0)	381 (25.7)	405 (26.4)	0.680	475 (16.5)	243 (16.6)	232 (16.4)	0.883	<0.001
Previous TIA	50 (1.7)	28 (1.9)	22 (1.4)	0.326	30 (1.0)	14 (1.0)	16 (1.1)	0.645	0.041
Myocardial infarction	46 (1.5)	22 (1.5)	24 (1.6)	0.861	38 (1.3)	24 (1.6)	14 (1.0)	0.127	0.508
Current smoking	960 (31.8)	483 (32.6)	477 (31.0)	0.365	890 (30.9)	455 (31.1)	435 (30.7)	0.844	0.458
CYP2C19 LOF allele carriers				0.952				0.458	0.066
Intermediate metabolizers	2,386 (79.0)	1,171 (79.0)	1,215 (79.1)		2,219 (77.0)	1,120 (76.5)	1,099 (77.6)		
Poor metabolizers	634 (21.0)	312 (21.0)	322 (21.0)		662 (23.0)	345 (23.6)	317 (22.4)		
Time to randomization (h)	14.0 (9.0–20.5)	13.7 (9.3–20.1)	14.3 (8.8–20.8)	0.680	14.0 (8.9–20.7)	13.4 (8.7–20.5)	14.5 (9.2–20.7)	0.055	0.727
Qualifying event				0.762				0.905	0.849
Ischemic stroke	2,426 (80.3)	1,188 (80.1)	1,238 (80.6)		2,320 (80.5)	1,181 (80.6)	1,139 (80.4)		
TIA	594 (19.7)	295 (19.9)	299 (19.5)		561 (19.5)	284 (19.4)	277 (19.6)		
NIHSS score in patients with qualifying ischemic stroke*	2 (1–3)	2 (1–3)	2 (1–3)	0.792	2 (1–3)	2 (1–3)	2 (1–3)	0.110	0.873
ABCD^2 score in patients with qualifying TIA†	4 (4–5)	5 (4–5)	4 (4–5)	0.462	4 (4–5)	4 (4–5)	5 (4–5)	0.591	0.809
Previous antiplatelet therapy‡	459 (15.2)	221 (14.9)	238 (15.5)	0.656	229 (8.0)	130 (8.9)	99 (7.0)	0.062	<0.001
Previous lipid-lowering therapy‡	343 (11.4)	164 (11.1)	179 (11.7)	0.611	113 (3.9)	69 (4.7)	44 (3.1)	0.027	<0.001
Symptomatic intracranial-artery stenosis	738 (26.5)	365 (26.6)	373 (26.4)	0.911	801 (29.8)	426 (31.1)	375 (28.4)	0.125	0.007
Symptomatic extracranial-artery stenosis	115 (4.1)	64 (4.7)	51 (3.6)	0.163	140 (5.2)	71 (5.2)	69 (5.2)	0.962	0.059

Values are presented as median (interquartile range) or n (%).

HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; TIA, transient ischemic attack; LOF, loss-of-function; NIHSS, National Institutes of Health Stroke Scale.

*NIHSS scores range from 0 to 42, with higher scores indicating more severe stroke; †The ABCD^2 score assesses the risk of stroke based on age, blood pressure, clinical features, duration of TIA, and the presence or absence of diabetes mellitus, with scores ranging from 0 to 7, with higher scores indicating greater risk; ‡Medication within 1 month before symptom onset; §*P* value indicated comparisons between patients with low non-HDL-C and high non-HDL-C.

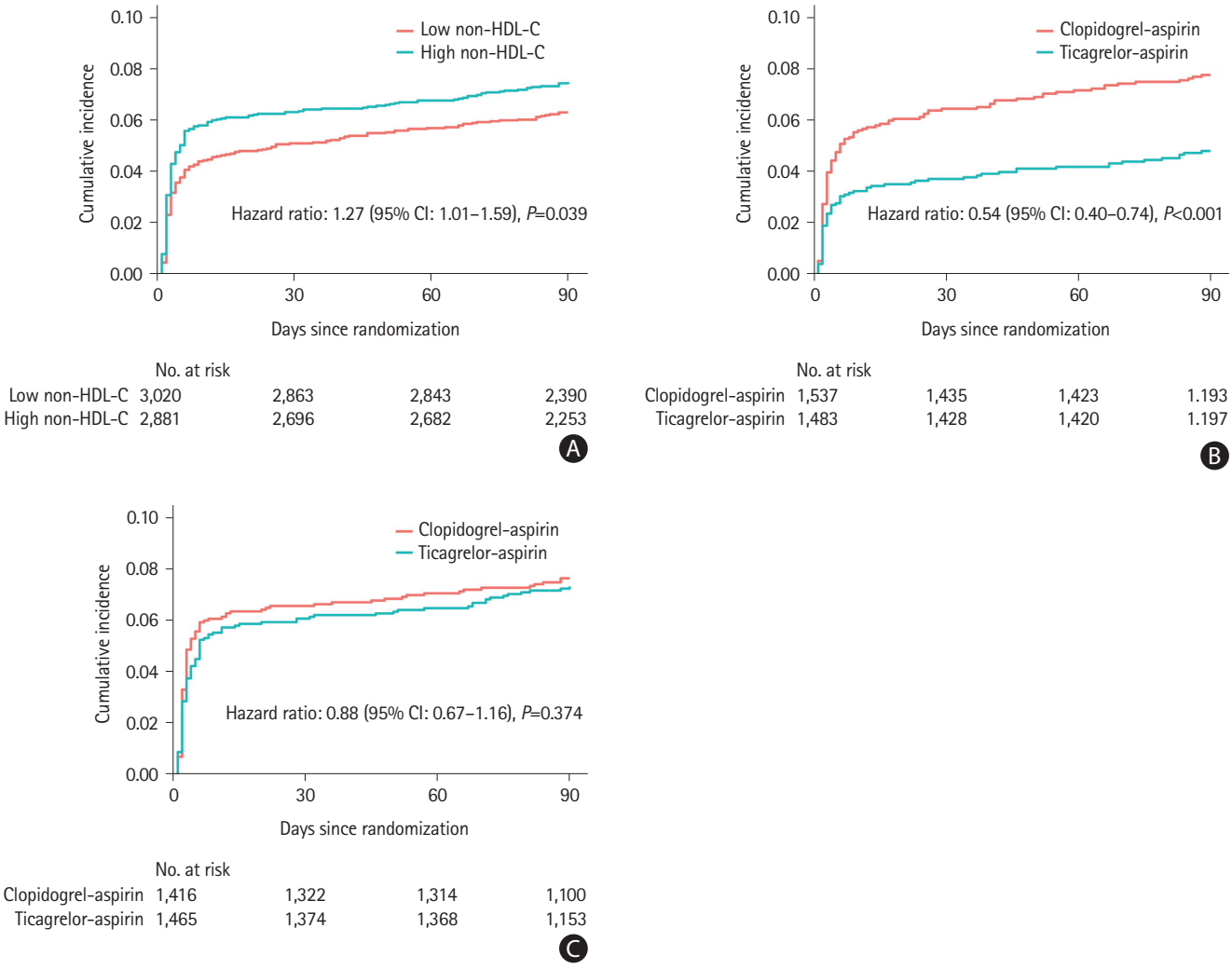

Figure 2. Cumulative probability of stroke recurrence in patients at 3-month follow-up according to non-HDL-C levels and dual antiplatelet therapy. (A) Non-HDL-C and stroke. (B) Low non-HDL-C. (C) High non-HDL-C. Low non-HDL-C represents non-HDL-C <3.5 mmol/L; High non-HDL-C represents non-HDL-C ≥3.5 mmol/L. HDL-C, high-density lipoprotein cholesterol; CI, confidence interval.

thrombotic risk through the megakaryocyte-platelet hemostatic axis;[17] thus, they are suggested to be related to the differences in platelet responsiveness to antiplatelet therapy for coronary artery disease or ischemic stroke.[24-27] Plasma cholesterol levels also appear to play a key role in regulating platelet activity, as hypercholesterolemia promotes platelet production and activation more potently than hypertriglyceridemia.[28-30] Non-HDL-C encompasses all plasma cholesterol levels, except HDL cholesterol. Several studies have further investigated the effects of non-HDL-C level on the human platelet activity. Results from the National Health and Nutrition Examination Survey involving approximately 10,000 participants indicated a positive correlation of serum non-HDL-C with platelet count and platelet-crit values.[31] The Suita study reported that collagen-induced platelet aggregability was increased in the highest quartile of non-HDL-C levels in the Japanese population.[32] Kim et al.[20] further enrolled a total of 1,045 type 2 diabetes patients from 11 hospitals in Korea, finding that only non-HDL-C was associated with aspirin resistance in obese type 2 diabetes patients. However, there was no relevant evidence to indicate the influence of non-HDL-C on the efficacy of antiplatelet agents. In this *post hoc* analysis of the CHANCE-2 trial, we found that ticagrelor-aspirin has apparent advantages over clopidogrel-aspirin in terms of the risk reduction of recurrent stroke and composite vascular events for patients with low non-HDL-C, but not for those with high non-HDL-C.

Lipid-lowering agents and antiplatelet drugs may act synergistically in the prevention of thrombotic vessel occlusions in atherosclerotic cardiovascular disease patients via inhibition of thromboxane-mediated autocrine and paracrine platelet functions.[33] Thus, we performed sensitivity analysis by excluding patients receiving lipid-lowering therapy, with the results of this

https://doi.org/10.5853/jos.2024.00367

Table 2. Effect of ticagrelor-aspirin versus clopidogrel-aspirin on efficacy and safety outcomes in patients stratified by non-HDL-C levels

Outcome	Non-HDL-C <3.5 mmol/L				Non-HDL-C ≥3.5 mmol/L				*P* for interaction
	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	
Primary outcome									
Stroke	71 (4.8)	119 (7.7)	0.54 (0.40–0.74)	<0.001	107 (7.3)	108 (7.6)	0.88 (0.67–1.16)	0.374	0.010
Secondary outcome									
Stroke within 30 days	55 (3.7)	99 (6.4)	0.51 (0.36–0.71)	<0.001	89 (6.1)	93 (6.6)	0.85 (0.63–1.14)	0.274	0.022
Composite vascular events†	93 (6.3)	146 (9.5)	0.59 (0.45–0.77)	<0.001	120 (8.2)	126 (8.9)	0.86 (0.66–1.11)	0.237	0.020
Ischemic stroke	70 (4.7)	116 (7.6)	0.55 (0.40–0.75)	<0.001	106 (7.2)	106 (7.5)	0.89 (0.68–1.17)	0.409	0.010
Disabling stroke‡	33 (2.2)	43 (2.8)	0.71 (0.44–1.14)	0.151	59 (4.0)	43 (3.0)	1.20 (0.80–1.80)	0.378	0.039
Primary safety outcome									
Severe or moderate bleeding§	5 (0.3)	8 (0.5)	0.72 (0.23–2.28)	0.578	4 (0.3)	2 (0.1)	2.32 (0.42–12.76)	0.334	0.425
Intracranial hemorrhage	1 (0.1)	4 (0.3)	0.24 (0.03–2.12)	0.197	2 (0.1)	2 (0.1)	1.11 (0.16–7.96)	0.914	0.545
Secondary safety outcome									
Any bleeding	84 (5.7)	44 (2.9)	1.97 (1.35–2.87)	<0.001	74 (5.1)	32 (2.3)	2.33 (1.53–3.56)	<0.001	0.627
Mortality	4 (0.3)	10 (0.7)	0.31 (0.09–1.14)	0.079	4 (0.3)	4 (0.3)	0.84 (0.21–3.42)	0.813	0.290

Values are presented as n (%) unless otherwise indicated.
HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; LOF, loss-of-function.
*Adjusted for age, sex, body mass index, Han ethnicity, medical history (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, and previous transient ischemic attack), *CYP2C19* LOF allele carriers, previous antiplatelet therapy, previous lipid-lowering therapy, and symptomatic intracranial artery stenosis; †Composite vascular events included ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, and vascular death; ‡A stroke was defined as disabling if the patient had a modified Rankin scale score >1 (indicating death or any degree of disability); §Severe or moderate bleeding and mild bleeding were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

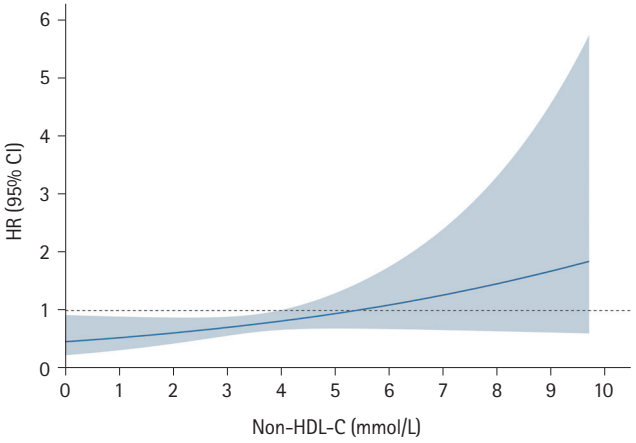

Figure 3. Effects of non-HDL-C as a continuous variable on the efficacy of ticagrelor-aspirin versus clopidogrel-aspirin in preventing stroke recurrence within 90 days. The shaded areas represent the 95% confidence intervals. non-HDL-C, non-high-density lipoprotein cholesterol; CI, confidence interval; HR, hazard ratio.

analysis showing that the benefit of ticagrelor-aspirin in preventing vascular events persisted even in patients not receiving lipid-lowering therapy. In addition, since LDL-C is the primary goal of secondary stroke prevention in many guidelines,[14-16,34] and there is a notable discordance between non-HDL-C and LDL-C levels,[35] we further conducted a sensitivity analysis according to baseline LDL-C levels, using the therapeutic target of 2.6 mmol/L for high-risk individuals as the cutoff.[36] Our results further showed that patients with high non-HDL-C levels did not benefit from ticagrelor-aspirin as much as patients with low non-HDL-C levels, regardless of whether LDL-C concentrations were controlled, demonstrating the independent role of non-HDL-C in stratifying the efficacy of dual antiplatelet therapy. In light of the findings described here, it is reasonable to consider non-HDL-C as a potential biomarker for predicting the response to dual antiplatelet therapy in patients with minor stroke or TIA. However, the exact mechanisms underlying these results remains unclear. Possible mechanisms include the following: First, high non-HDL-C levels can lead to endothelial damage and exacerbation of inflammatory responses, thus stimulating platelet activation and aggregation.[17-19] Additionally, non-HDL-C has previously been shown to be associated with plaque stability,[37,38] while a high non-HDL-C level has been identified as an independent risk factor for asymptomatic unstable carotid plaques.[37,38] Disruption of unstable carotid plaques can lead to thrombosis, resulting in cerebrovascular occlusion and infarction, which are correlated with the development of ischemic stroke and vascular recurrence events.[39,40] Thus, our findings illustrate that the presence of elevated non-HDL-C levels probably indicates unstable atherosclerotic plaques and severe lipid deposition, which may not be efficiently controlled by the ticagrelor-aspirin ther-

Table 3. Effect of high (≥3.5 mmol/L) non-HDL-C level on efficacy outcomes

Outcome	Overall		Ticagrelor-aspirin group		Clopidogrel-aspirin group	
	Adjusted HR (95% CI)*	*P*	Adjusted HR (95% CI)*	*P*	Adjusted HR (95% CI)*	*P*
Primary outcome						
Stroke	1.27 (1.01–1.58)	0.039	1.88 (1.32–2.69)	<0.001	1.01 (0.75–1.36)	0.944
Secondary outcome						
Stroke within 30 days	1.26 (0.98–1.61)	0.069	1.86 (1.25–2.78)	0.002	1.02 (0.74–1.41)	0.904
Composite vascular events†	1.13 (0.92–1.39)	0.239	1.55 (1.12–2.13)	0.008	0.94 (0.71–1.24)	0.658
Ischemic stroke	1.29 (1.03–1.62)	0.027	1.91 (1.33–2.73)	<0.001	1.02 (0.76–1.39)	0.880
Disabling stroke‡	1.44 (1.02–2.04)	0.037	2.07 (1.24–3.45)	0.005	1.02 (0.62–1.68)	0.936

HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; LOF, loss-of-function.
*Adjusted for age, sex, body mass index, Han ethnicity, medical history (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, and previous transient ischemic attack), *CYP2C19* LOF allele carriers, previous antiplatelet therapy, previous lipid-lowering therapy, and symptomatic intracranial artery stenosis; †Composite vascular events included ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, and vascular death; ‡A stroke was defined as disabling if the patient had a modified Rankin scale score >1 (indicating death or any degree of disability).

apy, according to the CHANCE-2 protocol. Second, patients with elevated non-HDL-C in the current study had more risk factors, including hypertension, diabetes mellitus, and dyslipidemia, as well as a higher proportion of symptomatic intracranial artery stenosis; the benefit of ticagrelor-aspirin therapy may be offset by these comorbidities. Moreover, consistent with previous results,[41] our study confirmed the positive association of high non-HDL-C levels with recurrent vascular events, particularly in patients receiving ticagrelor-aspirin therapy, which might attenuate its efficacy. Indeed, in patients with high non-HDL-C, these characteristics may generally reduce the efficacy of antiplatelet therapy, meaning that the superior efficacy of ticagrelor-aspirin over clopidogrel-aspirin may not be apparent in this group.

The following limitations merit consideration when interpreting our results. First, this analysis included only 5,901 patients who completed TC and HDL-C testing, representing only 92.0% of all patients of the CHANCE-2 trial. This may have caused selection bias; however, baseline characteristics were comparable between included and excluded patients, and we further adjusted for multiple confounding factors in the main analysis. The exploratory nature of this analysis could increase the risk of a type I error; thus, our results need to be verified in other studies.[42] Second, only baseline data of blood lipids were available for current analyses. Information on the dynamic changes during follow-up, particularly in patients with very high non-HDL-C concentrations, was not available, which may have provided more vulnerable information. However, results from the Framingham offspring study indicated that non-HDL-C concentrations were generally stable over the 30-year life course.[43] Third, equipment heterogeneity across 202 centers may lead to biased results; however, this effect was minimized due to strict quality control and routine practice at each hospital, and we therefore set study centers as a random effect in the models. Fourth, *CYP2C19* LOF allele non-carriers were not included in the CHANCE-2 trial. The efficacy of ticagrelor-aspirin versus clopidogrel-aspirin and the effect modification of non-HDL-C among *CYP2C19* fast metabolizers should therefore be investigated in future studies. Finally, the CHANCE-2 trial mainly involved Han Chinese patients, and the generalizability of our findings therefore requires further evaluation in other ethnicities.

Conclusions

This *post hoc* analysis of the CHANCE-2 trial suggested that baseline non-HDL-C levels may 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 TIA carrying *CYP2C19* LOF alleles. Patients with low non-HDL-C received more clinical benefit from ticagrelor-aspirin versus clopidogrel-aspirin after minor ischemic stroke or TIA compared to those with high non-HDL-C. Further large-scale randomized controlled clinical trials in other populations are required to confirm these findings.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.00367.

Funding statement

This work was supported by the Ministry of Science and Technology of the People's Republic of China (MOST), Beijing Municipal Science & Technology Commission, Chinese Stroke Association (CSA), and the Beijing Municipal Science & Technology Commission. Grants were received from the National Science

and Technology Major Project (2017ZX09304018), National Key Research and Development Program of China (2022YFC3600600), Training Fund for Open Projects at Clinical Institutes and Departments of Capital Medical University (CCMU2022ZKYXZ009), Beijing Natural Science Foundation Haidian original innovation joint fund (L222123), and Fund for Young Talents of Beijing Medical Management Center (QML20230505). Salubris contributed ticagrelor, clopidogrel, and the placebo at no cost and without restrictions. Chongqing Jingyin Bioscience Co., Ltd. provided the GMEX point-of-care genotyping system and technical support for CHANCE-2 at no cost and without restrictions.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: QX, AW, YW (Yongjun Wang). Study design: QX, XM, HL, XX, AW, YW (Yongjun Wang). Methodology: QX, XM, HL, XX, JL, YW (Yilong Wang), AW, YW (Yongjun Wang). Data collection: JJ, JL, YJ, YW (Yilong Wang), XZ, ZL, LL. Investigation: QX, XM, XX, JJ, XZ, ZL, LL. Statistical analysis: QX, AW. Writing-original draft: QX. Writingreview & editing: all authors. Funding acquisition: AW, YW (Yongjun Wang). Approval of final manuscript: all authors.

Acknowledgments

The authors would like to thank all study participants, their relatives, and members of the survey teams at the 202 centers involved the CHANCE-2 study.

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Supplementary Table 1. Baseline characteristics of included and excluded patients

Characteristics	Total (n=6,412)	Exclude (n=511)	Include (n=5,901)	*P*
Age (yr)	64.8 (57.0–71.4)	64.8 (57.0–72.5)	64.8 (56.9–71.3)	0.282
Female sex	2,170 (33.8)	191 (37.4)	1,979 (33.5)	0.078
Han ethnicity	6,282 (98.0)	498 (97.5)	5,784 (98.0)	0.388
BMI (kg/m^2)	24.5 (22.6–26.6)	24.2 (22.5–26.1)	24.5 (22.6–26.6)	0.145
Medical history				
Hypertension	4,730 (73.8)	373 (73.0)	4,357 (73.8)	0.678
Diabetes mellitus	2,042 (31.9)	165 (32.3)	1,877 (31.8)	0.823
Dyslipidemia	1,783 (27.8)	91 (17.8)	1,692 (28.7)	<0.001
Previous ischemic stroke	1,350 (21.1)	89 (17.4)	1,261 (21.4)	0.035
Previous TIA	88 (1.4)	8 (1.6)	80 (1.4)	0.696
Myocardial infarction	96 (1.5)	12 (2.4)	84 (1.4)	0.099
Current smoking	1,981 (30.9)	131 (25.6)	1,850 (31.4)	0.007
CYP2C19 LOF allele carriers				0.776
Intermediate metabolizers	5,001 (78.0)	396 (77.5)	4,605 (78.0)	
Poor metabolizers	1,411 (22.0)	115 (22.5)	1,296 (22.0)	
Time to randomization (h)	14.0 (8.9–20.5)	13.1 (8.5–20.3)	14.0 (9.0–20.5)	0.203
Qualifying event				0.913
Ischemic stroke	5,158 (80.4)	412 (80.6)	4,746 (80.4)	
TIA	1,254 (19.6)	99 (19.4)	1,155 (19.6)	
NIHSS score in patients with qualifying ischemic stroke*	2 (1–3)	2 (1–3)	2 (1–3)	0.914
ABCD^2 score in patients with qualifying TIA†	4 (4–5)	5 (4–5)	4 (4–5)	0.680
Previous antiplatelet therapy‡	748 (11.7)	60 (11.7)	688 (11.7)	0.956
Previous lipid-lowering therapy‡	499 (7.8)	43 (8.4)	456 (7.7)	0.578
Symptomatic intracranial-artery stenosis	1,639 (27.7)	100 (22.4)	1,539 (28.1)	0.009
Symptomatic extracranial-artery stenosis	271 (4.6)	16 (3.6)	255 (4.7)	0.294

Values are presented as median (interquartile range) or n (%).
BMI, body mass index; TIA, transient ischemic attack; LOF, loss-of-function; NIHSS, National Institutes of Health Stroke Scale.
*NIHSS scores range from 0–42, with higher scores indicating more severe stroke; †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 mellitus, with scores ranging from 0 to 7 and higher scores indicating greater risk; ‡Medication within 1 month before symptom onset.

Supplementary Table 2. Effect of ticagrelor-aspirin versus clopidogrel-aspirin on efficacy and safety outcomes stratified by non-HDL-C levels in the per protocol set

Outcome	Non-HDL-C <3.5 mmol/L				Non-HDL-C ≥3.5 mmol/L				*P* for interaction
	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	
Primary outcome									
Stroke	66 (5.0)	114 (8.1)	0.53 (0.39–0.73)	<0.001	104 (8.0)	105 (8.0)	0.92 (0.70–1.22)	0.572	0.007
Secondary outcome									
Stroke within 30 days	51 (3.8)	95 (6.8)	0.50 (0.35–0.71)	<0.001	87 (6.7)	91 (6.9)	0.88 (0.65–1.20)	0.419	0.016
Composite vascular events†	79 (5.9)	135 (9.6)	0.55 (0.41–0.73)	<0.001	111 (8.5)	120 (9.1)	0.87 (0.67–1.13)	0.293	0.010
Ischemic stroke	65 (4.9)	111 (7.9)	0.54 (0.39–0.75)	<0.001	103 (7.9)	103 (7.8)	0.93 (0.70–1.23)	0.614	0.007
Disabling stroke‡	31 (2.3)	39 (2.8)	0.75 (0.45–1.23)	0.250	58 (4.4)	40 (3.0)	1.32 (0.87–2.01)	0.188	0.053
Primary safety outcome									
Severe or moderate bleeding§	1 (0.1)	4 (0.3)	0.25 (0.03–2.22)	0.212	2 (0.2)	2 (0.2)	1.18 (0.16–8.44)	0.871	0.610
Intracranial hemorrhage	1 (0.1)	4 (0.3)	0.25 (0.03–2.22)	0.212	2 (0.2)	2 (0.2)	1.18 (0.16–8.46)	0.869	0.610
Secondary safety outcome									
Any bleeding	63 (4.7)	33 (2.3)	2.01 (1.30–3.11)	0.002	55 (4.2)	23 (1.7)	2.56 (1.56–4.21)	<0.001	0.416
Mortality	2 (0.2)	3 (0.2)	0.41 (0.04–4.07)	0.445	2 (0.2)	3 (0.2)	0.62 (0.10–3.83)	0.605	0.825

Values are presented as n (%) unless otherwise indicated.
HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; LOF, loss-of-function.
*Adjusted for age, sex, body mass index, Han ethnicity, medical history (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, previous transient ischemic attack), *CYP2C19* LOF allele carriers, previous antiplatelet therapy, previous lipid-lowering therapy, and symptomatic intracranial-artery stenosis; †Composite vascular events include ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, vascular death; ‡A stroke defined as disabling if the patient had a modified Rankin scale score of >1 (indicating death or any degree of disability); §Severe or moderate bleeding and mild bleeding were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

Supplementary Table 3. Effect of ticagrelor-aspirin versus clopidogrel-aspirin on efficacy and safety outcomes stratified by non-HDL-C levels among patients without previous lipid-lowering therapy

Outcome	Non-HDL-C <3.5 mmol/L				Non-HDL-C ≥3.5 mmol/L				*P* for interaction
	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	
Primary outcome									
Stroke	57 (4.3)	104 (7.7)	0.49 (0.35–0.69)	<0.001	100 (7.2)	106 (7.7)	0.84 (0.64–1.12)	0.236	0.012
Secondary outcome									
Stroke within 30 days	46 (3.5)	89 (6.6)	0.47 (0.32–0.68)	<0.001	83 (6.0)	92 (6.7)	0.80 (0.59–1.09)	0.156	0.031
Composite vascular events†	77(5.8)	126 (9.3)	0.56 (0.42–0.76)	<0.001	111(8.0)	123 (9.0)	0.82 (0.63–1.06)	0.131	0.041
Ischemic stroke	56 (4.3)	101 (7.4)	0.50 (0.35–0.70)	<0.001	99 (7.1)	104 (7.6)	0.85 (0.64–1.13)	0.262	0.012
Disabling stroke‡	27 (2.1)	38 (2.8)	0.63 (0.37–1.06)	0.084	57(4.1)	41 (3.0)	1.24 (0.82–1.87)	0.318	0.020
Primary safety outcome									
Severe or moderate bleeding§	3 (0.2)	7(0.5)	0.47 (0.12–1.87)	0.282	4 (0.3)	2 (0.2)	2.32 (0.42–12.76)	0.334	0.269
Intracranial hemorrhage	1 (0.1)	4 (0.3)	0.24 (0.03–2.12)	0.197	2 (0.1)	2 (0.2)	1.11 (0.16–7.96)	0.914	0.545
Secondary safety outcome									
Any bleeding	72 (5.5)	38 (2.8)	1.93 (1.28–2.91)	0.002	71 (5.1)	31 (2.3)	2.34 (1.52–3.59)	<0.001	0.617
Mortality	3 (0.2)	9 (0.7)	0.23 (0.05–1.06)	0.060	3 (0.2)	4 (0.3)	0.67 (0.15–3.04)	0.602	0.402

Values are presented as n (%) unless otherwise indicated.
HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; LOF, loss-of-function.
*Adjusted for age, sex, body mass index, Han ethnicity, medical history (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, previous transient ischemic attack), *CYP2C19* LOF allele carriers, previous antiplatelet therapy, previous lipid-lowering therapy, and symptomatic intracranial-artery stenosis; †Composite vascular events include ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, vascular death; ‡A stroke defined as disabling if the patient had a modified Rankin scale score of >1 (indicating death or any degree of disability); §Severe or moderate bleeding and mild bleeding were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

https://doi.org/10.5853/jos.2024.00367

Supplementary Table 4. Effect of ticagrelor-aspirin versus clopidogrel-aspirin on efficacy and safety outcomes stratified by non-HDL-C levels among patients with baseline LDL-C <2.6 mmol/L

Outcome	Non-HDL-C <3.5 mmol/L				Non-HDL-C ≥3.5 mmol/L				*P* for interaction
	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	
Primary outcome									
Stroke	57 (5.4)	85 (7.5)	0.61 (0.43–0.87)	0.006	12 (12.1)	4 (4.7)	2.44 (0.71–8.45)	0.158	0.029
Secondary outcome									
Stroke within 30 days	41 (3.9)	71 (6.3)	0.52 (0.35–0.78)	0.002	9 (9.1)	3 (3.5)	2.96 (0.69–12.65)	0.143	0.031
Composite vascular events†	71 (6.7)	104 (9.2)	0.63 (0.46–0.87)	0.005	13 (13.1)	5 (5.9)	2.20 (0.72–6.74)	0.166	0.021
Ischemic stroke	56 (5.3)	83 (7.3)	0.61 (0.43–0.88)	0.008	12 (12.1)	4 (4.7)	2.44 (0.71–8.45)	0.158	0.026
Disabling stroke‡	27 (2.5)	31 (2.7)	0.82 (0.48–1.41)	0.472	7 (7.1)	2 (2.4)	2.64 (0.46–15.09)	0.276	0.400
Primary safety outcome									
Severe or moderate bleeding§	4 (0.4)	5 (0.4)	1.15 (0.28–4.75)	0.843	0 (0.0)	0 (0.0)	NA		NA
Intracranial hemorrhage	1 (0.1)	3 (0.3)	0.31 (0.03–2.97)	0.309	0 (0.0)	0 (0.0)	NA		NA
Secondary safety outcome									
Any bleeding	63 (5.9)	31 (2.7)	2.08 (1.33–3.26)	0.001	6 (6.1)	4 (4.7)	1.65 (0.42–6.58)	0.476	0.245
Mortality	2 (0.2)	8 (0.7)	0.27 (0.06–1.27)	0.098	0 (0.0)	1 (1.2)	NA		NA

Values are presented as n (%) unless otherwise indicated.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; NA, not applicable; TIA, transient ischemic attack; LOF, loss-of-function.
*Adjusted for age, sex, body mass index, Han ethnicity, medical history (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, previous transient ischemic attack), *CYP2C19* LOF allele carriers, previous antiplatelet therapy, previous lipid-lowering therapy, and symptomatic intracranial-artery stenosis; †Composite vascular events include ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, vascular death; ‡A stroke defined as disabling if the patient had a modified Rankin scale score of >1 (indicating death or any degree of disability); §Severe or moderate bleeding and mild bleeding were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

Supplementary Table 5. Effect of ticagrelor-aspirin versus clopidogrel-aspirin on efficacy and safety outcomes stratified by non-HDL-C levels among patients with baseline LDL-C ≥2.6 mmol/L

Outcome	Non-HDL-C <3.5 mmol/L				Non-HDL-C ≥3.5 mmol/L				*P* for interaction
	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	Ticagrelor-aspirin	Clopidogrel-aspirin	Adjusted HR (95% CI)*	*P*	
Primary outcome									
Stroke	14 (3.4)	34 (8.5)	0.35 (0.18–0.67)	0.001	94 (6.9)	104 (7.8)	0.83 (0.62–1.11)	0.204	0.033
Secondary outcome									
Stroke within 30 days	14 (3.4)	28 (7.0)	0.44 (0.23–0.86)	0.016	79 (5.8)	90 (6.8)	0.80 (0.59–1.10)	0.169	0.167
Composite vascular events†	22 (5.3)	42 (10.5)	0.46 (0.27–0.77)	0.004	106 (7.8)	121 (9.1)	0.81 (0.62–1.06)	0.121	0.102
Ischemic stroke	14 (3.4)	33 (8.3)	0.36 (0.19–0.69)	0.002	93 (6.8)	102 (7.7)	0.84 (0.63–1.12)	0.228	0.036
Disabling stroke‡	6 (1.4)	12 (3.0)	0.38 (0.13–1.11)	0.078	52 (3.8)	41 (3.1)	1.16 (0.76–1.77)	0.491	0.045
Primary safety outcome									
Severe or moderate bleeding§	1 (0.2)	3 (0.8)	0.33 (0.03–3.59)	0.364	4 (0.3)	2 (0.2)	2.30 (0.42–12.63)	0.339	0.216
Intracranial hemorrhage	0 (0.0)	1 (0.3)	NA		2 (0.2)	2 (0.2)	1.14 (0.16–8.16)	0.896	NA
Secondary safety outcome									
Any bleeding	21 (5.0)	13 (3.3)	1.79 (0.87–3.66)	0.113	68 (5.0)	28 (2.1)	2.51 (1.60–3.93)	<0.001	0.643
Mortality	2 (0.5)	2 (0.5)	0.37 (0.03–4.45)	0.430	4 (0.3)	3 (0.2)	1.07 (0.24–4.89)	0.927	0.536

Values are presented as n (%) unless otherwise indicated.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval; NA, not applicable; TIA, transient ischemic attack; LOF, loss-of-function.
*Adjusted for age, sex, body mass index, Han ethnicity, medical history (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke, previous transient ischemic attack), *CYP2C19* LOF allele carriers, previous antiplatelet therapy, previous lipid-lowering therapy, and symptomatic intracranial-artery stenosis; †Composite vascular events include ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, vascular death; ‡A stroke defined as disabling if the patient had a modified Rankin scale score of >1 (indicating death or any degree of disability); §Severe or moderate bleeding and mild bleeding were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

https://doi.org/10.5853/jos.2024.00367