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Rationale and design of the ETN-STEP (Early administration of Tirofiban in mid to high risk patients with non-ST elevation acute coronary syndrome referred for percutaneous coronary intervention) project: A multi-center, randomized, controlled clinic trial in Chinese patients

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Abstract

As a member of Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, Tirofiban had been shown to improve myocardial reperfusion and clinical outcomes in patients undergoing percutaneous coronary intervention (PCI), but the optimal timing of administration of Tirofiban remains unclear. In order to compare the effects of upstream versus downstream administration of Tirofiban in Chinese patients with mid to high risk, non-ST elevation acute coronary syndrome (ACS) referred for PCI, a multi-center, randomized, controlled, prospective study will be conducted. A total of 500 mid to high risk, non-ST-segment elevation myocardial infarction (NSTEMI) ACS patients will be recruited for this study. Patients will be randomized to Tirofiban upstream administration group (initiated 12 h before PCI) and Tirofiban downstream administration group (initiated at cath-lab after angiography). Thrombolysis in myocardial infarction (TIMI) flow grades, TIMI myocardial perfusion grades (TMPG), and Corrected TIMI frame counting (CTFC) before and after PCI, as well as clinical outcomes during the hospital stay, and within 30 days after PCI will be compared between the two groups. This study will provide evidence on the optimal timing for initiating administration of Tirofiban in mid to high NSTEMI ACS subjects undergoing PCI.

1 Introduction

The efficacy of Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors in high risk, non-ST-segment elevation myocardial infarction (NSTEMI) acute coronary syndrome (ACS) patients has been well established.[1] According to the updated American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline, it is recommended in high risk patients undergoing invasive strategy that GP IIb/IIIa inhibitors should be chosen as the second antiplatelet therapy (Ia).[2] However, whether up stream use of GP IIb/IIIa could be better than provisional use in the cath lab remained to be answered. Most recently, the results of two meta analyses have been published,[3,4] showing that: (1) In NSTE ACS, treatment with upstream, small-molecule GP IIb/IIIa inhibitors provided a significant, but modest ischemic benefit when compared with initial placebo; (2) Compared with delayed, selective use at percutaneous coronary intervention (PCI), early upstream use was associated with a trend toward fewer ischemic events. However, these modest benefits were associated with an increased risk of bleeding. As the meta-analysis data were from studies on different brands of GPI, including Tirofiban, Etifibatide, Lamifiban, and Abciximab, it is still of interest to know whether a specific GP IIb/IIIa inhibitor would have a specific effect, especially in a Chinese population.

Consequently, we decide to perform a randomized, controlled clinical trial to compare early (prior to Transfer to the catheterization laboratory) *vs.* late (at the time of PCI) initiation of intravenous Tirofiban (which is the only GPI available in China) in NSTEMI ACS patients undergoing PCI.

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2   Rationale and strategy of ETN-STEP (Early administration of Tirofiban in mid to high risk patients with non-ST elevation, acute coronary syndrome referred for percutaneous coronary intervention)

Our primary aim will be to compare, in NSTE ACS patients, the efficacy of initiating Tirofiban 12 h before PCI (10 µg/kg bolus, followed by continuous infusion at 0.15 µg/kg per min for 12–24 h after PCI) *vs.* initiating Tirofiban at the time of PCI (10 µg/kg bolus, followed by continuous infusion at 0.15 µg/kg per min for 12–24 h after PCI). The procedures and strategy of ETN-STEP are presented in Figure 1.

3   End points and definitions

The primary endpoints will include both clinical endpoint and angiographic endpoint. The clinical end point is the composite endpoint, including myocardial infarction, target lesion revascularization and death at 30 days. The angiographic endpoints are the prevalence of thrombolysis in myocardial infarction (TIMI) III flow, TIMI myocardial perfusion grade (TMPG), and corrected TIMI frame counting (CTFC) before and after PCI.

4   Participating centers and sampling methods

Nine hospitals will participate in this study (shown in Table 1). Consecutive 500 in-patients with a diagnosis of mid to high risk NSTE ACS patients will be selected prospectively. Recruited patients will be asked to participate in a face to face interview, informed consent for follow-up contact will be obtained from the patients at enrollment. Criteria of inclusion and exclusion are outlined in Table 2.

Open-label randomization will be performed once the eligibility criteria are met. A 1: 1 computer-generated, random sequence supplied by an academic statistician, without blocking or stratification, will be used. Sealed envelopes indicating participant's study assignment will be sent to the study sites.

5   Data abstraction

Questionnaires will be developed for the study-wide use including three parts: Form 1, basic information; Form 2, PCI procedures; Form 3, follow-up information.
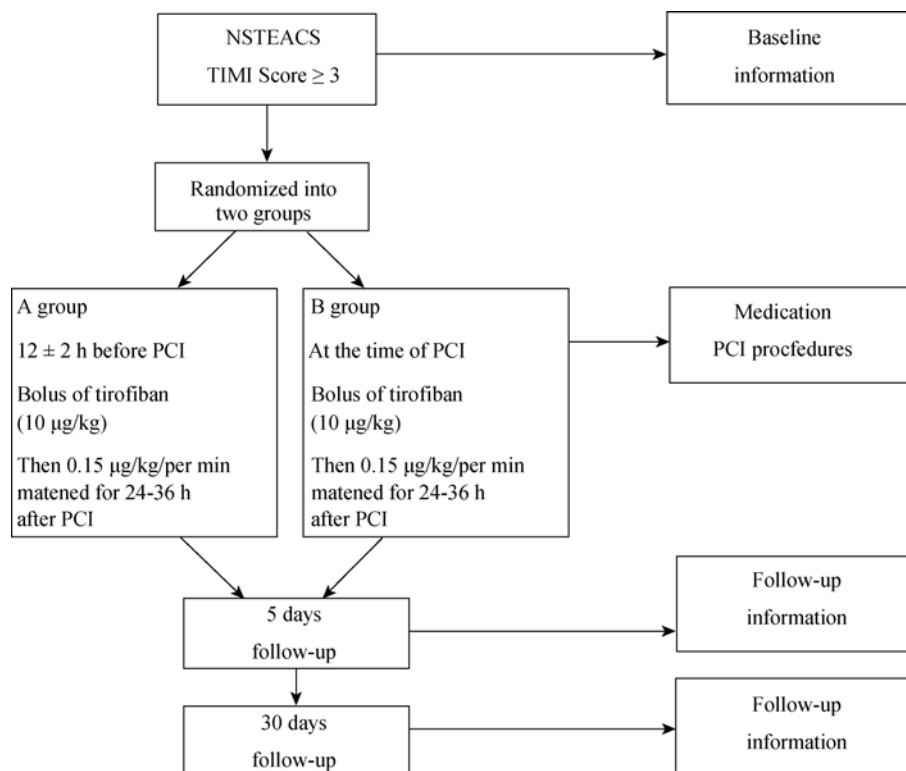

Figure 1.   Procedures and strategy of ETN-STEP. ETN-STEP: early administration of Tirofiban in mid to high risk patients with non-ST elevation, acute coronary syndrome referred for percutaneous coronary intervention; NSTE ACS: non-ST segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction.

Table 1. Descriptive characteristics of recruited hospitals.

Area in China	Province/City	Recruited hospital	Level of hospital	Teaching hospital
Northern	Beijing	Anzhen hospital	Tertiary	Yes
		First hospital affiliated to Peking University	Tertiary	Yes
		Fuwai hospital	Tertiary	Yes
		Military general hospital	Tertiary	Yes
	Hebei province	Cangzhou hospital	Tertiary	Yes
Southern	Shanghai	Shanghai Chest hospital	Tertiary	Yes
	Guangdong province	Guangdong province people hospital	Tertiary	Yes
	Wuhan	Wuhan Asian heart hospital	Tertiary	Yes
		Xiehe hospital affiliated to Tongji University	Tertiary	Yes

Table 2. Inclusion criteria of ETN-STEP project.

	Number of patient	Type of surveillance
Inclusion criteria	500	Medical record review
Must have a diagnosis of one of NSTE ACS and ready to PCI		
Must be ≥ 18 years old but ≤ 75 years		
TIMI Score ≥ 3		
Exclusive criteria		
High risk patients need to perform emergency PCI		
Contraindication of antithrombosis exist		
Pregnant or suspicious pregnant		
High risk for bleeding		
Allergy to the studied medication		

ETN-STEP: early administration of Tirofiban in mid to high risk patients with non-ST elevation, acute coronary syndrome referred for percutaneous coronary intervention; NSTE ACS: non-ST segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction.

Times of Tirofiban administration and interventional procedures, hospital-associated outcomes and follow-up information after discharge will be recorded. Standardized definitions for patient-related variables and clinical diagnoses will be used. Angiography will be sent to the core lab for analysis of angiographic endpoints.

6 Data management and quality control process

Completed questionnaires will be sent to the data management center, where they will be checked for possible errors or omissions by professionals. Two percent of the questionnaires will be verified, at random, by comparing the information with original medical records of in-patients and follow-up calls to selected outpatients. Any resulting data queries will be referred to the originating site before the forms are processed and computerized audit checks will be performed after data are is double inputted. Errors and illo-gicalities of selected data elements will be forwarded to the originating site for correction.

7 Proposed plan of analysis

Analysis of ETN-STEP will include qualitative and quantitative elements. The statistical significance of the differences between interventional group and control group with respect to the composite end point and its components will be assessed using logistic regression analysis. The incidence of events will be assessed using chi-square analysis. All tests will be two-sided, and statistical significance declared if $P < 0.05$. Cumulative event rates over time will be plotted using Kaplan-Meier curves.

8 Discussion

The ETN-STEP study will be the first randomized, prospective study to evaluate the upstream *vs*. downstream adm-

inistration (dispensing) of Tirofiban in Chinese ACS patients undergoing PCI. There are several unique features of this study. Firstly, we believe that it is more meaningful to address the time issue of GP IIb/IIIa administration in high ACS patients. Therefore, when screen the study subjects, we will use the TIMI risk score system to define the mid to high risk ACS patients. Although such a risk evaluating system may not be an optimal model in predicting the outcomes of ACS patients, it is easy to calculate, and furthermore, the results of the study may be more valuable in clinical practice by using such criteria. Secondly, the dose of Tirofiban used in this study may be different from that normally recommended, however, it is currently the dose we are routinely administering in the clinic.

In all, the findings of the ETN-STEP study will provide insight into the optimal timing for Tirofiban initiation in mid to high risk ACS Chinese patients undergoing PCI.

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