

# Rational and Design of ST-ON-SET: Assessment of Antiplatelet effect after Ticagrelor Loading Dose in STEMI Patients and NSTEMI Patients

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## Abstract

**Background:** Background: Delayed platelet inhibition by ticagrelor has been initially documented in STEMI subjects. To the best of our knowledge, no data exists about the direct description of early onset of platelet inhibition after ticagrelor loading dose (LD) in different clinical forms of ACS, especially in Chinese patients. The ST-ON-SET study is designed to address this unmet need.

**Method/Design:** The ST-ON-SET study is a single center, prospective, observational, open-label, investigator-initiated study. Platelet inhibition assessed by Light transmittance aggregometry (LTA) and plasma concentrations of ticagrelor and its metabolites would be investigated serially. The primary outcome is the inhibition of platelet aggregation measured by LTA at 2 hours after ticagrelor LD. Moreover, baseline inflammatory and thrombotic biomarkers would be measured to investigate the potential underlying influences of platelet inhibition.

**Conclusion:** The study is designed to characterize pharmacokinetic and pharmacodynamic profiles of ticagrelor LD in Chinese STEMI and NSTEMI patients. Furthermore, preliminary investigation of the underlying mechanism of initial delayed platelet inhibition by ticagrelor would be conducted.

**Keywords:** Acute coronary syndrome; ticagrelor; pharmacokinetics; pharmacodynamics

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## Background

Ticagrelor (formerly AZD6140) is the first reversibly binding oral, direct-acting P2Y<sub>12</sub> receptor antagonist. In PLATO study [1], ticagrelor has demonstrated its superiority regarding P2Y<sub>12</sub> receptor blockade and subsequently ischaemic events reduction compared to clopidogrel in acute coronary syndrome (ACS) patients. In terms of antiplatelet effect, ticagrelor is more potent than clopidogrel and produces a faster and stronger inhibition of platelet aggregation [2,3]. In healthy volunteers, ticagrelor reaches its maximal plasma concentration in about 1.5 hour, after 180 mg loading dose (LD)[2]. Likewise, a fast onset of action has also been described with a significant antiplatelet effect apparent as early as 30 minutes after 180 mg ticagrelor LD and achieving near-maximal (>80%) platelet

inhibiting response within 2 hours in stable coronary artery disease (CAD) patients [3]. However, in the clinical setting of ST segment elevation myocardial infarction (STEMI), more than a half of patients treated with ticagrelor still show high residual platelet reactivity(HRPR) 2 hours after the LD, and at least 4 h are required to achieve an effective platelet inhibition in the majority of subjects[4]. Moreover, the absence of any ticagrelor advantage versus clopidogrel on the ST resolution observed at day 3 in the recently reported PLATO ST elevation ECG study[5] might be associated with a delayed or incomplete platelet inhibition by ticagrelor.

Of note, the available studies about the early pharmacodynamic response of ticagrelor were conducted exclusively in single arena



of CAD using different platelet function assays. To the best of our knowledge, no data exists about the direct description of onset of platelet inhibition after ticagrelor LD in different clinical forms of ACS patients. Although the clinical efficacy of ticagrelor has been studied extensively in PLATO, a comprehensive characterization of its antiplatelet effect profile in different clinical arenas of ACS has not been elucidated. Therefore, the present study is designed to characterize PK/PD profiles of ticagrelor LD in Chinese STEMI and Chinese NSTEMI patients. In this study, platelet inhibition assessed by Light transmittance aggregometry (LTA) and plasma concentrations of ticagrelor and its metabolites would be investigated serially.

At the same time, we would also measure baseline coagulation function by Thromboelastography (TEG) and assess the baseline level of inflammatory markers to investigate the potential underlying influences of platelet inhibition.

## Methods

### Study design and duration

The ST-ON-SET (Assessment of antiplatelet effect after ticagrelor loading dose in STEMI patients and NSTEMI patients) study is a single center, prospective, observational, open-label, investigator-initiated study. For each patient, the study follow-up period is one month. Enrolment to the trial is planned to commence in September 2016.

### Selection criteria

Patients admitted with diagnosis of STEMI, within 12-48 h from the onset of symptoms, and not eligible for a primary PCI strategy would be enrolled into the STEMI group. At the same time, patients admitted with diagnosis of Non ST-segment elevation myocardial infarction (NSTEMI), within 48h from the last onset of symptoms would be enrolled into the NSTEMI group.

For patients who would be enrolled into STEMI group, the following two inclusion criteria had to be met: either persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block; a positive test of a biomarker (troponin T) in accordance with the universal definitions [6] indicating myocardial necrosis.

For patients who would be enrolled into NSTEMI group, two of the following criteria had to be met: a positive test of a biomarker (troponin T) in accordance with the universal definitions indicating myocardial necrosis [6]; ST-segment changes on electrocardiography, indicating ischemia that do not meet criteria for STEMI. Exclusion criteria are summarized in table 1.

### Treatment

Patients will be given 180 mg of ticagrelor as a loading dose, followed by 90 mg twice a day. At the same time, the participants will also be administered with 300mg of aspirin as loading dose, followed by 100mg daily.

Concomitant treatment with oral anticoagulant drugs is not permitted during the study. If treatment with oral anticoagulant drugs is considered essential during the study, study medication must be discontinued but may be resumed if anticoagulant therapy can be stopped. Furthermore, treatment

**Table 1.** Exclusion criteria

1. age $\leq$ 18 years;
2. active bleeding or bleeding diathesis or history of significant gastrointestinal bleed within 1 year;
3. any previous transient ischemic attack/stroke or history of intracranial hemorrhage;
4. administration in the week before the index event of clopidogrel, ticlopidine, prasugrel, ticagrelor;
5. known relevant hematological deviations;
6. life expectancy $\leq$ 1 year;
7. known severe liver or renal diseases;
8. patients with cardiogenic shock;
9. patients who are unable to swallow drug or vomit after intake ;
10. active cancer;
11. need for urgent revascularization;
12. patients with sick sinus syndrome, 2nd or 3rd degree atrioventricular block;
13. need treatment with oral anticoagulant;
14. known, clinically important thrombocytopenia(i.e. $< 100 \times 10^9/L$ ) or anaemia (i.e. $< 100g/L$ );
15. pregnancy or lactation;
16. any contraindication against the use of ticagrelor;
17. Concomitant use of morphine

with GPIIb/IIIa receptor antagonists is not allowed during the first 12 hours.

### Objectives and outcomes

The primary objective of this study is to observe the onset of antiplatelet effect of 180 mg LD ticagrelor in Chinese STEMI and NSTEMI patients. The corresponding outcome is the inhibition of platelet aggregation (IPA) measured by LTA at 2 hours after ticagrelor LD.

Additional second objectives are to describe the pharmacokinetic (PK) and pharmacodynamic (PD) profile of ticagrelor in Chinese STEMI and NSTEMI patients, to investigate the underlying influences of platelet inhibition, such as inflammatory markers and coagulation function, to evaluate safety of ticagrelor in Chinese STEMI and Chinese NSTEMI patients.

The second outcome measures including: (1) the IPA at 0, 1, 2, 4, 8 and 12 hours in Chinese STEMI and Chinese NSTEMI patients ; (2) plasma concentrations of ticagrelor and its active metabolite at 1, 2, 4, 8 and 12hours; (3) the level of white blood cell count (WBC), high-sensitivity C-reactive protein (hs-CRP) and fibrinogen (Fbg) at baseline; (4) the level of baseline R time value and maximal platelet activity(MA) measured by TEG; (5) bleeding events (by BARC classification) [7] at 30 days.

### Laboratory method

Blood samples for PD determination will be collected using disposable needles and sodium citrate tubes. LTA would be performed at LD-administration (hour 0) and at 1, 2, 4, 8, 12 hours

after the start of treatment using adenosine diphosphate (ADP) (5 and 20  $\mu\text{mol/L}$ ) as agonist. Inhibition of platelet aggregation (IPA) is defined as the percentage decrease in aggregation values (Aggmax) obtained at baseline(b) and after treatment(t):  $(\%PAb - \%PA_t) / \%PAb$ .

Blood samples for PK determination will be collected using disposable lithium heparinized tubes. The sample will be labeled, and placed on ice, until centrifugation, which will begin within 30 minutes after the sample is obtained. The sample will be centrifuged for 10 minutes at 4°C at a relative centrifugal force of 1500 g. The resulting plasma for ticagrelor and AR-C124910XX concentration will be transferred into a 1.8 mL polypropylene tube (Nunc Cryovial, Fisher Scientific No 12-565-163N, NNI No. 375418) with screw caps and immediately frozen upright at -20°C or below in a non frost-free freezer and kept frozen at this temperature before, during and after transport to the designated laboratory. The study flow chart is detailed in Figure 1.

### Adverse event monitoring

Serious and other adverse events would be recorded and reported in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines. Investigators are responsible for meeting all regulatory reporting requirements. The investigators are also responsible for reporting serious adverse events (SAE) to Ethics Committee in time per local requirements.

### Statistical analyses

Categorical data would be presented as frequencies and group percentages. Continuous data with normal and skewed distribution would be presented as mean $\pm$ SD and medians (first to third quartiles), respectively. The Kolmogorov-Smirnov test would be used to examine data distribution normality. Two-sample t test and Fisher exact test would be used for comparison of normally distributed continuous and categorical data, respectively. The Mann-Whitney U-test would be used for comparison of skewed continuous data. Either Pearson product correlation or Spearman Rank correlation method would be used to evaluate the correlation

among normal/non-normal distribution data. Analysis of platelet function data at different time points for the groups (NSTEMI and STEMI) will be performed by 2-way repeated measures analysis of variance to evaluate the effect of group, time, and group-time interactions. Analyses would be performed with SPSS version 19 (IBM Corporation, Somers, New York).

No exact data are available about the early pharmacodynamic response of ticagrelor in the clinical setting of STEMI and NSTEMI patients. A total of 30 patients, 50% STEMI and 50% NSTEMI are enrolled to determine PK/PD profiles after loading dose.

### Discussion

Delayed platelet inhibition by ticagrelor has been initially documented in STEMI subjects. To the best of our knowledge, no data exists about the direct description of early onset of platelet inhibition after ticagrelor LD in different clinical forms of ACS, especially in Chinese patients. The ST-ON-SET study is designed to address this unmet need. The conclusions of this study may provide theoretical basis for optimum usage of ticagrelor in clinical practice.

Theoretically, the physiological state of STEMI may affect antiplatelet agents' absorption, metabolism, and subsequent pharmacokinetics and pharmacodynamics [8]. In our study, the correlations between baseline inflammatory and thrombotic biomarkers and PK/PD levels would be investigated. TEG is a point-of-care coagulation test that may provide superior evaluation of coagulation disorders than routine coagulation tests [9,10]. The time to platelet-fibrin clot formation (reaction time, R time), a marker of the speed of thrombin generation, as measured by TEG may contribute to the overall antithrombotic properties of clopidogrel in patients undergoing stenting [11]. Interestingly, our recent study noticed an abrupt increase of thrombin-induced maximal platelet-fibrin clot strength (MA) measured by TEG, a marker of global platelet aggregability, in patients with AMI and a progressive decrease with time after the event [12]. Moreover, high MA was demonstrated as an independent determinant of platelet inhibition after anti-platelet treatment [13]. All these

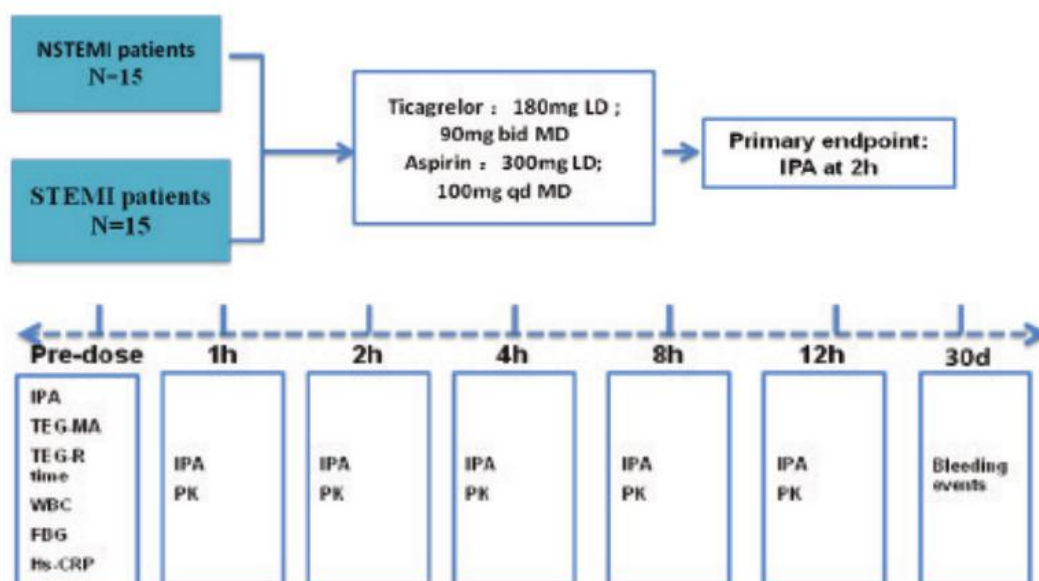


Figure 1. The study flow chart



findings suggest that STEMI, a highly prethrombotic milieu, may affect the delayed activity of ticagrelor. So we select baseline MA and R-time measured by TEG as coagulation maker to explore whether baseline coagulation function may affect the onset of ticagrelor. In addition, inflammation also participates in the pathophysiology of STEMI, there could exist a relationship between ticagrelor response and inflammatory status. As some studies have indicated that WBC, hs-CRP and Fbg as markers of inflammation were associated with the response of clopidogrel [14-17].

### Declarations of Interest

The authors declare no conflicts of interest.

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We are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. The authors agree to abide by the requirements of the "Statement of publishing ethics of the International Cardiovascular Forum Journal[18].

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