A Randomized Non-Inferiority Study of Low-dose and Standard-dose Ticagrelor After Intervention for Acute Coronary Syndrome: Study Protocol for the TIGER STUDY

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Study protocol

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Abstract

Background

Current guidelines recommend that patients with acute coronary syndrome (ACS) who have successfully undergone percutaneous coronary intervention (PCI) should continue to use dual antiplatelet therapy (DAPT) for 12 months. The long-term use of standard-dose dual antiplatelet therapy will increase the risk of bleeding. An optimized antiplatelet strategy that can prevent ischemic events and reduce the risk of bleeding remains to be explored.

Methods

The study is a prospective, multicenter, randomized, open-label, controlled study involving 2120 patients from six clinical centers in China. Through the Interactive Web Response System (IWRS), ACS patients undergoing successful PCI will be randomly divided into the low-dose ticagrelor group or the normal-dose ticagrelor group, after taking 100 mg aspirin and 90 mg ticagrelor bid for 1 week. The primary endpoint is a composite of cardiovascular death, non-fatal myocardial infarction, stent thrombosis, repeat revascularization, stroke, and bleeding events of grade 2 or higher according to Bleeding Academic Research Consortium [BARC] criteria at one year. The secondary endpoints are bleeding events of grade 2 or higher according to Bleeding Academic Research Consortium [BARC] criteria at one year.

Discussion

Recent studies have confirmed that 90 mg ticagrelor alone can safely and effectively reduce bleeding without increasing ischemic events of patients with ACS after PCI. Compared with standard-dose DAPT, whether low-dose ticagrelor combined with aspirin can ensure the anti-ischemic effect while reducing the bleeding risk remains unclear in Chinese patients.

The Tiger study will be the first large-scale, multicenter study to compare the efficacy and safety of low-dose and standard-dose ticagrelor combined with aspirin in ACS patients one week after successful PCI.

Trial registration

Clinicaltrials.gov, NCT04255602. Registered on 5 February 2020.

Background

Recent guidelines recommended 12-month dual antiplatelet therapy (DAPT) with aspirin and P2Y12 receptor antagonist ticagrelor for ACS patients who undergo PCI with drug-eluting stents (DES). [1, 2] However, standard-dose DAPT is accompanied with the incidence of bleeding events to 3% - 10%. [3] Gastrointestinal hemorrhage is even an independent risk factor for death in ACS patients.[4, 5] The optimized antiplatelet strategy, which could inhibit ischemic events while reducing bleeding events versus standard-dose DAPT, is of vital importance.
Recent clinical trials, such as TWILIGHT and Global Leaders have confirmed that 90 mg ticagrelor alone can safely and effectively reduce bleeding in patients with ACS after PCI. [6-8] Moreover, SMART-CHOICE trial suggested that P2Y12 monotherapy may be a better choice for the Asian ACS population. [9] These studies challenge the current DAPT strategy. However, aspirin should not be given up easily, considering that ticagrelor has a higher rate of discontinuation, the increased frequency of dyspnea and higher costs than aspirin. Therefore, the optimal DAPT strategy still needs to be explored.

The TIFU study indicated that the low-dose dual antiplatelet drugs may be another choice for ACS patients. [10] PEGASUS-TIMI 54 study and the latest ELECTRA study showed 60 mg ticagrelor has same platelet inhibitory effect as that of 90 mg ticagrelor in patients undergoing PCI. [11, 12] However, larger-scale and high-quality clinical controlled studies are required to confirm these findings.

The TIGER study decided to compare the safety and efficacy of low-dose DAPT (ticagrelor 60mg bid plus aspirin 100mg qd) and standard-dose DAPT (ticagrelor 90mg bid plus aspirin 100mg qd) following 1-week standard-dose DAPT in ACS patients after successful PCI, aiming to explore the optimal DAPT strategy for ACS patients.

**Methods**

**Study objectives and hypothesis**

The main purpose of this study is to compare the safety and efficacy of low-dose and standard-dose ticagrelor with aspirin in ACS patients one week after successful PCI. We hypothesized that low-dose ticagrelor group would be non-inferior to the standard-dose ticagrelor group in preventing ischemic events while reducing the risk of bleeding.

**Study design and setting**

The TIGER study is a prospective, multicenter, randomized, open-label, controlled clinical trial, involving 2120 participants from six heart clinical centers in China. All ACS patients who meet all the enrollment criteria will be randomly assigned to one of the two groups one week after the successful PCI: low-dose ticagrelor group (Ticagrelor 60mg+ASA 100mg; n=1060) and standard-dose ticagrelor group (Ticagrelor 90mg+ASA 100mg; n=1060), using the interactive web response system (IWRS), at a 1:1 ratio.

All patients will receive standard DAPT (aspirin 100mg qd + ticagrelor 90mg bid) therapy in the first week after PCI. Then patients will take different dose ticagrelor combined with aspirin according to their group within one year after surgery. To ensure drug compliance, telephone call will be done monthly by specific staff.

If patients are intolerance to ticagrelor or have ischemic or bleeding complications during the first week after PCI, he or she will be recorded as drop-out and will receive timely and carefully therapy according the exactly situations.
Clinical follow-up will be performed by telephone or office visit at 1 month, 6 months and 12 months after PCI. The research flow chart is shown in Figure 1. The follow-up schedule is shown in Table 1.

Randomization

Our study will strictly follow the principle of randomization. After signing of the informed consent, using the interactive web response system (IWRS), enrolled patients will be randomly divided into low-dose ticagrelor group (n=1060) and standard-dose ticagrelor group (n=1060). The randomization will be stratified by ACS (STEMI / non-STEMI / UAP), age (<75 / ≥75), sex (Male / Female), and diabetes (Yes / No).

Study population and enrollment criteria

In the TIGER study, a total of 2120 ACS patients receiving successful PCI and 1-week standard-dose DAPT will be enrolled in six cardiac clinical centers. Acute coronary syndrome (ACS) includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina.[13] It can be confirmed by clinical symptoms and relevant medical examination. Patients recruited must meet all inclusion criteria and without any exclusion criteria. Patients over 18 years old and less than 90 years old who were diagnosed with ACS and successfully received PCI are eligible for inclusion. The informed consent must be signed before they enter the study. Patients who are allergic to aspirin or ticagrelor cannot participate in the study. Since our study will last two years, patients with life expectancy less than two years need to be excluded. Meanwhile, considering the impact of pregnancy on individual physiology, pregnant women or women who are going to be pregnant in the next two years will not be recruited. Patients with a history of cerebral hemorrhage, stroke within half a year, active hemorrhage or known hemorrhage diseases will be excluded because of the great risk of bleeding. In order to ensure the compliance and safety of patients, patients with the following conditions should also be excluded, such as several liver and kidney disorders (ALT>5 times ULA, EGFR<15ml/min/1.73mm2), malignant tumor diseases, platelets less than $100 \times 10^9$ /L or hemoglobin less than 90 g/L, requiring oral anticoagulants, and patients considered unsuitable for this study by the researchers.[14, 15] In all cases, the investigator based on clinical factors and a review of the initial angiogram will make the final decision whether or not to recruit the patient. All the inclusion and exclusion criteria details are described in Table 2.

Interventions

Antiplatelet drugs are needed to prevent stent thrombosis before and after PCI with DES in ACS patients. If the ACS patient is not taking aspirin before, 300mg loading dose aspirin must be taken at least 24 hours before PCI. Aspirin will then continue to be administered at a dose of 100mg once daily until one year after intervention. Similarly, if the patient did not take ticagrelor, they should use 180 mg loading dose ticagrelor at least 2 hours before PCI. Even if patients cannot get ticagrelor two hours before operation, they will get it in the cardiac catheterization room before it. Within one week after the operation, oral administration of ticagrelor 90mg twice daily should be continuously applied in both groups. Then, patients will be given the corresponding dose ticagrelor (90mg bid or 60mg bid) according to the group
they entered. The use of aspirin and ticagrelor will last for one year after PCI. Notably, additional antiplatelet drugs will not be allowed to use during the period of the study. In our study, only second-generation drug-eluting stents will be used.

Outcomes

The primary endpoint is the composite endpoint of cardiovascular death, non-fatal myocardial infarction, stent thrombosis, revascularization, stroke, and bleeding events of grade 2 or higher according to Bleeding Academic Research Consortium [BARC] criteria within one year after PCI. [16] The secondary endpoints are bleeding events of grade 2 or higher according to Bleeding Academic Research Consortium [BARC] criteria within one year after PCI. [16] All clinical outcomes are defined according to the Academic Research Consortium (ARC).[17] All adverse events will be reported to the ethics committee (EC) in a given time. The endpoints will be adjudicated by the Clinical Event Adjudication Committee (CEAC).

Sample size calculation

In our study, we assume that the composite of MACCE and BARC2 or higher bleeding events rate in the control group will be 5% at 1 year in ACS after PCI according to previous studies (STOD-DAPT2, RESET). [18,19] The sample size of the study should not be smaller than 1930 (965 per group) to guarantee 80% power of the study at the significance level of 0.05. Considering 10% of the patients would be lost in the follow-up period, we determined the final sample size to be 2120 patients (1060 per group).

Statistical analysis

The efficacy endpoint analyses will be performed in the intent-to-treat population, safety endpoints analyses will be performed in the safety analysis population. The time-to-event analysis will be performed on the primary efficacy outcome, cumulative event rates will be estimated with the Kaplan-Meier method and compared with log-rank tests. If the upper limit of the 1-sided 95% CI of the difference were less than the prespecified noninferiority margin, low dose DAPT strategy will be considered noninferior to standard DAPT strategy in one-year period after PCI in ACS patients. Hazard ratio (HR) will be estimated with the use of Cox proportional-hazards model, after controlling for ACS, age, sex, and diabetes. Patients who were lost to follow-up were censored at the time of the last known contact. Sensitivity analysis such as landmark analysis will also be conducted.

Continuous variable will be described as mean (std) or median (interquartile range) as appropriate, categorical variables will be described as counts and percentages. P values and CIs were 2-tailed except those for noninferiority testing of the primary end point.

No interim efficacy analysis is planned in this study, an independent data monitor committee (IDMC) will be set up to assess the safety of subjects periodically as previously described.

Ethical considerations
The researchers must obtain the approval of the study protocol and informed consent from the ethics committee. Meanwhile, researchers will be responsible for regular reporting as required by the institutional committee over the whole study period.

Any protocol amendments as well as associated informed consent changes will be submitted to ethics committee and written approval must be obtained prior to implementation. Regarding the enrolled patients, we must obtain the informed consent signed by them in advance. The privacy of patients will be kept in strictly confidential during and after the TIGER study. All questions of privacy and secrecy are listed in the informed consent form (ICF). Enrolled patients have the right to withdraw from the trial anytime during the process of the study.

Independent data monitor committee (IDMC) will be notified of all serious adverse events and unanticipated adverse device events occurring during the study. IDMC will also review compiled adverse event data at periodic intervals and report to the ethics committee any safety concerns and recommendations for suspension or early termination of the trial.

**Study organization**

The TIGER study is a multicenter, prospective, randomized, open-label, controlled study designed and initiated by Zhongshan hospital affiliated to Fudan University and Tongren Hospital affiliated to Shanghai Jiaotong University Medical College. Dr Junbo Ge is the chairman, and Doctor Lei Hou is the Principal investigator. We guarantee to obtain the informed consent and approval of the ethics committee before starting any research procedure. This study will compare the safety and efficacy of low- and standard-dose ticagrelor combined with aspirin in ACS patients one week after undergoing successful PCI with DES. The executive committee will be responsible for the scientific operational of the study. The independent data monitoring committee (IDMC) will be responsible for reviewing the data on a regular basis and determining the safety scope of the test, as well as the termination of the test, and the executive committee will finally decide whether to terminate the study ahead of time based on the recommendation of IDMC. The study will fully follow the ethical principles of the Helsinki declaration.

**Discussion**

The introduction of second-generation drug-eluting stents, and optimal medical therapy has significantly decreased the incidence of stent thromboses. Bleeding has gradually emerged as a predictor of early and late mortality in patients with ACS.[3] Therefore, avoiding bleeding events has become essential after using antiplatelet drugs for ACS patients undergoing PCI.

Previous studies have shown the advantage of short period of DAPT strategy in preventing ischemic events and reducing the risk of bleeding.[7, 9, 18] However, ACS patients usually present with concomitant diseases such as ischemic stroke and **transient ischemic attack** in which aspirin is essential for the secondary prevention. On the other hand, some small-scale studies showed that ticagrelor 60 mg bid
achieved high peak levels through platelet inhibition in nearly all patients, similar to that of ticagrelor 90mg bid. [11, 20]

Therefore, we designed the TIGER study to compare the safety and efficacy of low-dose and standard-dose ticagrelor combined with aspirin in patients suffering from ACS after successful PCI. We believe the TIGER study will offer a good choice to find an optimal antiplatelet strategy for ACS patients after PCI.

**Trial status**

Recruitment started on February, 2020 and is planned to end in February, 2022, with 2120 patients randomized. The current protocol version is 1.1, dated February 1st 2020.

**Abbreviations**

ACS: Acute coronary syndrome; DAPT: Dual antiplatelet therapy; PCI: Percutaneous coronary intervention; DES: Drug eluting stent; IWRS: Interactive Web Response System; IDMC: Independent data monitor committee; CEAC: Clinical Event Adjudication Committee.

**Declarations**

**Limitation**

The open-label design is a limitation of the study.

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of the Tongren Hospital affiliated to Medical College of Shanghai Jiaotong University. Prior to participation, all subjects provide written informed consent.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

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Authors' contributions

Junbo Ge, Lei Hou and Yanan Pang codesigned the study. Sicheng Wu designed the statistical plan. Yanan Pang, Minglu Ma, Dong Wang, Hongyi Wu, Wei Hu, Zhibing Wang and Yan Chen screened and enrolled participants, arranged informed consent from the participants, provided patient care and took samples. Lei Hou and Minglu Ma wrote the manuscript. All authors critically reviewed the report.

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Tables

Table 1: Follow-up schedule

| Follow-up time point (after PCI) | ± Days |
|---------------------------------|-------|
| 1 month                         | 20    |
| 6 months                        | 20    |
| 12 months                       | 20    |

Table 2: Enrollment criteria

| Inclusion criteria |
|--------------------|
| 1. Patients over 18 years old and less than 90 years old on admission |
| 2. Patients diagnosed with ACS undergoing successful PCI with drug eluting stent |
| 3. Written informed consent |

| Exclusion criteria |
|--------------------|
| 1. Patients who are allergic to aspirin and ticagrelor |
| 2. Pregnant women or women who plan to become pregnant within 2 years |
| 3. Patients with a life expectancy < 2 years |
| 4. History of previous cerebral hemorrhage or patients who suffered from a stroke within half a year |
| 5. Patients with active bleeding or any known bleeding diseases |
| 6. Several hepatorenal insufficiency (ALT > 5-fold ULA, EGFR<15ml/min/1.73mm²) |
| 7. Patients with active malignant tumor disease |
| 8. Platelets <100×10^9/L or hemoglobin < 90g/L |
| 9. Patients with oral anticoagulants |
| 10. Patients who are unsuitable for the trial according to the investigator |

Figures
ACS patients undergoing successfully PCI and meeting the inclusion criteria

One-week standard-dose dual antiplatelet therapy

Randomly dividing 2120 enrolled patients into two groups at a 1:1 ratio

Ticagrelor 90mg bid plus aspirin 100mg qd
Stratified randomization
Ticagrelor 60mg bid plus aspirin 100mg qd

Intension-to-treat population

Data analysis at 1, 6, 12 months follow-up

**Figure 1**
Flow chart

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Ethicalapproval.jpg
- Funding.jpg
- SPIRITchecklist1.docx
- informedconsent1.docx