Ticagrelor-Aspirin versus Clopidogrel-Aspirin in *CYP2C19* Loss-of-Function Carriers with Minor Stroke or TIA Stratified by Risk Profile

Abstract

Background and Objective: Genotype data of the Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trial showed that efficacy of clopidogrel-aspirin depended on *CYP2C19* genotype and risk profile. A stratification of patients who carried *CYP2C19* loss of function (LOF) alleles according to risk of recurrent stroke may be important for selecting optimal antiplatelet therapy. We aimed to compare the efficacy and safety of ticagrelor–aspirin versus clopidogrel–aspirin in *CYP2C19* LOF carriers with minor stroke or transient ischemic attack (TIA) stratified by risk profile.

Methods: Data were obtained from Ticagrelor or Clopidogrel with Aspirin in High Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial. Low and high risk profiles were defined by Essen Stroke Risk Score (ESRS) (<3 [low risk] and ≥3 [high risk], respectively).

Results: A total of 6,412 *CYP2C19* LOF carriers were enrolled, ticagrelor–aspirin was associated with a reduced risk of primary outcome (new stroke within 90-day follow-up) in patients at low risk (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.48-0.82), but not in those at high risk (HR, 0.97; 95% CI, 0.73-1.29), compared with clopidogrel–aspirin (*P*=0.02 for interaction). Secondary outcomes generally went in the same direction as the primary outcome. The primary safety

outcome of severe or moderate bleeding did not differ based on risk profile (*P*=0.24 for interaction), though the incidence of total bleeding was greater with ticagrelor–aspirin than clopidogrel–aspirin among patients at low risk (*P*<0.01 for interaction). Analysis in the per-protocol population yielded similar results.

Discussion: This post-hoc analysis of CHANCE-2 trial showed that *CYP2C19* LOF carriers with minor stroke or TIA at low risk of recurrent stroke received a greater benefit from ticagrelor–aspirin than clopidogrel–aspirin.

Classification of Evidence: This study provides Class II evidence that *CYP2C19* LOF carriers with minor stroke or TIA at low risk, but not at high risk, of recurrent stroke (by ESRS score) received a greater benefit from ticagrelor–aspirin than clopidogrel-aspirin.

Keywords: CHANCE-2; Stroke; Ticagrelor; Clopidogrel; Essen Stroke Risk Score

Clinical trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT04078737

Introduction

Among patients with an acute minor stroke or transient ischemic attack (TIA), the risk of another stroke within 3 months after the initial event is approximately 5 to 10%.[1-3] Clinical trials have shown that early initiation of dual antiplatelet therapy with clopidogrel–aspirin compared to aspirin alone significantly reduced the incidence of stroke events during the first 3 months follow-up.[4, 5] However, clopidogrel is a prodrug requiring conversion into its active metabolite by hepatic cytochrome p450 (CYP). Clopidogrel is less effective for the secondary prevention of stroke in carriers of *CYP2C19* loss-of-function (LOF) alleles, which are presented in 25% of white patients and in 60% of Asian patients.[6, 7] Genotype data from the Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trial showed that efficacy of clopidogrel-aspirin was further influenced by risk profile assessed by the Essen Stroke Risk Score (ESRS).[8] The ESRS is an easy-to-use 9-point scale derived and validated from the datasets of large clinical trials, and it can help physicians predict the risk of recurrent stroke and cardiovascular events in patients with acute ischemic stroke.[9, 10] The results of CHANCE trial showed that *CYP2C19* LOF carriers who were at high risk (ESRS≥3) received a greater benefit from clopidogrel-aspirin.[8] These findings indicated that stratification of patients who carried *CYP2C19* LOF alleles according to risk of recurrent stroke may possibly be important for selecting optimal antiplatelet therapy.

The Ticagrelor or Clopidogrel with Aspirin in High Risk Patients with Acute

Nondisabling Cerebrovascular Events II (CHANCE-2)[11] trial was conducted among patients with minor stroke or TIA who carried *CYP2C19* LOF alleles and showed that the risk of stroke within 90 days was modestly lower with ticagrelor–aspirin than with clopidogrel–aspirin. However, whether the benefit of ticagrelor–aspirin compared with clopidogrel-aspirin for patients who carried *CYP2C19* LOF alleles differed by risk profiles remains unascertained. Therefore, our study utilized data from the CHANCE-2 trial to investigate whether the efficacy and safety of ticagrelor–aspirin versus clopidogrel–aspirin therapy were stratified by risk profile assessed using the ESRS in *CYP2C19* LOF carriers with minor stroke or TIA.

Methods

Study Population

This study was a post-hoc analysis of the CHANCE-2 trial. The detailed study design of the CHANCE-2 trial has been described elsewhere.[12] Briefly, the CHANCE-2 trial is a multicenter, randomized, double-blind, placebo-controlled trial conducted at 202 centers in China from September 23, 2019 to March 22, 2021. The study was designed to compare dual antiplatelet therapy with ticagrelor plus aspirin (placebo clopidogrel plus a 180 mg loading dose of ticagrelor on day 1, followed by 90 mg twice daily on days 2-90) with clopidogrel plus aspirin (placebo ticagrelor plus a 300 mg loading dose of clopidogrel on day 1, followed by 75 mg daily on days 2-90) among 6,412 patients with minor stroke or TIA within 24 hours of symptom onset and who carried *CYP2C19* LOF alleles. The study protocol and statistical analysis plan

are available in the Supplement.

Risk Stratification by ESRS

Based on the baseline information of the CHANCE-2 trial, the ESRS was calculated for all patients at the time of admission: 2 points for age >75 years and 1 point each for age 65-75 years, hypertension, diabetes mellitus, myocardial infarction, other cardiovascular disease (except myocardial infarction and atrial fibrillation), peripheral arterial disease, current or past smoking, and previous TIA or ischemic stroke. The ESRS with a range from 0 to 9 was categorized as low risk (<3) and high risk (≥3).[8-10] In addition to the components of ESRS, the modified ESRS was generated by adding 1 point each for waist circumference ≥90 cm, stroke subtype except small artery occlusion, and men. The modified ESRS with a range from 0 to 12 was also categorized as low risk (<6 in men and <5 in women) and high risk (≥6 in men and ≥5 in women), which was used in the sensitivity analysis.[13, 14]

Outcomes Assessment

The primary outcome was new ischemic or hemorrhagic stroke within 90 days. Secondary outcomes included new stroke within 30 days, a vascular event (a composite of stroke, TIA, myocardial infarction, or death from vascular causes) within 90 days, and ischemic stroke within 90 days. 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.[15] Secondary safety outcome was any bleeding through 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. The committee members classified ischemic stroke subtypes on the basis of available medical records, including imaging data.

Statistical Analysis

Baseline characteristics were compared between groups categorized by ESRS levels. Continuous variables were presented in medians (interquartile ranges) and compared between groups using the nonparametric Wilcoxon test. Categorical variables were presented as percentages and tested by chi-squared test. Kaplan-Meier product limit method was used to generate survival plots, and the significance of differences between groups was tested by the log-rank test. Differences in the outcomes during the 90-day follow-up period were assessed using a Cox proportional hazard regression model, and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. When there were multiple events of the same type, the time to the first event was used in the model. Data from patients who had no event during 90-day follow-up were censored at termination of the trial or nonvascular death. For each model, the proportional hazards assumption was assessed by testing the interaction of treatment by time in the model. Whether the treatment effect differed in different risk profile categories was examined by testing the interactions of treatment by ESRS categories in the Cox model. Sensitivity analyses were performed using modified ESRS to

redefine risk profile and in the per-protocol population. All statistical analyses were performed with SAS statistical software, version 9.4 (SAS Institute Inc). All tests were 2-sided, and P <0.05 was considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The standard protocol and informed consent were approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2019-035-02) and all participating centers. Written informed consent was provided by all the patients or their representatives before enrollment. The trial was registered at ClinicalTrials.gov (Registration-URL: http://www.clinicaltrials.gov; unique identifier: NCT04078737).

Data Availability

Data are available to researchers on request for purposes of reproducing the results or replicating the procedure by directly contacting the corresponding author.

Results

Baseline Characteristics

Table 1 shows baseline characteristics of the study cohort stratified by ESRS levels and treatment. There were 3,899 patients (60.8%) at low risk (ESRS <3) and 2,513 patients (39.2%) at high risk (ESRS ≥3). The differences in all study variables between ticagrelor–aspirin group and clopidogrel–aspirin group were not significant except time from symptom onset to randomization and previous antiplatelet therapy in

147 the low risk group, and ESRS in the high risk group. Baseline characteristics stratified
148 by modified ESRS and treatment are presented in eTable 1 in the Supplement. All the
149 characteristics were well balanced except history of myocardial infarction in the low
150 risk group and history of TIA or ischemic stroke in the high risk group.
151
152 **Efficacy Outcomes**
153 Within 90 days follow-up, recurrent stroke occurred in 198 patients (7.9%) in patients
154 at high risk and 236 patients (6.0%) in patients at low risk (*P*=0.004). The
155 relationships between treatment assignment and outcome differed by baseline risk
156 estimated by ESRS (*P*=0.02 for interaction). Ticagrelor–aspirin compared with
157 clopidogrel–aspirin was associated with a reduced incidence of new stroke in patients
158 at low risk (HR, 0.63; 95% CI, 0.48-0.82; *P*<0.001) but not in those at high risk (HR,
159 0.97; 95% CI, 0.73-1.29; *P*=0.08) (Table 2). Cumulative risk of new stroke among
160 patients at low or high risk by treatment assignment is shown in Figure 1; those at low
161 risk and treated with ticagrelor–aspirin experienced the lowest risk of new stroke
162 (*P*<0.001, log-rank test). Similar results were observed for the secondary outcomes of
163 new stroke within 30 days, combined vascular event and ischemic stroke within 90
164 days (Table 2). The results were replicated in the sensitivity analysis using modified
165 ESRS to redefine different risk groups, the incidence of new stroke was higher in
166 patients at high risk (100 patients, 8.95%) than that in patients at low risk (334
167 patients, 6.31%) (*P*=0.001) (eTable 2 and eFigure 1 in the Supplement). Results of the
168 per-protocol analysis were consistent with the intention-to-treat analysis (eTable 3-4

in the Supplement).

Safety Outcomes

Patients at low (ESRS<3) or high risk (ESRS ≥3) in the ticagrelor–aspirin group and the clopidogrel–aspirin group had a similar incidence of severe or moderate bleeding (0.1% and 0.3% in low risk group vs 0.6% and 0.5% in high risk group; *P*=0.24 for interaction) (Table 2). As the secondary safety outcome, the incidence of any bleeding was higher in the ticagrelor–aspirin than in the clopidogrel–aspirin among patient at low risk (5.8% vs 1.9%) but not among patients at high risk (4.6% vs 3.4%) (*P*=0.01 for interaction between ESRS categories and treatment). The results were similar for the modified ESRS and in the per-protocol analysis (eTable 2-4 in the Supplement).

Classification of Evidence: This study provides Class II evidence that *CYP2C19* LOF carries with minor stroke or transient ischemic attack at low risk, but not at high risk, of recurrent stroke (by ESRS score) received a greater benefit from ticagrelor–aspirin than clopidogrel-aspirin.

Discussion

In this post-hoc analysis of the CHANCE-2 trial, we found that among patients with minor stroke or TIA who were *CYP2C19* LOF carriers, ticagrelor–aspirin versus clopidogrel–aspirin was associated with a significantly decreased risk of new stroke in patients at low risk of recurrent stroke. Overall, among patients at low risk, the

incidence of total bleeding events was greater with ticagrelor–aspirin, mainly owing to mild bleeding, but there was not an increased incidence of moderate or severe bleeding. Our findings indicated that risk stratification by ESRS may provide additional information on identifying patients who may receive greater benefit from ticagrelor–aspirin therapy.

The prognosis of minor stroke or TIA is quite variable and is influenced by the prevalence and levels of prognostic factors. Large population and clinical studies have identified risk factors that are associated with poor clinical outcomes in patients with stroke or TIA, including older age, smoking, hypertension, diabetes mellitus, cardiovascular disease, and peripheral artery disease.[9, 10, 16-18] Additionally, these risk factors may influence the selection of antiplatelet therapy. For instance, the POPular AGE trial showed in patients aged 70 years or older presenting with non-ST elevation acute coronary syndrome, clopidogrel was a favorable alternative to ticagrelor.[19] A meta-analysis of randomized trials reported in smokers, patients with clopidogrel received a better clinical benefit in reducing cardiovascular outcomes than those with ticagrelor.[20] The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial showed that in patients with acute coronary syndrome with or without ST-segment elevation, ticagrelor as compared with clopidogrel significantly reduced the incidence of cardiovascular death.[21] Data from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study reported that the absolute benefit of clopidogrel over aspirin for subsequent combined vascular events was amplified in patients with a

history of diabetes or ischemic events.[22] Based on these factors, ESRS was derived from the patients with ischemic stroke in the large-scale CAPRIE[9] trial and was validated in the Reduction of Atherothrombosis for Continued Health (REACH) registry population, and could predict the risk of recurrent stroke and cardiovascular events in patients with acute ischemic stroke.[10] Consistent with previous studies, our study also found that a higher ESRS score was associated with a higher risk of recurrent stroke within 90-day follow-up.

Previous studies suggested that in addition to modification of these stroke risk factors, a stratification of patients according to risk of recurrent stroke assessed by ESRS may provide support to optimize treatment regiments. Subgroup analysis of CAPRIE trial showed that clopidogrel compared to aspirin was particularly beneficial to patients at high risk, defining as >4% per year for recurrent stroke as assessed by the ESRS.[9] A prospective cohort study conducted among Chinese patients with TIA or ischemic stroke admitted to 132 hospitals throughout China, and suggested that clopidogrel may be preferable to aspirin in patients with an ESRS >3, and aspirin may be preferred over clopidogrel for patients with an ESRS ≤3 for the secondary prevention of non-cardioembolic ischemic stroke.[23] Except for risk profile, *CYP2C19* genotype was also used to individualize antiplatelet therapy. A meta-analysis showed that *CYP2C19* genetic testing could guide patients undergoing percutaneous coronary intervention to select optimal antiplatelet therapy, thus may reduce the risk of major adverse cardiovascular events.[24] Furthermore, post-hoc analysis of the CHANCE trial

showed that the benefit of clopidogrel in Chinese minor stroke or TIA patients depended on both *CYP2C19* genotype and risk profile. Overall, *CYP2C19* LOF carriers do not benefit from dual antiplatelet therapy with clopidogrel–aspirin, but there is significant benefit for LOF carriers who are at high risk (ESRS ≥3).[25] Such findings suggested that ticagrelor not reducing the risk of recurrent stroke over clopidogrel in high risk *CYP2C19* LOF carriers. Similarly with these studies, our analysis found that the efficacy of clopidogrel–aspirin was associated with a similar incidence of recurrent stroke with ticagrelor–aspirin among *CYP2C19* LOF carriers at high risk, but in patients at low risk, ticagrelor–aspirin was associated with a lower risk of stroke.

The mechanisms underlying our findings are complex and multifactorial. First, it is appropriate to speculate that patients at high stroke risk assessed by ESRS were more likely to have thrombotic tendencies, systematic inflammation, and other basic diseases related to stroke[26], antithrombotic treatment alone may not be sufficient for adequate protection against ischemic events[27], thus there were not apparent differences in the efficacy between ticagrelor–aspirin and clopidogrel–aspirin among patients at high risk. Second, as previously reported[8], stroke patients with *CYP2C19* LOF alleles at high risk also received a significant benefit from clopidogrel–aspirin treatment, which could explain why ticagrelor-aspirin did not exhibit a stronger effect in reducing recurrent stroke over clopidogrel among these patients to some extent. Additionally, the proportion of patients in the high risk group on antiplatelet therapy

prior to the index event was higher, and there was no washout period for the prior anti-platelet treatment, which may lead to a higher antiplatelet load in these patients and the unapparent benefit of ticagrelor-aspirin therapy. These findings suggest that the risk profile, according to ESRS levels, should be taken into consideration in the implementation of antiplatelet therapy in clinical practice, ticagrelor-aspirin is associated with a lower risk of recurrent stroke in low risk *CYP2C19* LOF carriers when compared to clopidogrel-aspirin.

Our study has several limitations. First, our cohort was made up of Chinese population, a population has a higher incidence of intracranial-artery stenosis than non-Asian population, and ticagrelor and clopidogrel may have different effects in other population, which might limit generalizability. Second, this study was a post-hoc analysis, thus the results should be interpreted with caution and needed to be further confirmed by other studies. Third, the washout period of the prior antiplatelet treatments was not available in our study, which may have influenced the benefits of ticagrelor in patients at low risk.

Conclusions

This post-hoc analysis of CHANCE-2 trial found that among *CYP2C19* LOF carriers with minor stroke or TIA, ticagrelor–aspirin was superior to clopidogrel-aspirin in reducing the risk of subsequent stroke in those at low risk (ESRS<3). The risk of severe or moderate bleeding did not differ between the two treatment groups across

different risk groups, but the risk of any bleeding was higher with ticagrelor–aspirin in patients at low risk.

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Figure and legends

Figure 1. Cumulative Probability of Stroke According to treatment and risk profile

C denotes clopidogrel; ESRS denotes Essen Stroke Risk Score; T denotes ticagrelor.

Table 1. Baseline Characteristics According to Risk Profile

Characteristics	Low Risk, ESRS <3			High Risk, ESRS ≥3		
	Ticagrelor -Aspirin (N=1940)	Clopidogrel -Aspirin (N=1959)	*P* value	Ticagrelor -Aspirin (N=1265)	Clopidogrel -Aspirin (N=1248)	*P* value
Median age (IQR) -yr	60.5(54.4-66.5)	60.8(54.4-66.2)	0.74	70.9(65.8-77.2)	70.1(65.6-76.6)	0.05
Female sex - no. (%)	678 (34.9)	663 (33.8)	0.47	412(32.6)	417(33.4)	0.65
Median BMI (IQR), kg/m^2	24.5(22.7-26.7)	24.2(22.6-26.4)	0.05	24.5(22.6-26.6)	24.4(22.5-26.5)	0.42
Median ESRS (IQR)	2(1-2)	1(1-2)	0.61	3(3-4)	3(3-4)	0.03
ESRS components, no. (%)						
Age						
<65 yr	1347(69.4)	1370(69.9)	0.90	255(20.2)	280(22.4)	0.04
65-75 yr	517(26.6)	510(26.0)		571(45.8)	548(43.3)	
>75 yr	76(3.9)	79(4.0)		462(36.5)	397(31.8)	

Hypertension	910(46.9)	932(47.6)	0.68	1066(84.3)	1047(83.9)	0.80
Diabetes	272(14.0)	244(12.5)	0.15	536(42.4)	511(40.9)	0.47
Myocardial infarction	9(0.5)	4(0.2)	0.16	45(3.6)	38(3.0)	0.47
Other heart diseases	36(1.9)	44(2.2)	0.39	188(14.9)	194(15.5)	0.63
Peripheral vascular disease	2(0.1)	2(0.1)	0.99	4(0.3)	5(0.4)	0.72
Smoker	616(31.8)	643(32.8)	0.47	612(48.4)	587(45.4)	0.08
History of TIA or ischemic stroke	169(8.7)	151(7.7)	0.25	531(42.0)	567(58.5)	0.33
CYP2C19 LOF carriers - no. (%)						
Intermediate metabolizers	1515(78.1)	1531(78.2)	0.96	971(76.8)	984(78.8)	0.21
Poor metabolizers	425(21.9)	428(21.8)		294(23.2)	264(21.2)	
Median time from symptom onset to randomization (IQR) — hr.	13.7(9.2-20.3)	14.9(9.2-21.0)	0.02	13.4(8.6-20.5)	13.2(8.3-20.0)	0.55
Qualifying event - no. (%)						
Ischemic stroke	1567(80.8)	1596(81.5)	0.58	1010(79.8)	985(78.9)	0.57

TIA	373(19.2)	363(18.5)		255(20.2)	263(21.1)	
Median NIHSS score in patients with qualifying ischemic stroke (IQR) *	2(1-3)	2(1-3)	0.85	2(1-3)	2(1-3)	0.33
Median $ABCD^2$ score in patients with qualifying TIA (IQR) †	4(4-5)	4(4-5)	0.28	5(4-6)	5(4-6)	0.05
Previous antiplatelet therapy - no. (%)‡	112(5.8)	85(4.3)	0.04	273(21.6)	278(22.3)	0.67
Previous lipid-lowering therapy - no. (%)‡	73(3.8)	56(2.9)	0.11	185(14.6)	185(14.8)	0.89

BMI denotes body mass index; ESRS denotes Essen Stroke Risk Score. IQR denotes interquartile range. IS denotes ischemic stroke. TIA denotes transient ischemic attack. LOF denotes loss-of-function.

* National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe stroke.

† $ABCD^2$ score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes, with scores ranging from 0 to 7 and higher scores indicating greater risk.

‡ Medication within 1 month before symptom onset.

Table 2. Efficacy and Safety Outcomes of Patients With Different Antiplatelet Therapies Stratified by Risk Profile

Outcome	Low risk, ESRS <3				High Risk, ESRS ≥3				P_{int}
	Ticagrelor-Aspirin, event rate (%)*	Clopidogrel-Aspirin, event rate (%)*	HR (95%CI)	*P* value	Ticagrelor-Aspirin, event rate (%)*	Clopidogrel-Aspirin, event rate (%)*	HR (95%CI)	*P* value	
Primary outcome									
Stroke	92 (4.7)	144 (7.4)	0.63(0.48-0.82)	<0.001	99 (7.8)	99 (7.9)	0.97(0.73-1.29)	0.08	0.02
Secondary outcomes									
Stroke within 30 days	78 (4.0)	126 (6.4)	0.62(0.46-0.82)	<0.001	78 (6.2)	79 (6.3)	0.97(0.70-1.34)	0.86	0.02
Composite vascular events†	111 (5.7)	167 (8.5)	0.66(0.52-0.84)	<0.001	118 (9.3)	126 (10.1)	0.92(0.71-1.19)	0.53	0.04
Ischemic stroke	92 (4.7)	142 (7.2)	0.64(0.49-0.83)	<0.001	97 (7.7)	96 (7.7)	0.98(0.73-1.30)	0.87	0.02
Primary safety outcome									
Severe or moderate bleeding‡	2 (0.1)	5 (0.3)	0.39(0.08-2.02)	0.26	7 (0.6)	6 (0.5)	1.27(0.42-3.81)	0.67	0.24
Secondary safety outcome									

Any bleeding	112 (5.8)	37 (1.9)	3.27(2.24-4.79)	<0.001	58 (4.6)	43 (3.4)	1.26(0.83-1.90)	0.28	0.01

CI denotes confidence interval. ESRS denotes Essen Stroke Risk Score. HR denotes hazard ratio. mRS denotes modified Rankin Scale. TIA denotes transient ischemic attack.

* Event rates for ordinal stroke or TIA are raw estimates, whereas event rates for other outcomes are Kaplan-Meier estimates of the percentage of patients with events at 90 days.

† Composite vascular events include ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, vascular death.

‡ Severe or moderate bleeding and mild bleeding were defined according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria.