

Optimal strategy of switching from clopidogrel to ticagrelor in Chinese acute coronary syndrome patients with complicated coronary artery disease: the switching from clopidogrel to ticagrelor (SHIFT-CACS) study

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Abstract

Background: The dose and time point for switching from clopidogrel to ticagrelor remain controversial, especially for Chinese acute coronary syndrome (ACS) patients with complicated coronary artery disease (CAD). Hence, the purpose of this study was to further explore the optimal dose and time point for the switching strategy to balance the increase in platelet inhibition and the decrease in adverse events in Chinese ACS patients with complicated CAD managed by percutaneous coronary intervention (PCI).

Methods: From July 2017 to December 2017, the prospective, randomized, open-label study (the SwitchING from clopidogrel to ticagrelor study) assigned the eligible Chinese ACS patients with complicated CAD managed by PCI ($n = 102$) for 90 mg of ticagrelor at 12 h (T-90 mg-12 h), 90 mg of ticagrelor at 24 h (T-90 mg-24h) or 180 mg ticagrelor at 24 h (T-180 mg-24 h) after the last dose of clopidogrel. The primary endpoint was the comparison of maximal platelet aggregation (MPA) values at 2 h after switching strategies among the three groups. In addition, the MPA values at baseline, 8 h and before discharge and the rates of high on-treatment platelet reactivity were evaluated, the incidences of bleeding episodes and dyspnea during hospitalization and at 30-day follow-up in our study were also recorded. The MPA was measured by light transmittance aggregometry in our study. A repeated-measures analysis of variance (ANOVA) model and one-way ANOVA were used to compare data for the primary endpoint.

Results: The MPA values were significantly decreased in the T-180 mg-24 h group compared with the T-90 mg-12 h group ($P = 0.017$) and decreased numerically compared with the T-90 mg-24 h group ($P = 0.072$) at 2 h. In particular, the MPA values were markedly reduced in the T-90 mg-24 h group compared with the T-90 mg-12 h group at 8 h after switching treatment ($P = 0.002$). There was no significant difference among the three groups in all bleedings and dyspnea events.

Conclusions: The optimal treatment strategy recommended in this study for Chinese ACS patients with complicated CAD managed by PCI is 180 or 90 mg of ticagrelor at 24 h after the last dose of clopidogrel. In addition, a negative interaction was detected in this study between the overlap for clopidogrel and ticagrelor at 12 h after the last dose of clopidogrel.

Trial Registration: ClinicalTrials.gov, NCT03577652; <http://clinicaltrials.gov/ct2/show/NCT03577652>.

Keywords: Clopidogrel; Drug substitution; Pharmacology; Ticagrelor

Introduction

Dual anti-platelet therapy is the cornerstone in the management of acute coronary syndrome (ACS), including complicated coronary artery disease (CAD) managed by percutaneous coronary intervention (PCI).^[1,2] Complicated CAD is strongly associated with poor prognosis, requiring more potent inhibition of platelet aggregation.^[3-5] As a member of the new chemical class cyclopentyl-triazolo-pyrimidines of the P2Y₁₂ blockers, ticagrelor provides faster, greater, and more consistent P2Y₁₂ inhibition than clopidogrel.^[6,7] Compared with

clopidogrel, ticagrelor is related to a lower risk of ischemic events, as shown in the PLATElet inhibition and patient outcomes (PLTAO) randomized trial, especially in the patients with complicated CAD.^[8-10] However, ticagrelor is also associated with an increased incidence of bleeding complications not related to coronary artery bypass surgery compared with clopidogrel, and dyspnea is more common among patients receiving ticagrelor.^[11-13] Additionally, confirmation of the diagnosis of complicated CAD often requires coronary angiography. As noted previously, more patients were treated with clopidogrel than ticagrelor before coronary angiography in clinical

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practice. This treatment scheme may lead to the switch from clopidogrel to ticagrelor in patients becoming common in the real world. The latest guidelines referenced the only trial on switching between clopidogrel and ticagrelor, which was conducted for powering of clinical endpoints, hence that study was not specifically contributing to a switching strategy including the best timing, dosage, and specific population.^[1,8] Hence, the purpose of this study was to further explore the optimal dose and time point for the switching strategy to balance the increase in platelet inhibition and the decrease in adverse events in Chinese ACS patients with complicated CAD managed by PCI.

Methods

Ethical approval

This study was approved by local ethics committee of the General Hospital of Northern Theater Command and informed consent was obtained from every candidate at the beginning of the study. The trial was carried out in accordance with the principles of the *Declaration of Helsinki*.^[14]

Study design

The SwitchING from clopidogrel to ticagrelor study (Clinicaltrials.gov, NCT03577652) was a prospective, randomized, open-label, single-center study. From July 2017 to December 2017, we enrolled Chinese ACS patients with complicated CAD who had been treated with a maintenance dose or loading dose of clopidogrel before coronary angiography and underwent successful drug-eluting stent implantation [specific study inclusion criteria are shown in the Supplementary materials Table S1, <http://links.lww.com/CM9/A94>]. Combining the clinical actual circumstances in China with the Synergy Between PCI With Taxus and Cardiac Surgery score, complicated CAD was defined as follows in this trial: (1) left main disease; (2)

lesion length >20 mm; (3) tortuous lesions (≥ 3 coronary artery branches and bent $\geq 45^\circ$ along at least one arterial trunk); (4) small vascular lesions (blood vessel diameter ≤ 2.75 mm); (5) bifurcation lesions; (6) heavy calcification; and (7) in-stent restenosis.^[15] We excluded patients for whom ticagrelor treatment was contraindicated or those at a high-risk for bleeding [specific study exclusion criteria are shown in the Supplementary materials Table S1, <http://links.lww.com/CM9/A94>].

Randomization and treatment

After PCI, the eligible patients were randomly allocated into three groups: group A, which received 90 mg of ticagrelor plus 100 mg of aspirin at 12 h after the last dose of clopidogrel (T-90 mg-12 h); group B, which received 90 mg of ticagrelor plus 100 mg of aspirin at 24 h after the last dose of clopidogrel (T-90 mg-24 h); and group C, which received 180 mg of ticagrelor plus 100 mg of aspirin at 24 h after the last dose of clopidogrel (T-180 mg-24 h). All patients were then given 90 mg of ticagrelor twice daily plus 100 mg of aspirin once daily at the beginning of the next administration and the treatment maintained for at least 30 days after discharge. Other cardiac medications were given at the direction of physicians. The randomization sequence was generated by using random number table. A flow diagram of the study is presented in Figure 1A.

Platelet function assessments

Venous blood samples were collected from every patient at the following time points: baseline (before accepting the first ticagrelor dose; for example, the venous blood samples in the T-90 mg-12 h group were collected at 12 h after the last clopidogrel treatment but before the first ticagrelor treatment), 2 h after conversion (2 h after the first administration of the scheduled ticagrelor treatment), 8 h after conversion (8 h after the first administration of the scheduled ticagrelor treatment), and before discharge (2 h

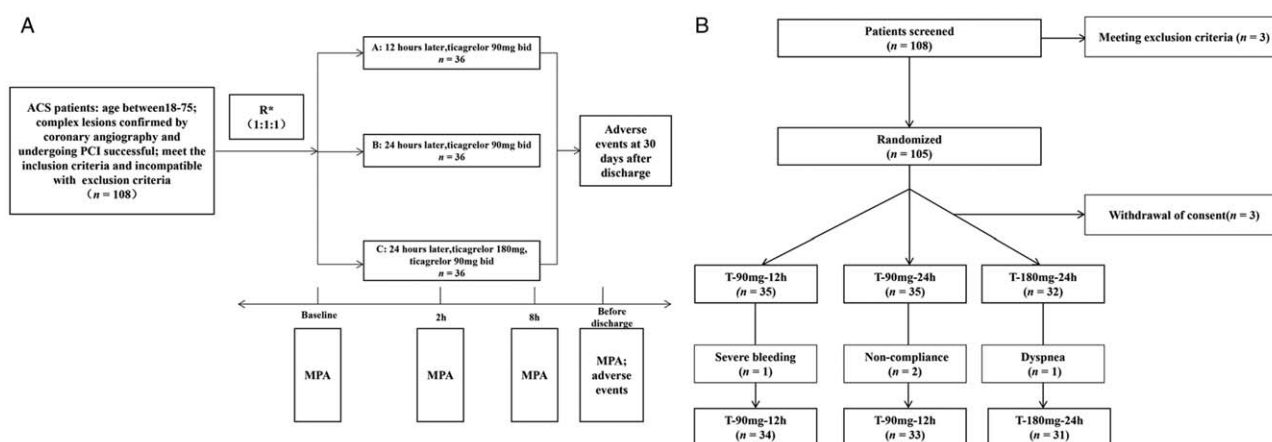


Figure 1: Study design and patient disposition. (A) Adverse events include bleeding episodes and dyspnea. The MPA was measured by light transmittance aggregometry. Baseline values were measured while on clopidogrel maintenance therapy. Before discharge values were measured at 2 h after the last dose of ticagrelor during hospital. (B) Patient disposition. In total, 102 patients of the intention-to-treat analysis population formed the efficacy and safety endpoint cohorts. T-90 mg-12 h: Maintenance dose of 90 mg of ticagrelor at 12 h after the last clopidogrel treatment; T-90 mg-24 h: Maintenance dose of 90 mg of ticagrelor at 24 h after the last clopidogrel treatment; T-180 mg-24 h: Loading dose of 180 mg of ticagrelor at 24 h after the last clopidogrel treatment. ACS: Acute coronary syndrome; MPA: Maximal platelet aggregation; PCI: Percutaneous coronary intervention; R*: Randomization.

after the last dose of ticagrelor during hospitalization). Samples were measured by light transmittance aggregometry (LTA) following the application of 20 $\mu\text{mol/L}$ adenosine diphosphate (ADP). Maximal platelet aggregation (MPA) was determined to represent the extent of platelet aggregation and expressed as the maximum percent change in light transmittance.^[16-18] In accordance with previous studies, high on-treatment platelet reactivity (HPR) was defined as MPA >59% (LTA, 20 $\mu\text{mol/L}$ ADP) in the present study.^[19,20]

Outcomes and follow-up

The primary endpoint was the comparison of MPA values at 2 h after switching strategies among the three groups. The secondary endpoints included comparisons of MPA values at the remaining time points among all three groups and the rates of HPR in all three groups at each pre-set time point. Adverse events comprised of bleeding events (defined according to the Bleeding Academic Research consortium [BARC] criteria, thrombolysis in myocardial infarction [TIMI] criteria and PLATO bleeding criteria) and dyspnea at 30 days after discharge and during hospitalization were also evaluated.^[8,21-23] All participants were contacted by a phone call to assess study endpoints. The clinical incidents were gathered by the treating clinicians and were analyzed by investigators.

Statistical analysis

The intention-to-treat analysis was used to analyze the results in our study. Based on preliminary experiment in this study and the previous research, we estimated that the mean MPA of treating with 180 mg ticagrelor would be 17% at 2 h after switching treatment and a loading dose of ticagrelor therapy would result in a decrease in MPA of 40% compared with 90 mg ticagrelor therapy.^[24,25] A sample size of 32 patients per group would be required with a 80% power and an α of 0.05. Therefore, considering a dropout rate of approximately 10%, 36 patients in each group were needed to ensure complete data. The mean \pm standard deviation (SD) was presented for the continuous variables, and categorical variables were expressed as counts and percentages. The Kolmogorov-Smirnov test was performed to estimate whether a normal distribution was observed among continuous variables. If normality assumptions were not satisfied, the Kruskal-Wallis test was used, and data were expressed as medians. Categorical variables were compared by the χ^2 test or Fisher exact test between groups, and we used one-way analysis of variance (ANOVA) to analyze continuous variables. A repeated-measures ANOVA model and one-way ANOVA were used to compare data at the primary endpoint and at each pre-set time point among all three groups as well as evaluating the difference between groups overtime points. A linear regression model was used to assess the association between the MPA levels and the time interval or dosage. A two-tailed value of $P < 0.05$ was used to demonstrate a statistically significant difference for all the statistical analyses. Statistical analyses were performed with SPSS version 24.0 software (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics

A total of 102 Chinese patients were included in the intention-to-treat analysis and formed the efficacy and safety populations. Four patients pre-maturely dropped out from the study because of severe side effects and non-compliance, hence, a total of 98 patients completed the entire follow-up [Figure 1B]. Table 1 summarizes the baseline characteristics of the study cohort, which were balanced among all the treatment groups. The angiographic and procedural characteristics are described in the Supplementary materials Table S1, <http://links.lww.com/CM9/A94>.

Pharmacodynamic findings

In general, MPA levels were lower over the study time course with T-180 mg-24 h group *vs.* T-90 mg-12 h group ($P = 0.010$), but similar to T-90 mg-24 h group ($P = 0.184$). There were differences numerically in MPA levels over time between T-90 mg-12 h group and T-90 mg-24 h group ($P = 0.191$).

Platelet function as expressed by MPA was measured by LTA and illustrated in Figure 2 and the Supplementary materials Table S3, <http://links.lww.com/CM9/A94>. The baseline levels of MPA were balanced among the groups ($P = 0.941$). The MPA values in all three conversion strategies were significantly reduced after the switch from clopidogrel to ticagrelor compared with baseline levels in our study [Supplementary materials Figure S1, <http://links.lww.com/CM9/A94>]. At 2 h after switching from clopidogrel to ticagrelor, the MPA values were lower in the T-180 mg-24 h group than in the T-90 mg-12 h group (28.22% *vs.* 17.23%, $P = 0.017$), and there was a non-significant decrease in MPA values between the T-180 mg-24 h group and T-90 mg-24 h group (25.44% *vs.* 17.23%, $P = 0.072$). The difference in platelet aggregation in the T-180 mg-24 h group compared with the other groups persisted at the 8 h time point (28.46% *vs.* 12.19%, $P_{(T-180 \text{ mg-24 h } vs. \text{ T-90mg-12 h})} < 0.001$; 18.20% *vs.* 12.19%, $P_{(T-180 \text{ mg-24 h } vs. \text{ T-90 mg-24 h})} = 0.073$). The rates of HPR were not markedly different at each time point among three groups [Table 2].

Then we analyzed platelet reactivity between the T-90 mg-24 h and the T-90 mg-12 h group to investigate whether exposure to clopidogrel could interfere with ticagrelor-induced anti-platelet effects. Notably, there was a significant difference in MPA values between the T-90 mg-24 h and the T-90 mg-12 h groups at 8 h after switching the treatment (28.46% *vs.* 18.20%, $P = 0.002$). The repeated measures ANOVA analysis confirmed that the study treatment (group A *vs.* group B *vs.* group C) and the pre-set time points (baseline, 2 and 8 h, before discharge) indeed had an effect on platelet aggregation ($F = 151.621$, $P_{(\text{pre-set time points})} < 0.001$; $F = 3.448$, $P_{(\text{study treatment})} = 0.036$). Furthermore, there was an interaction effect between the pre-set time points and the study treatment ($F = 5.276$, $P_{(\text{interaction})} = 0.002$), and the significant difference in MPA values between the T-90 mg-24 h and the T-90 mg-12 h groups at 8 h was validated by simple effect analysis ($t = 10.257$, $P = 0.006$). The baseline variables,

Table 1: Baseline characteristics of the Chinese patients with acute coronary syndrome patients with complicated coronary artery.

Variables	T-90 mg-12 h (n = 35)	T-90 mg-24 h (n = 35)	T-180 mg-24 h (n = 32)	Statistics	P
Age (years)	57.06 ± 10.53	59.46 ± 9.15	60.97 ± 8.11	1.500*	0.228
Male	29 (82.9)	29 (82.9)	22 (68.8)	2.584†	0.275
BMI (kg/m ²)	27.16 ± 3.39	26.66 ± 3.06	26.30 ± 3.79	0.545*	0.582
Smoking	19 (54.3)	21 (60.0)	13 (40.6)	2.629†	0.269
Diabetes mellitus	14 (40.0)	12 (34.3)	11 (34.4)	0.320†	0.852
Hypertension	21 (60.0)	18 (51.4)	19 (59.4)	0.644†	0.725
Dyslipidemia	29 (82.9)	25 (71.4)	19 (63.3)	6.155†	0.119
Prior MI	5 (14.3)	10 (28.6)	3 (9.4)	4.653†	0.098
Prior stroke	5 (14.3)	4 (11.4)	2 (6.3)	1.157†	0.619
Prior PAD	3 (8.6)	0	0	4.019†	0.105
Prior PCI	8 (22.9)	10 (28.6)	3 (9.4)	3.936†	0.140
Presentation				2.191†	0.345
STEMI	1 (2.9)	3 (8.6)	4 (12.5)		
UA or NSTEMI	34 (97.1)	32 (91.4)	28 (87.5)		
Medications					
Beta-blocker	29 (82.9)	26 (74.3)	26 (81.3)	0.883†	0.643
CCB	17 (48.6)	14 (40.0)	10 (31.3)	2.087†	0.352
Statins	35 (100.0)	35 (100.0)	32 (100.0)	–	1.000
ACEI or ARB	23 (65.7)	25 (71.4)	29 (90.6)	6.081†	0.048
PPI	2 (5.7)	4 (11.4)	2 (6.3)	0.933†	0.727
Diuretic	2 (5.7)	4 (11.4)	3 (9.4)	0.805†	0.759
CYP2C19 genotype				2.392†	0.664
Extensive metabolizers	15 (42.9)	12 (34.3)	13 (41.9)		
Intermediate metabolizers	12 (34.3)	18 (51.4)	13 (41.9)		
Poor metabolizers	8 (22.8)	5 (14.3)	5 (16.2)		
Lesion types of target vessel					
Left main disease	0	2 (5.7)	2 (6.3)	2.265†	0.460
Long lesions	35 (100.0)	34 (97.1)	30 (93.8)	2.068†	0.307
Tortuous lesions	0	1 (2.9)	2 (6.3)	2.068†	0.307
Small vascular lesions	1 (2.9)	3 (8.6)	3 (9.4)	1.450†	0.621
Heavy calcification	2 (5.7)	3 (8.6)	4 (12.5)	1.002†	0.624
In-stent restenosis	2 (5.7)	4 (11.4)	3 (9.4)	0.805†	0.759
Platelet counts (×10 ⁹ /L)	222.31 ± 65.40	232.29 ± 50.78	209.00 ± 45.19	1.519*	0.224
CrCl (mL/min)	107.04 ± 29.22	104.55 ± 27.52	105.17 ± 33.83	0.064*	0.938
Hematocrit (%)	43.38 ± 4.39	42.47 ± 3.99	42.27 ± 3.74	0.728*	0.486

Data were shown as n (%) or mean ± SD. *F test, †χ² test. T-90 mg-12 h: Maintenance dose of 90 mg of ticagrelor at 12 h after the last clopidogrel treatment; T-90 mg-24 h: Maintenance dose of 90 mg of ticagrelor at 24 h after the last clopidogrel treatment; T-180 mg-24 h: Loading dose of 180 mg of ticagrelor at 24 h after the last clopidogrel treatment; BMI: Body mass index; MI: Myocardial infarction; PAD: Peripheral arterial disease; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina; NSTEMI: Non-ST-segment elevation myocardial infarction; CCB: Calcium-channel inhibitor; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; PPI: Proton-pump inhibitor; CrCl: Creatinine clearance; –: Not applicable; SD: Standard deviation.

the time interval (the time interval from the last dose of clopidogrel administration to the shift to ticagrelor) and the dosage of ticagrelor were included in a stepwise linear regression model to assess the association between the MPA at 8 h and the time interval or dosage. The results showed that the MPA at 8 h was a negative correlation to the time interval (*Beta* = -0.360, *P* < 0.001). It was also noticeable that compared with the T-90 mg-24 h group, the T-90 mg-12 h group exhibited a numerical increase in the proportion of patients with HPR at either 2 or 8 h after switching the treatment strategy (8.6% vs. 5.7%, *P*_(2h) = 0.367; 5.7% vs. 0, *P*_(8h) = 0.327) [Table 2].

Safety and tolerability

First, one case of fundus hemorrhage occurred in the T-90 mg-12 h group, and this patient withdrew from the study.

In addition, none of the patients suffered life-threatening adverse events in our study during the whole follow-up period. At 30 days after discharge, the incidence of BARC one bleeding events was 34.3% in the T-90 mg-12h group, 42.9% in the T-90 mg-24 h group, and 31.3% in the T-180 mg-24 h group (*P* = 0.587). The results of bleeding episodes classified by BARC, TIMI, or PLATO criteria were shown in Table 3, with similar conclusions were achieved. Dyspnea occurred in the T-90 mg-12 h group for 10 (28.6%) events, in the T-90 mg-24 h group for 10 (28.6%) events, in the T-180 mg-24 h group for 8 (25.0%) events at 30 days after discharge (*P* = 0.932). The majority of dyspnea events were mild and only one patient with dyspnea in the T-180 mg-24 h group dropped out prematurely because of intolerance. The median duration in our hospital for PCI-treated patients is 6 (5–7) days. The results during hospitalization were the same as those at

30 days after discharge [Table 3]. No deaths were reported during the whole follow-up period.

Discussion

Among Chinese patients with ACS with complicated CAD managed by PCI, considering all outcomes of the platelet function assays and adverse events, switching to a loading dose of ticagrelor or a maintenance dose of ticagrelor at 24 h after the last dose of clopidogrel is the optimal transformation strategy. Switching from clopidogrel to a bolus of 180 mg of ticagrelor in the early phase is consistent with the updated ESC dual anti-platelet guidelines, whereas the switching strategy without a reloading dose is similar to SHIFT-OVER study.^[1,25,26] Yet, they lack the best switching time as well as Chinese patients with complicated CAD. However, it is important to concentrate on the best switching time, as a result of, during non-acute phase (≥ 24 h from ACS or PCI),

switching to a loading dose of ticagrelor pre-maturely, high bleeding risk might be observed in Chinese patients, who are inclined to have a higher bleeding risk than non-Asians.^[27,28] Moreover, Chinese patients with a high mortality of CAD or Asians with a different response to ticagrelor were not included in the ESC dual anti-platelet guidelines and other trials.^[29-31] A well-known fact is that, treatment with ticagrelor is preferred in patients with complicated CAD, as ticagrelor has been shown to be superior to clopidogrel in reducing the recurrence of ischemic events.^[6-10] However, in the real world, treatment with clopidogrel is more common before coronary angiography because of costs and side effects; thus, various conversion regimens from clopidogrel to ticagrelor have been conducted in clinical practice and are still under debate.^[25,26] In the PLATO trial, nearly half of patients initiated clopidogrel treatment and then switched to a 180 mg loading dose of ticagrelor followed by 90 mg of ticagrelor twice daily regardless of the timing of their last dose of clopidogrel, and all patients received benefits from ticagrelor therapy.^[8] The strategy of switching from clopidogrel to ticagrelor was performed in patients with stable CAD who were either responders or non-responders according to HPR status in the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study. The RESPOND study, in which various pharmacodynamic assays were performed, indicated that all patients who switched their treatment to ticagrelor showed a significant reduction in platelet reactivity.^[24] The above two large studies were not tailored to determine the optimal switching strategy, whereas our study analyzed the dose and time point of switching from clopidogrel to ticagrelor in Chinese patients with ACS with complicated CAD by comparing the pharmacodynamic assessments and adverse events among three groups with different dosages and timing. For pharmacodynamic assessments, routine platelet function testing was not recommended by the guidelines as a result of low cost-effectiveness and poor accuracy which attributed to individual difference, operational error, and laboratory environment. However, certain predictability for ischemic events of platelet function testing and the clinical utility of platelet function testing for guiding anti-platelet therapy has been proved by some previous trials. So, it is beneficial to evaluate the effect of anti-platelet drugs via using platelet function testing, especially for acute phase. Additionally, the LTA with strong clinical practicability and long experience for good predictability

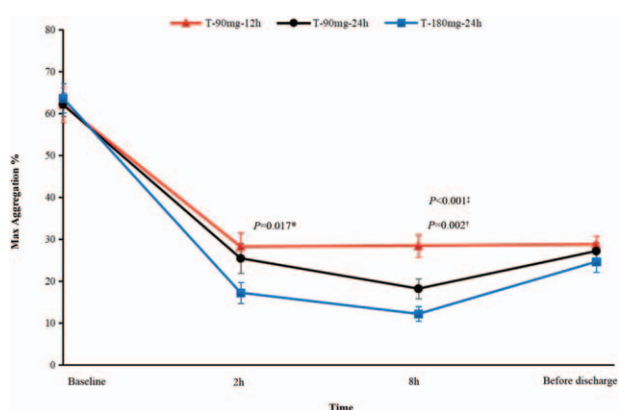


Figure 2: Pharmacodynamic comparisons among groups. Comparisons of mean maximal platelet aggregation measured by light transmittance aggregometry among groups after switching from clopidogrel to ticagrelor therapy. Data were shown as the mean \pm SE. Baseline values were measured while on clopidogrel maintenance therapy. Before discharge values were measured at 2 h after the last dose of ticagrelor during hospital. The $P^{\#}$ value denoted the T-90 mg-12 h group comparing with the T-180 mg-24 h group at 2 h after switching strategies; the $P^{\$}$ value denoted the T-90 mg-12 h group comparing with the T-90 mg-24 h group at 8 h after switching strategies; The $P^{\&}$ value denoted the T-90 mg-12 h group comparing with the T-180 mg-24 h group at 8 h after switching strategies. MPA: Maximal platelet aggregation; SE: Standard error; T-90 mg-12 h: Maintenance dose of 90 mg of ticagrelor at 12 h after the last clopidogrel treatment; T-90 mg-24 h: Maintenance dose of 90 mg of ticagrelor at 24 h after the last clopidogrel treatment; T-180 mg-24 h: Loading dose of 180 mg of ticagrelor at 24 h after the last clopidogrel treatment.

Table 2: High on-treatment platelet reactivity events of the Chinese patients with acute coronary syndrome and complicated coronary artery (MPA >59%).

Variables	T-90 mg-12 h (n = 35)	T-90 mg-24 h (n = 35)	T-180 mg-24 h (n = 32)	χ^2	P
Baseline	25 (71.4)	23 (65.7)	22 (68.8)	0.266	0.876
2 h	3 (8.6)	2 (5.7)	0	2.630	0.367
8 h	2 (5.7)	0	0	2.593	0.327
Before discharge	0	0	0	-	1.000

Data were shown as n (%). Baseline values were measured while on clopidogrel maintenance therapy. Before discharge values were measured at 2 h after the last dose of ticagrelor during hospital. MPA: Maximal platelet aggregation; T-90 mg-12 h: Maintenance dose of 90 mg of ticagrelor at 12 h after the last clopidogrel treatment; T-90 mg-24 h: Maintenance dose of 90 mg of ticagrelor at 24 h after the last clopidogrel treatment; T-180 mg-24 h: Loading dose of 180 mg of ticagrelor at 24 h after the last clopidogrel treatment; -: Not applicable.

Table 3: Bleedings and dyspnea events of the Chinese patients with acute coronary syndrome patients with complicated coronary artery.

Variables	T-90 mg-12 h (n = 35)	T-90 mg-24 h (n = 35)	T-180 mg-24 h (n = 32)	χ^2	P
During hospitalization					
BARC 1	3 (8.6)	4 (11.4)	3 (9.4)	0.280	1.000
BARC 2	0	0	0	-	1.000
BARC 3-5	0	0	0	-	1.000
TIMI major	0	0	0	-	1.000
TIMI minor	0	0	0	-	1.000
TIMI minimal	3 (8.6)	4 (11.4)	3 (9.4)	0.280	1.000
PLATO major	0	0	0	-	1.000
PLATO minor	0	0	0	-	1.000
PLATO minimal	3 (8.6)	4 (11.4)	3 (9.4)	0.280	1.000
Dyspnea	7 (20.0)	4 (11.4)	7 (21.9)	1.458	0.482
30 days after discharge					
BARC 1	12 (34.3)	15 (42.9)	10 (31.3)	1.065	0.587
BARC 2	1 (2.9)	0	0	1.782	1.000
BARC 3-5	0	0	0	-	1.000
TIMI major	0	0	0	-	1.000
TIMI minor	1 (2.9)	0	0	1.782	1.000
TIMI minimal	12 (34.3)	15 (42.9)	10 (31.3)	1.065	0.587
PLATO major	0	0	0	-	1.000
PLATO minor	1 (2.9)	1 (2.9)	0	1.149	1.000
PLATO minimal	12 (34.3)	14 (40.0)	10 (31.3)	0.584	0.747
Dyspnea	10 (28.6)	10 (28.6)	8 (25.0)	0.141	0.932

Data were shown as events (%). Comparison of adverse events, including bleeding and dyspnea, among the three groups during hospitalization and at 30 days after discharge. T-90 mg-12 h: Maintenance dose of 90 mg of ticagrelor at 12 h after the last clopidogrel treatment; T-90 mg-24 h: Maintenance dose of 90 mg of ticagrelor at 24 h after the last clopidogrel treatment; T-180 mg-24 h: Loading dose of 180 mg of ticagrelor at 24 h after the last clopidogrel treatment; BARC: Bleeding Academic Research Consortium criteria; TIMI: Thrombosis in myocardial infarction; PLATO: PLATelet inhibition and patient outcomes; -: Not applicable.

was employed in this study to balance the debate of the low cost-effectiveness and accuracy in Chinese patients.^[1,32,33] Finally, the results revealed that the T-180 mg-24 h group and the T-90 mg-24 h group exhibited the greatest efficacy in the pharmacodynamic assessments. The most common reasons for discontinuing ticagrelor therapy are bleeding and dyspnea, and treatment interruption is associated with poor prognosis.^[34] Moreover, these adverse events are typically observed when patients are treated with a high-dose of ticagrelor.^[35] However, treatment of patients with a 180 mg bolus of ticagrelor did not increase the proportion of adverse events compared with managed by the standard dose in the present study.

Another noticeable discovery is that the difference between the T-90 mg-12 h group and the T-90 mg-24 h group in pharmacodynamic assessments suggests the presence of a negative pharmacodynamic interaction between the overlap for clopidogrel and ticagrelor at 12 h after the last dose of clopidogrel. However, this finding was contrary to the Comparative Pharmacodynamic Study of Ticagrelor versus Clopidogrel and Ticagrelor in Patients Undergoing Primary Percutaneous Coronary Intervention (CAPITAL RELOAD) study reported in 2014, which demonstrated a positive pharmacodynamic interaction between clopidogrel and ticagrelor regardless of the interval time.^[36] Importantly, according to a recent study, we inferred that the occupied P2Y₁₂ receptors might be incompletely cleared at 12 h compared to 24 h after the application of clopidogrel.^[37] This phenomenon corresponded to the inhibition of platelet aggregation by clopidogrel, which

could last for a longer time.^[26] Thus, we hypothesized that a higher level of occupied P2Y₁₂ receptors, which was inversely proportional to time, corresponded with a stronger influence on the subsequent binding drugs. We tried to acquire some clues for further exploring the drug interactions based on the recently updated viewpoints. The traditional non-competitive mode of inhibiting the ADP binding site with ticagrelor was challenged by a competitive mode, in which the Cys194 residue of the P2Y₁₂ receptor protein contributed to the recognition of ticagrelor, whereas clopidogrel interacted with the Cys97 residue of the receptor protein, but structurally, the two residues were not the unique binding sites, and whether the distance between the two residues was far enough to not severely affect the binding of ticagrelor with P2Y₁₂ when clopidogrel was bound still requires further clarification.^[38-40] All the above new viewpoints might be coincided with the mild negative impact on ticagrelor pharmacodynamics at 12 h after the last dose of clopidogrel. As we all know, the early phase after PCI or ACS could be a potential vulnerable period for ischaemic complications especially in patients with complicated CAD, who may be more prone to stent thrombosis.^[41,42] Overall, the assumption of the interaction of receptor binding sites and the updated mechanisms might make it possible for us to avoid the transformation that occurs at 12 h after medication, which is based on the possible negative pharmacodynamics between the overlap for clopidogrel and ticagrelor detected in this study at 12 h after clopidogrel treatment. This finding further supports that the optimal transformation time point is 24 h after the

last clopidogrel treatment, which concurred with the pharmacodynamic assessments above. Additional larger studies are warranted to assess the pharmacokinetics to verify this conclusion.

The present study was certainly not without limitations. First, our study was an open-label study with inherent biases. Nevertheless, all the adverse events that occurred during hospitalization were adjudicated by clinicians who were unaware of treatment allocations to minimize the potential biases. Second, although a larger sample size and a various measure of platelet functions were needed in our study, such studies are difficult to implement because we are a developing country and the platelet function testing by verifynow and vasodilator stimulated phosphoprotein costs more than 10% of a per capita disposable income every year in Liaoning, China.^[43] Nevertheless, the results of the pharmacodynamics and adverse reactions might still provide a reference for switching from clopidogrel to ticagrelor treatment. Third, 180 mg of ticagrelor at 12 h after clopidogrel treatment was not evaluated in our study because Asians are believed to have a higher bleeding risk during anti-thrombotic therapy.^[27,28] Whether there are benefits to this switching therapies remains unknown. Finally, the potential interrelationship observed between the overlap for clopidogrel and ticagrelor in our study did not lead to a definitive conclusion due to the absence of pharmacokinetic measurements of ticagrelor, its major metabolite and the active metabolite of clopidogrel. Therefore, the potential mechanism of the interaction between the overlap for these drugs warrants further study.

In conclusion, the present study showed that ACS Chinese patients with complicated CAD managed by PCI can indeed benefit from switching from clopidogrel to ticagrelor for platelet inhibition. Our data suggests based on the pharmacodynamic assessments and adverse events that switching to ticagrelor with a bolus of 180 or 90 mg at 24 h after the last dose of clopidogrel is the optimal therapy in Chinese patients with ACS with complicated CAD managed by PCI. Furthermore, this study indicates that there seems to be a negative interaction between the overlap for clopidogrel and ticagrelor at 12 h after the last dose of clopidogrel. Additional larger studies are warranted to further verify the conclusions of our trial.

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Conflicts of interest

None.

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