Ticagrelor-Aspirin versus Clopidogrel-Aspirin among *CYP2C19* Loss-of-Function Carriers with Minor Stroke or TIA in Relation to Renal Function: A Post Hoc Analysis of CHANCE-2 Trial

Short title: Renal function and dual antiplatelet therapy

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ABSTRACT

Background: Evidence on the risk-benefit ratio of dual antiplatelet therapies among stroke patients with impaired renal function is limited and inconsistent.

Objective: To investigate the effect of renal function on the efficacy and safety of ticagrelor-aspirin versus clopidogrel-aspirin treatment.

Design: Post hoc analysis of a multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov: NCT04078737).

Setting: 202 centers in China.

Patients: *CYP2C19* loss-of-function allele carriers with minor stroke or transient ischemic attack.

Intervention: Ticagrelor-aspirin and clopidogrel-aspirin.

Measurements: Renal function was evaluated by estimated glomerular filtration rate (eGFR) levels. The primary efficacy and safety outcomes were recurrent stroke and severe or moderate bleeding within 90 days, respectively.

Results: Among 6,378 patients, 4,050 (63.5%) patients had normal (eGFR≥90 mL/min/1.73m^2), 2,010 (31.5%) patients had mildly decreased (eGFR 60-89 mL/min/1.73m^2), and 318 (5.0%) patients had moderately to severely decreased (eGFR<60 mL/min/1.73m^2) renal function. The corresponding differences in recurrent stroke between ticagrelor-aspirin and clopidogrel-aspirin for normal, mildly decreased and moderately to severely decreased renal function was -2.8 percentage point (95% CI, -4.4 to -1.3 percentage point) (hazard ratio [HR], 0.63 [CI, 0.49 to 0.81]), -0.2 percentage point (CI, -2.4 to 2.0 percentage point) (HR, 0.98 [CI, 0.69 to

1.39]), and 3.7 percentage point (CI, -2.3 to 10.1 percentage point) (HR, 1.31 [CI, 0.48 to 3.55]) respectively. Rates of severe or moderate bleeding did not substantially differ by treatment assignments across eGFR categories.

Limitation: Renal function was only evaluated by using eGFR and the proportion of patients with severely decreased renal function was low.

Conclusion: Patients with normal, rather than impaired renal function, received greater benefit from ticagrelor-aspirin versus clopidogrel-aspirin.

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Keywords: Ticagrelor-aspirin; Clopidogrel-aspirin; Estimated glomerular filtration rate; Stroke

Introduction

Impaired renal function is associated with abnormalities in platelet function, which may explain increases in both thrombotic and hemorrhagic complications in patients with stroke[1-5]. Antiplatelet therapies can reduce thrombotic risk in patients with impaired renal function but come at the expense of impaired hemostasis. This may alter the risk-benefit ratio with antiplatelet therapies in stroke patient with impaired renal function. Therefore, determining the optimal antiplatelet strategies in this population is of utmost importance.

Dual antiplatelet therapy with clopidogrel-aspirin is often recommended for preventing stroke[6-8]. Ticagrelor, a reversible and direct-acting oral antagonist of P2Y12 inhibitor, can provide greater, faster, and more consistent P2Y12 inhibition than clopidogrel[9, 10]. Ticagrelor has been shown to be an effective antiplatelet therapy for the prevention of recurrent stroke[11], particularly in those carrying *CYP2C19* loss-of-function (LOF) alleles[12,13]. Reduced renal clearance of clopidogrel (and less so ticagrelor) could increase the risk of increased plasma concentrations in patients with impaired renal function and so renal function needs to be considered when selecting optimal antiplatelet therapy. Some studies suggested that patients with impaired renal function may not derive the same degree of benefit from clopidogrel therapy as those with normal renal function.[14, 15] In contrast, some studies have suggested that patients with impaired renal function received more benefit from clopidogrel or ticagrelor[16, 17]. Additionally, uncertainties remain about whether the benefit of ticagrelor-aspirin

versus clopidogrel-aspirin is in relation to renal function among *CYP2C19* LOF alleles carriers with minor ischemic stroke or transient ischemic attack (TIA).

Using data from the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events-II (CHANCE-2) trial, we investigated the efficacy and safety of ticagrelor-aspirin versus clopidogrel-aspirin in patients with minor stroke or TIA who carried *CYP2C19* LOF alleles with different renal function evaluated by estimated glomerular filtration rate (eGFR) levels.

Methods

Study design and populations

This study is a post hoc analysis of the CHANCE-2 trial. Details on the design, protocol and primary results of CHANCE-2 have been published elsewhere[12, 18]. Briefly, CHANCE-2 trial was a randomized, double-blind, controlled trial conducted at 202 centers across mainland China from September 23, 2019 to March 22, 2021 (ClinicalTrials. gov: NCT04078737). A total of 6,412 patients who met the following inclusion criteria were enrolled: (1) age of 40 years or older; (2) mild acute ischemic stroke (National Institutes of Health Stroke Score of ≤3) or a high-risk TIA ($ABCD^2$ score of ≥4); (3) a carrier of *CYP2C19* LOF alleles; (4) administration of the trial drug within 24 hours of symptom onset; and (5) signed informed consent. The protocol of the trial was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2019-035-02) and each participating site. All participants or

their representatives provided written informed consent before enrollment.

Randomization and treatment

Within 24 hours after symptom onset, eligible patients carrying *CYP2C19* LOF alleles were randomly assigned in a 1:1 ratio to receive ticagrelor–aspirin or clopidogrel–aspirin. Patients were randomly assigned a number corresponding to a medication kit that was given to each patient. Patients in the ticagrelor-aspirin group received the clopidogrel placebo and a 180 mg loading dose of ticagrelor on day 1 followed by 90 mg twice daily for days 2-90. Patients in the clopidogrel-aspirin group received the ticagrelor placebo and a 300 mg loading dose of clopidogrel, followed by 75 mg daily together for days 2-90. Both groups received a 75 to 300 mg loading dose of aspirin on day 1, followed by 75 mg daily for 21 days.

Calculation of eGFR

Venous blood samples were obtained before randomization and were sent for laboratory analysis of creatinine concentration. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (CKD-EPI)[19]: $eGFR=141\times\min(SCr/k,1)^{\alpha}\times\max(SCr/k,1)^{-1.209}\times0.993^{Age}\times1.018$ (if female), where SCr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1. CKD-EPI China equation was calculated with coefficient of 1.1[20]. According to the National Kidney Foundation Kidney Disease Outcomes

Quality Initiative (NKF-KDOQI) guidelines[21, 22], normal renal function was defined as eGFR≥90 mL/min/1.73m^2, mildly decreased renal function was defined as eGFR of 60 to 89 mL/min/1.73m^2, moderately decreased renal function was defined as eGFR of 30 to 59 mL/min/1.73m^2, and severely decreased renal function was defined as eGFR <30 mL/min/1.73m^2.

Outcomes Assessment

The primary outcome was a new ischemic or hemorrhagic stroke within 90 days. Secondary outcomes included new stroke within 30 days, composite vascular events (stroke, TIA, myocardial infarction and vascular death), ischemic stroke, disabling stroke (with a subsequent modified Rankin Scale [mRS] score of 2 or higher; range 0 to 6 with higher scores reflecting greater handicap) at Day 90, and ordinal severity of stroke or TIA (severity measured using a six-level ordered categorical scale that incorporates subsequent stroke or TIA events and mRS score at Day 90:[5] fatal stroke [stroke with subsequent mRS score of 6], severe stroke [stroke with subsequent mRS score of 4 or 5], moderate stroke [stroke with subsequent mRS score of 2 or 3], mild stroke [stroke with subsequent mRS score of 0 or 1], TIA, and no stroke or TIA) through 90 days of follow-up.

The primary safety outcome was severe or moderate bleeding defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria within 90 days[23]. Secondary safety outcomes included any

bleeding, death, adverse events and severe adverse events through 90 days of follow-up.

Statistical analysis

Continuous variables are presented as median with interquartile range (IQR) and categorical variables as frequencies and percentages. The differences in the proportions for the dichotomous outcomes between treatment groups, and their corresponding 95% confidence intervals (CIs), were estimated based on Newcombe-Wilson[24], with stratification by eGFR category. Kaplan-Meier analysis was used to calculate the cumulative incidence of the primary outcome during 90-days follow-up for each eGFR category. Differences in the outcome end points during the 90-day follow-up period were assessed using a Cox proportional hazards regression model, with study centers set as a random effect, and hazard ratios (HRs) with 95% CIs were reported. When there were multiple events of the same type, the time to the first event was used in the model. Patients without any events during 90-day follow-up were censored at the time of termination of the trial or nonvascular death. Similar methods were used for the comparison of the secondary outcomes of new stroke events, clinical vascular events, ischemic stroke, and disabling stroke and for comparison of the safety outcomes. Shift analysis was performed for the secondary outcome of ordinal stroke or TIA between the two treatment groups using ordinal logistic regression, and the common odds ratio and 95% CI reported. To test the robustness of the findings, sensitivity analyses were performed by calculating eGFR using CKD-

EPI for Chinese population and in the per-protocol population. All statistical analyses were performed with SAS statistical software, version 9.4 (SAS Institute Inc).

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Results

Baseline characteristics

Of the 6,412 eligible patients recruited to the CHANCE-2 trial, 6,378 (99.47%) patients with eGFR measurement were analyzed in the current study (Figure 1). The median age of enrolled patients was 64.5 (IQR, 57.0 to 71.4) years, and 2,165 (33.9%) were women. Overall, 4,050 (63.5%) patients had normal renal function (eGFR≥90 mL/min/1.73m^2), 2,010 (31.5%) patients had mildly decreased renal function (eGFR of 60-89 mL/min/1.73m^2), 309 (4.8%) patients had moderately decreased renal function (eGFR of 30-59 mL/min/1.73m^2), and 9 (0.2%) patients had severely decreased renal function (eGFR <30 mL/min/1.73m^2). Considering the small sample size of patients with moderately and severely decreased renal function, those patients

were combined into one group as moderately to severely decreased renal function (eGFR<60 mL/min/1.73m^2). The baseline characteristics in the ticagrelor-aspirin and clopidogrel-aspirin groups across the three eGFR categories were well balanced (Table 1).

Efficacy outcomes

The primary efficacy outcome of recurrent stroke within 90 days occurred in 189 (5.9%) patients receiving ticagrelor-aspirin and 243 (7.6%) patients receiving clopidogrel-aspirin. Ticagrelor-aspirin compared with clopidogrel-aspirin was associated with a reduced rate of recurrent stroke in patients with normal renal function (5.2% vs. 8.1%; difference, -2.8 percentage point [95% CI, -4.4 to -1.3 percentage point]; HR, 0.63 [CI, 0.49 to 0.81]), but not in those with mildly decreased renal function (6.7% vs.6.9%; difference, -0.2 percentage point [CI, -2.4 to 2.0 percentage point]; HR, 0.98 [CI, 0.69 to 1.39]), or those with moderately to severely decreased renal function (9.8% vs 6.1%; difference, 3.7 percentage point [CI, -2.3 to 10.1 percentage point]; HR, 1.31[CI, 0.48 to 3.55]) (Table 2 and Figure 2). Similar results were present for the secondary outcomes of combined vascular event, ischemic stroke, and ordinal stroke or TIA within 90 days of follow-up (Table 2).

Results of the sensitivity analysis by calculating eGFR using CKD-EPI for Chinese population were consistent with the primary analysis, showing that the difference in the rate of recurrent stroke between ticagrelor-aspirin group and clopidogrel-aspirin

was -2.4 percentage point [CI, -3.8 to -1.1 percentage point]) (HR, 0.68 [CI, 0.54 to 0.84]) in patients with normal renal function (Table S1 and Figure S1). Additionally, the per-protocol analysis yielded similar results to the intention-to-treat analysis; the HR for recurrent stroke in ticagrelor-aspirin group compared with clopidogrel-aspirin group was 0.61 (CI, 0.48 to 0.79) in patients with normal renal function (Table S2 and Figure S2).

Safety outcomes

The rate of primary safety outcome of severe or moderate bleeding in the ticagrelor-aspirin group and the clopidogrel-aspirin group was similar in patients with normal renal function (0.2% vs 0.3%; difference, -0.1 percentage point [CI, -0.5 to 0.2 percentage point], HR, 0.59 [CI, 0.17 to 2.01]); mildly decreased renal function (0.4% vs 0.3%; difference, 0.1 percentage point [CI, -0.6 to 0.7 percentage point], HR, 1.28 [CI, 0.28 to 5.75]); and moderately to severely decreased renal function (0.7% vs 0.6%; difference, 0.0 percentage point [CI, -2.8 to 3.0 percentage point]) (Table 3). Similar results were yielded for second safety outcomes. Sensitivity analyses were consistent with the main analysis (Table S1-S2).

Discussion

Based on the CHANCE-2 trial, our study found that ticagrelor-aspirin, compared with clopidogrel-aspirin, substantially reduced the risk for recurrent stroke within 90 days of follow-up in patients with normal renal function, but this benefit was not apparent

in those with mildly or moderately to severely decreased renal function. Meanwhile, there was no absolute increase in severe or moderate bleeding events with ticagrelor-aspirin treatment across eGFR categories although this was based on small numbers.

Many post hoc analyses have evaluated the effect of renal function on the efficacy and safety of antiplatelet therapies and yielded divergent results on this context. Some studies observed a significant benefit of intensive antiplatelet therapies among patients with normal renal function. For example, in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, clopidogrel versus placebo reduced the composite of death, myocardial infarction, and stroke in patients with normal renal function and acute coronary syndrome (ACS) after percutaneous coronary intervention, but with a trend in the opposite direction with an absolute increased event rate in patients with mild or moderate renal dysfunction[14]. A post hoc analysis of the CHANCE trial found that clopidogrel plus aspirin compared with aspirin alone in patients with normal renal function and mild renal insufficiency resulted in a significant reduction in new stroke events and combined vascular events at 90 days of follow-up, but this benefit was not apparent in moderate chronic kidney disease (CKD) patients[15]. In accordance with the above studies, our study was conducted among *CYP2C19* LOF allele carriers with minor ischemic stroke or TIA, showing that ticagrelor-aspirin, of which ticagrelor can provide more consistent P2Y12 inhibition than clopidogrel[9, 10], was associated with a lower risk of recurrent stroke in patients with normal renal function compared with clopidogrel-aspirin, while the benefit was

not observed in patients with mildly or moderately to severely decreased renal function.

However, as opposed to the results, some studies showed reduced or lack of effect with intensive antiplatelet therapies among patients with normal renal function. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, there was a modest absolute and relative reduction in the primary ischemic end point with clopidogrel versus placebo among patients with renal dysfunction compared with those with normal renal function, although without any significant interaction[16]. Subgroup analysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial showed that ticagrelor significantly reduced the rate of ischemic end points and mortality compared to clopidogrel in ACS patients with CKD, also the interactions between creatinine clearance and randomized treatment on any of the outcome variables were nonsignificant[17].

Although the reasons for these inconsistent results are unclear, plausible explanations may include the highly heterogeneous target populations across these studies, as well as the different treatment assignments and trial design paradigms. In addition, potential mechanisms underlying our results may be a synergistic relationship between the thrombotic effects of renal dysfunction and the antithrombotic effects of dual antiplatelet treatment. First, decreased renal function is characterized as a state with a prothrombotic tendency, and is associated with anemia, homocysteinemia,

reduced nitric oxide, oxidative stress, inflammation, and conditions promoting coagulation; all these pathological processes may be related to the development of recurrent stroke in the course of decreased renal function[25-27]. The levels of platelet inhibition from different antiplatelet therapies may not be sufficient for adequate protection against ischemic events in these patients at high risk. Second, differences in the pharmacodynamic and pharmacokinetic profiles of ticagrelor and clopidogrel[28] mean the excretion of ticagrelor is less dependent on renal function as compared with clopidogrel[29-31]. One pharmacological study showed that 26.5% of ticagrelor is excreted through kidney, and the recovery of ticagrelor and its active metabolites in the urine is less than 1% of the dose[32]. As for clopidogrel, almost 50% of clopidogrel as well as part of its active metabolite was excreted in the urine[33]; hence, renal clearance is of minor importance in the excretion of ticagrelor as compared with clopidogrel. For patients with decreased renal function, the excretion of clopidogrel and its active metabolites will be limited leading to an increase in half-life and higher peak concentration in the body. As a result, the benefit of ticagrelor over clopidogrel may not be observed in patients with decreased renal function.

For the safety outcomes of bleeding risk, a substudy of PLATO study also found that major bleedings were not significantly increasing in ticagrelor group compared with clopidogrel group[17]. The TWILIGHT-CKD (The Ticagrelor With Aspirin or Alone in High Risk Patients After Coronary Intervention) trial showed that among CKD patients undergoing percutaneous coronary intervention, ticagrelor monotherapy

316 reduced the risk of bleeding without a significant increase in ischemic events as
317 compared with ticagrelor plus aspirin[34]. In line with these studies, our study found
318 that patients receiving ticagrelor-aspirin did not show an absolute increase in severe or
319 moderate bleeding events across different eGFR categories, although the number of
320 bleeding events was relatively small in our study. However, it should be noted that the
321 incidence of total bleeding, mainly mild bleeding, was greater with ticagrelor-aspirin
322 in different eGFR categories. Additionally, several previous studies have
323 demonstrated that patients with impaired renal function have a higher bleeding
324 tendency regardless of antiplatelet therapies[35-37]. Taken together, these findings
325 indicated that the bleeding risk should be carefully assessed and monitored in clinical
326 utility of antiplatelet therapies.
327
328 There were several limitations to the study. First, renal function was defined by eGFR
329 only, with no data available on the presence of albuminuria or proteinuria. Although it
330 will be more precise to diagnose CKD based on the combination of eGFR and
331 albuminuria/proteinuria, the collection and measurement of urine samples in the acute
332 stage of stroke/TIA is challenging in a large population. Ideally, albuminuria and
333 proteinuria would be assessed in future investigations. Second, only a minority of
334 patients had moderately to severely decreased renal function, thus caution is needed
335 when interpreting the efficacy and safety of dual antiplatelet therapy in stroke patients
336 with moderately to severely decreased renal function. However, although specific
337 recommendations for antiplatelet therapy in this special population are not available,

the present study may provide some valuable information. A prospective and well-designed study in stroke patients with impaired renal function would be needed for further evaluation. Third, this study was a post hoc analysis, which increases the risk of a type I error, so our result need to be confirmed by other studies.[38] Finally, all patients in the CHANCE-2 trial were Chinese, which may limit the generalizability of the findings to other populations.

Conclusions

Based on the CHANCE-2 trial, our study showed that among *CYP2C19* LOF carriers with minor stroke or TIA, ticagrelor-aspirin compared with clopidogrel-aspirin was associated with a reduced risk of recurrent stroke and without any significant increase in severe or moderate bleeding events among patients with normal renal function, while patients with impaired renal function did not derive the same benefit from ticagrelor-aspirin. The findings suggest that renal function should be considered when deciding on the use of ticagrelor-aspirin versus clopidogrel-aspirin.

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Data sharing statement

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

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Figure legends

Figure 1. The flowchart of the study

eGFR = estimated glomerular filtration rate.

Figure 2. Cumulative Probability of Stroke According to treatment and eGFR category

CI = confidence interval; eGFR = estimated glomerular filtration rate.