Genotype-guided dual antiplatelet use for TIA and minor stroke by imaging status: a subgroup analysis of the CHANCE-2 trial

Running Title: Imaging status and ticagrelor therapy

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Summary for Social Media

1. **NA**
2. What is the current knowledge on the topic?

   The CHANCE trial and POINT trial indicated that TIA or minor stroke with positive diffusion-weighted imaging (DWI) was associated with an increased risk of recurrent stroke, especially in patients with multiple acute infarctions. The two trials also confirmed that these patients received a more pronounced benefit from dual antiplatelet therapy (DAPT) with clopidogrel/aspirin.
3. What question did this study address?

   Can patients with TIA/minor stroke with or without positive DWI receive consistent benefits from gene-directed dual antiplatelet therapy (DAPT)?
4. What does this study add to our knowledge?

   In this prespecified analysis of the CHANCE-2 trial, DAPT combining ticagrelor and aspirin was associated with a decreased risk of recurrent stroke in *CYP2C19* loss-of-function alleles carriers with positive DWI when compared with DAPT combining clopidogrel and aspirin. This association was not observed in patients without visible evidence of acute infarction.
5. How might this potentially impact on the practice of neurology?

   Patients with acute infarction received the most pronounced clinical benefit from genotype-guided DAPT.

ABSTRACT

Objective

This study was performed to investigate whether ticagrelor/aspirin versus clopidogrel/aspirin can further reduce the residual risk of stroke recurrence in patients with positive diffusion-weighted imaging (DWI) in the High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial.

Methods

Patients with DWI data in the CHANCE-2 trial were included and divided into those with and without acute infarction according to their DWI findings. The primary efficacy outcome and safety outcome were stroke recurrence and moderate to severe bleeding within 3 months of follow-up, respectively.

Results

Of the 6412 patients enrolled in the CHANCE-2 trial, 5796 (90.4%) patients with DWI data were included in the subgroup analysis. A total of 4369 patients (75.4%) had an acute infarction on DWI. Patients with positive DWI had higher risk of recurrent stroke (8.1%) than those without infarction (2.2%) within 3-month follow-up. Compared with clopidogrel/aspirin, ticagrelor/aspirin was associated with lower risk of stroke in patients with positive DWI (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.52–0.80; $P < .001$) than in those negative DWI (HR, 1.22; 95% CI, 0.55–2.72; $P = .63$), with a significant interaction association (P for interaction = .049). The risk of moderate to severe bleeding was similar between ticagrelor/aspirin and clopidogrel/aspirin treatment in different groups.

Interpretation

Our study demonstrate that imaging evaluation should be emphasized before targeting the best candidates for genotype-guided dual antiplatelet therapy in future clinical research and practice.

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

Introduction

Patients with transient ischemic attack (TIA) or minor ischemic stroke (hereafter referred to as minor stroke) have a high risk of stroke recurrence during both short- and long-term follow-up.[1-4] According to recent guidelines, dual antiplatelet therapy (DAPT) with clopidogrel/aspirin is recommended for recurrent stroke prevention in patients with TIA and non-cardioembolic minor stroke.[5-7] The last decade has witnessed a significant reduction in stroke recurrence in such patients, and this reduction is mostly attributed to implementation of standardized early intervention and secondary prevention strategies.[2-4] However, the risk of stroke recurrence is still approximately 5% within 1 year after TIA or minor stroke,[2] and this risk may gradually increase to 9.5% over the next 4 years as indicated in the international TIAregistry.org project.[3]

Recently, the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial[8] and the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial[9] indicated that TIA or minor stroke with acute infarction was associated with an increased risk of recurrent stroke,[10,11] especially in patients with multiple acute infarctions (MAIs).[11] Additionally, both the CHANCE and POINT trials confirmed that these patient populations received a more pronounced benefit from DAPT with clopidogrel/aspirin.[10,11] However, even after DAPT, TIA or minor stroke with acute infarction still had an unacceptably high residual risk of stroke recurrence (approximately 7%–10%) within 3 months after symptom onset,[10,11] which was much higher than that in the TIAregistry.org project (3.7%). Therefore, new treatment strategies are urgently needed for these specific populations with a high risk

of stroke recurrence.

In the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial,[12,13] ticagrelor/aspirin was superior to clopidogrel/aspirin for stroke prevention in patients with minor stroke or TIA with CYP2C19 loss-of-function alleles and did not increase the risk of moderate to severe bleeding. The CHANCE-2 trial also indicated that genotype-guided DAPT was a practical stroke treatment strategy.[14] However, whether this genotype-guided strategy can further reduce the risk of recurrent stroke after standard treatment in these high-risk patients (those with TIA and minor stroke with infarction) remains unclear. In this prespecified exploratory analysis of the CHANCE-2 trial, we investigated the efficacy and safety of ticagrelor/aspirin versus clopidogrel/aspirin in patients with minor stroke or TIA with or without infarction, and we searched for a treatment-by-with/without positive DWI interaction. Moreover, we investigated whether the benefits are consistent between patients with MAIs (which have a higher risk of recurrence) and patients with a single acute infarction (SAI).

Methods

Overview of the CHANCE-2 trial

The CHANCE-2 trial was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial at 202 centers in China involving patients with non-cardioembolic high-risk TIA or minor stroke with CYP2C19 loss-of-function alleles from 23 September 2019 to 22 March 2021. The detailed design and methods of the

trial have been previously described.[12,13] In total, 6412 patients were randomized (1:1) to receive either ticagrelor/aspirin (placebo clopidogrel plus a 180-mg loading dose of ticagrelor on day 1, followed by 90 mg twice daily on days 2–90) or clopidogrel/aspirin (placebo ticagrelor plus a 300-mg loading dose of clopidogrel on day 1, followed by 75 mg daily on days 2–90). A randomization sequence was generated centrally using the permuted fixed-size block randomization method from the Statistics and Data Centre at the China National Clinical Research Centre for Neurological Diseases. The randomization computer program established the treatment assignment based on the current status of the treatment group distribution within each clinical center as well as the overall balance of the treatment assignment. Following this randomized allocation, the study intervention was administered to the patient as early as possible. The trial was 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.

Data collection and image analysis

The patients' baseline data, including their demographic characteristics, cardiovascular risk factors, medical history, physical examination findings, laboratory test results, medical treatments, pre-stroke modified Rankin Scale (mRS) score, National Institutes of Health Stroke Scale (NIHSS) score, and $ABCD^2$ score, were collected after admission through face-to-face interviews by trained neurologists at the participating

hospitals in accordance with a standard data collection protocol developed by the steering committee.

All patients underwent standard imaging examinations during hospitalization, including brain magnetic resonance imaging (MRI), intracranial and extracranial vascular imaging, cardiac rhythm examination, and cardiac structure imaging. Imaging data were collected from individual centers in Digital Imaging and Communications in Medicine (DICOM) format. Doppler ultrasound, electrocardiography, or echocardiography data were collected from individual centers in medical report format.

The results of MRI with a diffusion-weighted imaging (DWI) sequence were collected from individual centers in DICOM format and analyzed centrally. The central reviewers were blinded to the patients' baseline and outcome information. The patients were divided into those with positive DWI and with negative DWI according to the infarction patterns. Patients with positive DWI were further grouped into those with an SAI and MAIs. Positive DWI were diagnosed based on the presence of hyperintense lesions on DWI. Uninterrupted lesions visible in contiguous territories were considered SAIs, and more than one topographically distinct lesion (separated in space or discrete on contiguous slices) was considered MAIs.[11]

Symptomatic intracranial-artery stenosis and symptomatic extracranial-artery stenosis were defined when more than 50% stenosis or occlusion was found and there was evidence of a cerebral infarction in the territory of the stenotic or occlusive artery or if clinical symptoms matched the supplied brain territory of the affected artery (without acute infarction on DWI). Intracranial arteries assessed included middle

cerebral (M1 and M2), anterior cerebral, posterior cerebral, basilar arteries and intracranial portion of the vertebral (V4), and extracranial arteries assessed included common carotid, proximal internal carotid, and the extracranial portion of the vertebral (V1, V2, V3). CT angiography, MR angiography or digital subtraction angiography were chosen to evaluate intracranial-artery stenosis, while CT angiography, MR angiography, digital subtraction angiography or doppler ultrasound were chosen to evaluate extracranial-artery stenosis. All clinical and image data were interpreted centrally by experienced neurologists at the Tiantan Neuroimaging Center of Excellence (T-NICE) of Beijing Tiantan Hospital. Further details of the image analysis protocol and methods were previously reported.[15,16]

Outcome assessment

The primary outcome was a new ischemic or hemorrhagic stroke at 3 months. The secondary outcomes were ischemic stroke, composite vascular events (stroke, TIA, myocardial infarction, and vascular death), disabling stroke (with a subsequent mRS score of ≥2 on a scale of 0–6, with higher scores reflecting worse outcomes) at 3 months. 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 at 3 months.[17] The secondary safety outcomes were intracranial hemorrhage, any bleeding and death at 3 months.

Statistical analysis

Continuous variables are presented as median with interquartile range, and categorical

variables are presented as frequency and percentage. The baseline characteristics between the ticagrelor/aspirin and clopidogrel/aspirin groups with different etiology classifications were compared by the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. Kaplan–Meier analysis was used to calculate the cumulative incidence of outcome during the 90-day follow-up for each group. Differences in the outcome endpoints during the 90-day follow-up period were assessed using a Cox proportional hazards regression model with the study centers set as a random effect, and the hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. 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 the study 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. We assessed interactions between the treatment assignment and presence/absence of acute infarction by including terms for treatment, subgroup, and treatment-by-subgroup interaction in the Cox model. Confounding factors were selected if the univariate analysis revealed statistically significant differences at baseline, including age, sex, medical history (hypertension, diabetes mellitus, previous ischemic stroke, previous TIA), current smoking, type of CYP2C19 loss-of-function allele carrier, median time from symptom onset to randomization, qualifying event, previous antiplatelet therapy, previous lipid-lowering therapy, symptomatic intracranial artery stenosis, symptomatic extracranial artery stenosis. All statistical analyses were performed with SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC,

USA). All tests were two-sided, and $P < .05$ was considered statistically significant.

Results

Patient demographics and baseline characteristics

Of the 6412 patients enrolled in the CHANCE-2 trial, 5796 (90.4%) patients with DWI data were included in the subgroup analysis (mean [standard deviation] age, 64.9 [13] years; 3832 [66.1%] men). A patient flow diagram is shown in eFigure 1 in the Supplement. A total of 4369 patients (75.4%) had an acute infarction on DWI (including 2741 with an SAI and 1628 with MAIs). The baseline characteristics and clinical outcome were similar between the included and excluded patients (eTable 1 in the Supplement).

Table 1 and eTable 2 show the demographic and clinical characteristics of patients with or without acute infarction and with different treatments (ticagrelor/aspirin or clopidogrel/aspirin). Patients with positive DWI were more likely to be men, have vascular risk factors (hypertension diabetes mellitus current smoker), and be an intermediate metabolizer according to the presence of the CYP2C19 loss-of-function allele. Patients with negative DWI were more likely to be younger, have a history of TIA/stroke, and be a poor metabolizer according to the presence of the CYP2C19 loss-of-function allele. The two treatment groups in both patients with and without acute infarction were well balanced according to their baseline characteristics. Table 2 and eTable 3 show the demographic and clinical characteristics of patients with SAI and MAIs. Patients with MAIs were more likely to be men, be older, have atherosclerotic disease (TIA, stroke, or myocardial infarction), and have a higher NIHSS score.

Baseline characteristics and outcome at 3-month follow-up in patients with different infraction number are shown in eTable 4 in the Supplement.

Efficacy outcomes

Overall, the rate of recurrent stroke was 6.7% (387 patients) at 3 months in this sub-study population. The risk of recurrent stroke was 8.1% (10.8% in patients with MAIs and 6.5% in patients with an SAI) and 2.2% in patients with and without acute infarction, respectively. Patients with MAIs (HR, 5.66; 95% CI, 3.68-8.70; P < .01) and SAI (HR, 4.52; 95% CI, 2.96-6.89; P < .01) had a higher risk of stroke at 3 months than patients with negative DWI (Figure 1 and eTable 5 in the Supplement) even after adjustment. Further, there was no statistical difference about the risk of recurrent stroke at 3-month between MAIs and SAI even after adjustment (HR, 1.25; 95% CI, 0.99-1.59; P =0.07) (eTable 6 in the Supplement).

Among the 4369 patients with positive DWI, the stroke recurrence rates were 10.8% (176 patients) and 6.5% (179 patients) in patients receiving clopidogrel/aspirin and ticagrelor/aspirin, respectively (HR, 0.65; 95% CI, 0.52–0.80; *P* < .001). Among the 1427 patients with negative DWI, the stroke recurrence rates were 1.9% (14 patients) and 2.8% (18 patients) in patients receiving clopidogrel/aspirin and ticagrelor/aspirin, respectively (HR, 1.22; 95% CI, 0.55–2.72; *P* = .63). There was a significant interaction effect of treatment × with/without infarction (*P* = .049), even after adjusted confounding factors: including age, sex, medical history (hypertension, diabetes mellitus, previous ischemic stroke, previous TIA), current smoking, type of CYP2C19 loss-of-function allele carrier, median time from symptom onset to randomization,

qualifying event, previous antiplatelet therapy, previous lipid-lowering therapy, symptomatic intracranial artery stenosis, symptomatic extracranial artery stenosis. (Table 3, Figure 2 A-B). The association of ticagrelor/aspirin vs. clopidogrel/aspirin with clinical outcomes stratified by the diagnosis assigned at randomization (minor ischemic stroke vs TIA) were shown in the eTable 7 in the Supplement as well.

Among the 2741 patients with an SAI, the stroke recurrence rates were 7.8% (107 patients) and 5.2% (72 patients) in patients receiving clopidogrel/aspirin and ticagrelor/aspirin, respectively (HR, 0.64; 95% CI, 0.48–0.87; P = .005). Among the 1628 patients with MAIs, the stroke recurrence rates were 13.0% (104 patients) and 8.7% (72 patients) in patients receiving clopidogrel/aspirin and ticagrelor/aspirin, respectively (HR, 0.61; 95% CI, 0.45–0.84; P = .002). There was no significant interaction effect of treatment × with/without infarction (P > .05) (Table 3, eTable 8 in supplement, Figure 2 C-D).

Safety outcomes

Patients with positive and negative DWI in the ticagrelor/aspirin and clopidogrel/aspirin groups had a similar rate of severe or moderate bleeding (0.1% vs. 0.3% in patients with negative DWI and 0.4% vs. 0.3% in patients with positive DWI) (Table 1). Additionally, patients with an SAI or MAIs in the ticagrelor/aspirin and clopidogrel/aspirin groups also had a similar rate of severe or moderate bleeding (0.5% vs. 0.4% in patients with SAI and 0.3% vs. 0.2% in patients with MAIs) (P > .05 for all) (Table 2).

Discussion

In this subgroup analysis of the CHANCE-2 trial, patients with positive DWI and with CYP2C19 loss-of-function alleles received a more pronounced clinical benefit from ticagrelor/aspirin treatment than did patients with negative DWI without increasing the risk of moderate to severe bleeding. Additionally, this benefit was consistent in patients with SAI and MAIs.

We also found that the proportion of patients with new acute infarction (75.4%) was similar to that in the CHANCE imaging sub-study (76.6%)[11] but much higher than that in the POINT trial (36.8%)[10]. One possible explanation for this difference is that only 55.9% of patients underwent MRI evaluations in the POINT trial with the remaining patients undergoing computed tomography evaluations, whereas all patients in the present sub-analysis of the CHANCE-2 underwent MRI examinations with DWI. The sensitivity and specificity of MRI (especially with DWI) for acute cerebral infarction is much higher than that of computed tomography, which could lead to a lower detection rate of acute infarction in patients with TIA or minor stroke. Additionally, the rate of stroke recurrence within 3 months of follow-up (8.1%) was similar to that in the CHANCE imaging subgroup (8.5%) but slightly higher than that in the POINT trial (5.5%). This difference might be explained by the higher proportion of intracranial artery stenosis (which is associated with a high risk of stroke recurrence) observed in the Chinese stroke population of the Chinese Intracranial Atherosclerosis (CICAS) study[18] as well as the international Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial.[19] At

baseline, we found a higher proportion of prior antiplatelet treatment in patients with negative DWI than that in patients with positive DWI, which might be attributed to was the higher proportion of stroke and TIA history in patients with negative DWI. In addition, we believe that the higher proportion of intermediate metabolizers in the negative DWI group was caused by the play of chance, and more research should explore this phenomenon.

In this study, we reconfirmed that patients with positive DWI had a higher recurrent stroke rate than patients with negative DWI, which is consistent with the findings of the POINT and CHANCE trials as well as former cohort studies.[2,10,11,16,20] Additionally, we further validated that the number of acute infarctions can be used to efficiently stratify the risk of recurrent stroke in patients with TIA and minor stroke, and we confirmed that MAIs were associated with the highest risk of recurrence in patients with CYP2C19 loss-of-function alleles.[2,11] The above results indicated that some of those patients with TIA and minor stroke negative DWI probably did not have real ischemic events[10] and that those patients with MAIs on DWI are particularly unstable as previous reported.[2,11,16,21-23]

We also found that patients with positive DWI and CYP2C19 loss-of-function alleles receive a more pronounced clinical benefit from ticagrelor-aspirin treatment than do patients with negative DWI. Importantly, this benefit was consistent in patients with SAI and MAIs. In the Platelet Reactivity in Acute Stroke or Transient Ischaemic Attack (PRINCE) trial,[24] patients with minor stroke or TIA who were treated with ticagrelor/aspirin had a lower proportion of high platelet reactivity than those who were

treated with clopidogrel/aspirin, particularly those who were carriers of the CYP2C19 loss-of-function allele. Therefore, more potent DAPT with ticagrelor/aspirin leads to a lower rate of stroke recurrence in patients with CYP2C19 loss-of-function alleles. Both the POINT and CHANCE trials indicated that patients with TIA or minor stroke with negative DWI receive little benefit from DAPT with clopidogrel/aspirin.[10,11] Our study showed that TIA or minor stroke without acute infarction do not appear to derive any additional benefit from DAPT with ticagrelor/aspirin vs. clopidogrel/aspirin. The potential reason may be the lower risk of stroke recurrence in patents with negative DWI and the fact that a very large sample size is needed to observe a relatively small benefit; however, the sample size of patients with no infarction was insufficient in our study.

Several important issues should be noted. First, timely DWI examination is very important. More than 50% of stroke recurrences occurred within 7 days after TIA or minor stroke during the 90-day follow-up.[2,8,9] Therefore, a delayed MRI examination would lead to a lower risk stratification value and impede rapid selection of the patients who would benefit most from therapy. Second, although patients with TIA and minor stroke with negative DWI had a relatively low risk of stroke recurrence within 3 months (2.2%) in the current study, it was still much higher than the risk in patients without a history of TIA/stroke. Even patients with non-consensus or atypical TIA would have a higher stroke risk than that in the background population.[25] Therefore, treatment should not be delayed because of an insignificant benefit from DAPT in patients with TIA or minor stroke without acute infarction. Third, the residual risk of recurrence remains as

high as 5.2% and 8.7% in patients with an SAI and MAIs, respectively. Future research should explore combination therapy (including antiplatelet therapy, anti-inflammatory therapy, and perfusion improvement) or intensive antiplatelet therapy (triple antiplatelet therapy).

Strengths and limitations

Although this is the first study to compare gene-guided DAPT in patients with TIA and minor stroke with positive/negative DWI using centralized DWI data, it still had some limitations. First, 616 (9.6%) patients had no DWI data, and this may have led to bias. However, the baseline characteristics and recurrent stroke rate at 3 months of follow-up were similar between patients with and without DWI data. Second, all patients in the CHANCE-2 trial were Chinese with more patients with intracranial-artery stenosis, which may limit the generalizability of the findings to other populations. Finally, all patients in the CHANCE-2 trial had CYP2C19 loss-of-function alleles, and whether the findings can be generalized to patients without CYP2C19 loss-of-function alleles is unclear.

Conclusions

In this subgroup analysis of the CHANCE-2 trial, patients with acute infarction on DWI received a more pronounced clinical benefit from ticagrelor-aspirin treatment than did patients with negative DWI without increasing the risk of moderate to severe bleeding. Additionally, the benefit was consistent in patients with SAI and MAIs. Imaging

evaluation should be emphasized before targeting the best candidates for genotype-guided DAPT in future clinical research and practice.

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Author Contributions

J.J., X.X., S.C.J., P.M.B., X.M., and Yo.W. contributed to the conception and design of the study; J.J., X.X., A.W., Q.X., H.L., and Y.J. contributed to the acquisition and analysis of data; J.J., X.X., Z.L., X.Z., L.L. and Yi.W. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

PMB has consulted for DiaMedica, Moleac, Phagenesis and Roche. SCJ's institution has received support from AstraZeneca for research and consulting related to the THALES trial and from Johnson and Johnson/BMS for research planning. Other authors declare no financial or other competing interests relevant to the manuscript.

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Figure legends

Figure 1. Kaplan–Meier curves of stroke recurrence at 3-month follow-up in patients with different numbers of infarctions.

Figure 2. Kaplan–Meier curves of stroke recurrence at 3-month follow-up in patients with different numbers of infarctions and different dual antiplatelet therapy.