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Early Administration of Tirofibanin Mid- to High-risk Patients with Non-ST Elevation Acute Coronary Syndrome Referred for Elective Percutaneous Coronary Intervention (ETN-STEP): A Multi-center Randomized Controlled Clinical Trial in China

Jianping Li[1], Bo Zheng[1], Xingang Wang[1], Tieci Yi[1], Wei Dong[2], Zhan Gao[3], Shaoping Nie[4], Yawei Luo[4], Xiaobo Mao[5], Xi Su[6], Hui Chen[7], Ning Tan[8], Xufen Cao[9], Jun Zhang[9] and Yong Huo[1]*

[1]*Department of Cardiology, Peking University First Hospital, China*

[2]*General Hospital of the People's Liberation Army, China*

[3]*Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China*

[4]*Beijing Anzhen Hospital, Capital Medical University, China*

[5]*Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, China*

[6]*Wuhan Asia Heart Hospital, China*

[7]*Shanghai Chest Hospital, China*

[8]*Guangdong General Hospital, China*

[9]*Cangzhou Central Hospital, China*

***Corresponding author:** *Yong Huo, Department of Cardiology, Peking University First Hospital, China, Tel: 861083572283, Fax: 861066137748, E-mail: huoyong@263.net.cn*

Abstract

Aims: The objective of this randomized controlled clinical trial was to evaluate the efficacy and safety of upstream administration of Tirofiban in mid- to high-risk patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing early percutaneous coronary intervention (PCI).

Methods and results: A total of 478 patients with mid- to high-risk NSTE-ACS were randomized into two groups: 220 patients in the upstream group who received tirofiban 12 hours before PCI, and 258 patients in the downstream group who received tirofiban after angiography. Use of tirofiban lasted till 24-36 hours after PCI in both groups. Coronary blood flow and myocardial perfusion were evaluated as primary endpoints. Major adverse cardiovascular events (MACEs) and bleeding events were evaluated as secondary endpoints.

Results: Results showed that the percentage of TIMI myocardial perfusion grade 3 after PCI was significantly higher (93.8% vs 87.2%, P=0.02) and the corrected TIMI frame count was significantly lower (16.0 vs 18.0, P=0.002) in the upstream group compared with the downstream group.

Conclusions: In mid- to high-risk NSTE-ACS patients assigned to an invasive strategy, upstream use of tirofiban improved myocardium perfusion after PCI.

Keywords

Non-ST-segment elevation acute coronary syndrome, Tirofiban, Upstream

Introduction

Platelets play a critical role in the pathogenesis of acute coronary syndrome (ACS), and percutaneous coronary intervention (PCI) could further activate the platelets. As a result, antiplatelet therapy has become the fundamental treatment in ACS patients receiving PCI. Glycoprotein IIb/IIIa(GPIIb/IIIa) receptor antagonist, a potent intravenous antiplatelet agent blocking the final common pathway leading to platelet aggregation, has been shown to be a more efficient antiplatelet therapy compared with aspirin and clopidogrel. Guidelines from the American College of Cardiology/American Heart Association and the European Society of Cardiology recommended the use of GPIIb/IIIa in ACS patients receiving PCI [1,2]. However,

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the optimal time of initiation of this antiplatelet therapy remains unclear.

Data from a previous meta-analysis have shown that upstream use of small molecular GPIIb/IIIa receptor antagonists resulted into a lower incidence of MACEs, but a higher incidence of bleeding, compared to delayed, provisional use in the catheter lab in non-ST-segment elevation myocardial infarction (NSTEMI) patients [3]. In the EARLY ACS trial [4], patients treated with PCI receiving upstream eptifibatide sustained less ischemic events compared to patients with delayed provisional use. Kunadian and colleagues had explored the effect of different treatment strategy on angiographic outcomes, and discovered that early routine use of eptifibatide resulted in fewer angiographic procedural complications [5]. As heterogeneity exist among different small molecular weight of GPIIb/IIIa antagonists, and studies on tirofiban are relatively fewer, so we conducted the Early Administration of tirofiban in mid- to high-risk patients with non-ST elevation acute coronary syndrome referred for Elective Percutaneous Coronary Intervention (ETN-STEP) to compare the efficacy and safety of upstream versus downstream administration of tirofiban, which is the only available GPIIb/IIIa receptor antagonist in China currently, in mid to high risk NSTE-ACS patients referring to PCI.

Methods

Study design and patient population

ETN-STEP was a randomized, open labeled, controlled, multicenter trial conducted in nine medical centers in China [6]. The study protocol was approved by the local institutional review board at each participating center.

Mid- to high- risk NSTEMI ACS patients aged 18 to 75 years, who were suitable for an early invasive strategy (within 72 hours), were eligible for the trial. NSTEMI ACS is defined by electrocardiographic (ECG) ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or angina equivalent) [1]. Risk stratification was based on the subject's TIMI risk score, and mid- to high risk is defined as TIMI risk score ≥3 [7]. Each participant must sign a written informed consent.

Exclusion criteria included patients with very high risk (with refractory angina, severe heart failure or cardiogenic shock, life-threatening ventricular arrhythmias, or haemodynamic instability, or after resuscitation), severe congestive heart failure, severe hepatic and/or renal dysfunction, increased risk of bleeding (active bleeding, major surgery or trauma within the past three months, stoke within the past six months), anemia (hemoglobin<9g/dl) or thrombocytopenia (platelet count<90×10^9/L), pregnancy or suspicious pregnancy (women in child-bearing age must have a baseline test of β-hCG) and acute pericarditis.

Procedure and follow up

Eligible subjects were randomly assigned into two groups in a 1:1 ratio: 1) Upstream group: tirofiban was initiated 12 hours before PCI according to the following strategy: 10μg/kg bolus infusion, followed by continuous infusion at a rate of 0.15μg/kg/min, till 24-36 hours after PCI; 2) Downstream group: tirofiban was initiated in the catheter lab after PCI had been decided, according to the following strategy: 10μg/kg bolus infusion, followed by continuous infusion at a rate of 0.15μg/kg/min, till 24-36 hours after PCI. The randomization was performed with the use of computer generated random sequences, without blocking or stratification. Sealed envelopes indicating participant's study assignment were sent to the study sites.

PCI was performed following the Chinese Guidelines of Percutaneous Coronary Intervention [8]. A loading dose of 300mg clopidogrel and 300mg aspirin was administered before the procedure. After PCI, a maintaining dose of clopidogrel 75mg/d and aspirin 100mg/d was initiated. Heparin was used during the procedure, and a dose of 60units per kilogram of body weight was recommended.

Measurements of blood cell counts, hemoglobin, hematocrit, international ratio (INR), activated partial thrombin time (APTT), lipids, hepatic and renal function, were performed at baseline, and 48 hours after PCI. Levels of myocardial markers (cTnI and CK-MB) were measured at baseline, 6 hours, 12 hours, 24 hours and 48 hours after PCI.

Participants were followed up and their clinical information was collected at the end of 5 days and 30 days after PCI.

Outcomes and definitions

The primary endpoints of this study were angiographic parameters, including the TIMI flow grade, TIMI myocardial perfusion grade (TMPG) and corrected TIMI frame count (CTFC) of the culprit artery before and after PCI. Angiograms were recorded at a rate of 30 frames per second, and were sent to the core lab in Peking University First Hospital for evaluation of the angiographic parameters. A skilled interventional cardiologist was responsible for reading these parameters.

Major adverse events (MACEs), including peri-procedural myocardial infarction, target lesion revascularization (TLR) and cardiac death at 30 days were evaluated as the secondary endpoints. Bleeding was also taken as a secondary endpoint. Bleeding was categorized as TIMI major bleeding (any intracranial hemorrhage or overt bleeding associated with hemoglobin decrease ≥5g/dl from baseline), TIMI minor bleeding (clinically overt bleeding associated with hemoglobin ≥3g/dl but ≤5g/dl from baseline), and non-TIMI bleeding (defined as clinically overt signs of bleeding associated with a fall in haemoglobin of less than 30g/L, or haematocrit <9% that did not otherwise meet criteria for minor or major bleeding) [9-11].

Statistical analysis

The primary endpoint of the study was TMPG and CTFC, according to the results from previous studies [12,13], we assuming a 30% difference between the upstream group and the downstream group, we estimated that 422 patients would provide ≥ 80% power (1-β ≥80%, α=0.05) to detect such difference. Considering the rate of lost of follow up, we decided to enroll 500 patients (250 patients in each group).

Statistical analysis was performed using SPSS18.0 (SPSS Inc., Chicago, Illinois). Continuous data were expressed as mean values ± standard deviation (SD). Categorical data were expressed as number and proportion (%). Continuous data were compared using the t test. Categorical data were compared using the chi-square test or Fisher's exact test when expected cell values were less than 5. A multivariate Logistic regression analysis was applied to examine the effect of early initiation of tirofiban on the endpoints after adjusting other variables, including age, gender, hypertension, diabetes and chronic kidney disease. All tests were two-sided, and any P value of less than 0.05 was considered statistically significant.

Results

Between January 2010 and September 2011, 517 ACS patients who met the inclusion criteria were enrolled in this study. After exclusion of 32 patients who did not receive PCI and 7 patients who were lost to follow-up, a total of 478 patients (258 in the downstream group, 220 in the upstream group) were included for final analyses (Figure 1).

Baseline characteristics of the two study groups are summarized in Table 1. Demographic characteristics of the two groups were well balanced with regard to age, gender, history of myocardial infarction, history of PCI and coronary artery bypass grafting (CABG), history of hypertension, hyperlipidemia, and clinical manifestation (NSTEMI or unstable angina pectoris, UAP). There was a higher frequency of diabetes mellitus in the early initiation group than in the late initiation group (31.8% vs 23.3%, p=0.04) (Table 1).

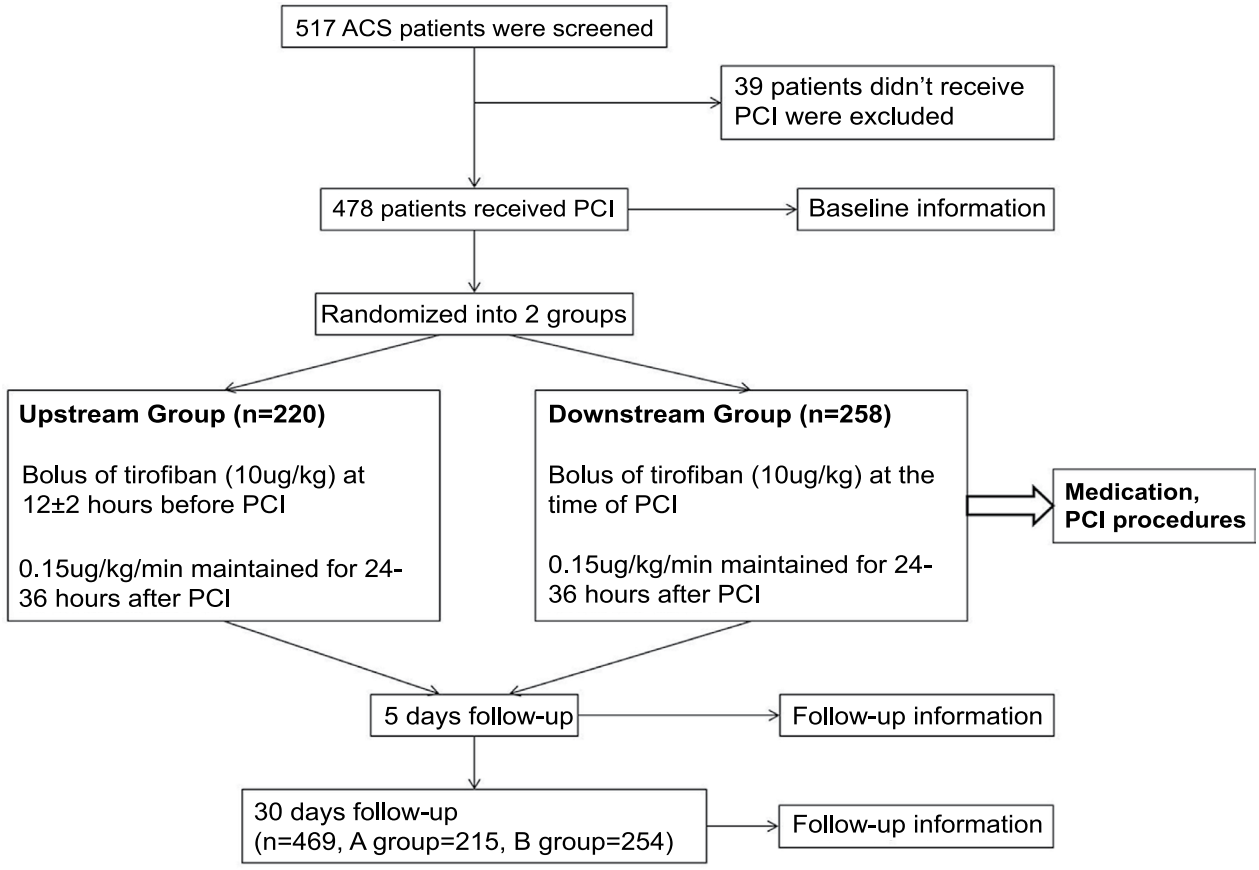

Figure 1: Trial profile

ACS: Acute Coronary Syndrome, PCI: Percutaneous Coronary Intervention

Table 1: Demographic characteristics of study subjects

	Upstream group (n=220)	Downstream group (n=258)	P value
Age (years)	57.6 ± 8.7	57.8 ± 8.6	0.78
Male	159(72.3)	183(70.9)	0.75
Weight (kg)	71.4 ± 11.3	71.3 ± 10.3	0.93
Height (cm)	167.7 ± 7.3	166.9 ± 7.4	0.26
BMI (kg/m^2)	25.3 ± 3.1	25.6 ± 2.9	0.42
Hypertension	135(61.4)	166(64.3)	0.50
Diabetes	70(31.8)	60(23.3)	0.04
Hyperlipidemia	58(26.4)	78(30.2)	0.35
Smoking	116(52.7)	142(55.0)	0.78
Hematocrit (%)	40.8 ± 8.8	42.3 ± 11.8	0.13
Hemoglobin (g/L)	136.6 ± 19.4	138.3 ± 19.7	0.36
Platelet count(×10^9/L)	215.1 ± 63.6	219.5 ± 65.5	0.46
Admission diagnosis			0.86
NSTEMI	69(31.4)	79(30.6)	
UAP	151(68.6)	179(69.4)	
Lesion type			0.29
A	20(10.4)	28(11.7)	
B	129(66.8)	143(59.6)	
C	44(22.8)	69(28.7)	

*BMI: Body Mass Index, NSTEMI: Non-ST Segment Elevation Myocardial Infarction, UAP: Unstable Angina Pectoris.

Table 2: Use of tirofiban and other antithrombotic medications

	Upstream group (n=220)	Downstream group (n=258)	P value
Duration of tirofiban infusion (hours)	35.4 ± 12.6	27.9 ± 9.2	0.00
Dose of tirofiban (ml)※	433.2 ± 167.0	352.9 ± 136.9	0.00
Aspirin 300mg loading, N (%)	87 (39.5)	86 (33.3)	0.15
Aspirin 100mg daily, N (%)	179 (81.4)	209 (81.0)	0.92
Clopidogrel 300mg loading, N (%)	123 (55.9)	139 (53.9)	0.66
Clopidogrel 75mg daily, N (%)	218 (99.1)	253 (98.1)	0.35
Dose of heparin (IU)	4134.2 ± 1658.8	4592.6 ± 2926.9	0.05

※100ml tirofiban contains 5 mgtirofiban

Table 3: TIMI flow grade and TIMI myocardial perfusion grade before and after PCI

		Upstream N (%)	Downstream N (%)	P
TIMI flow grade				
before PCI	0,1,2	59 (30.9)	75 (30.6)	0.52
	3	132 (69.1)	170 (69.4)	
after PCI	0,1,2	3 (1.5)	4 (1.6)	0.62
	3	192 (98.5)	240 (98.4)	
TMPG				
before PCI	0,1,2	59 (30.4)	82 (33.7)	0.26
	3	135 (69.6)	161 (66.3)	
after PCI	0,1,2	12 (6.2)	31 (12.8)	0.02
	3	181 (93.8)	212 (87.2)	

*TMPG: TIMI Myocardial Perfusion Grade

Table 2 lists the dosage of tirofiban and other antithrombotic therapies in the study population. The duration of tirofiban infusion was 35.4 hours in the upstream group and 27.9 hours in the downstream group. The total dose of tirofiban was 433.2ml (21.66mg) in the upstream group and 352.9ml (17.65mg) in the late downstream group. The dosages of aspirin, clopidogrel and heparin were not significantly different between the two groups.

In the upstream group, infusion of tirofiban was stopped in 5.9% (13/220) of patients because of bleeding events and in 4 patients for other reasons (severe joint swelling, inadvertent withdrawal by the physician, not receiving PCI and unknown reason, each in 1 case). In the downstream group, use of tirofiban was terminated in 6.2% of patients (16/258) due to bleeding events and in 5 patients for other

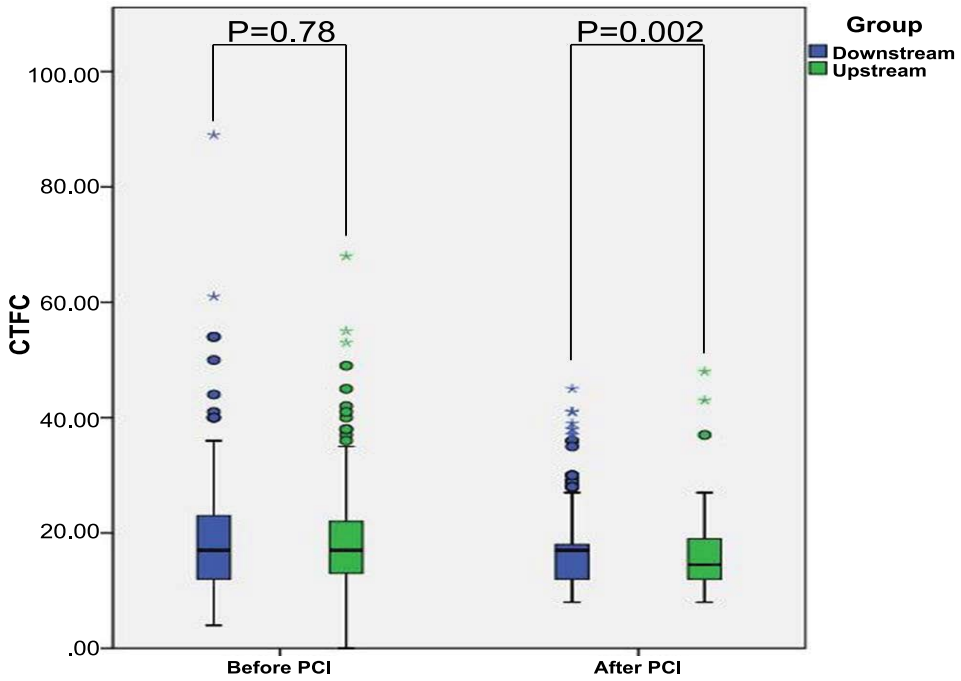

Figure 2: Corrected TIMI frame count before and after PCI

CTFC was significantly lower in the upstream group than in the downstream group (16.0 vs 18.0, P=0.002). CTFC: corrected TIMI frame count; PCI: Percutaneous Coronary Intervention

Table 4: MACEs and bleeding events during hospitalization

	Upstream N (%)	Downstream N (%)	P value
MACEs	38 (17.3)	35 (13.6)	0.32
Periprocedure MI	37 (16.8)	35 (13.6)	
TLR	0	0	
Cardiac death	1 (0.5)	0	
Bleeding	19 (8.99)	23 (8.6)	0.92
Major Bleeding	1 (0.50)	2 (0.75)	
Minor Bleeding	5 (2.49)	2 (0.75)	
Non-TIMI Bleeding	13 (6.00)	19 (7.10)	

*MACEs: Major Adverse Cardiovascular Events, MI: Myocardial Infarction, TLR: Target Lesion Revascularization.

Thirty-day follow-up was available in 469 patients. From discharge to 30 days follow up, no more death, recurrent MI, TLR, bleeding was recorded.

causes (allergy, vomiting, and patient incompliance, inadvertent withdrawal by the physician and unknown reason, each in 1 case).

TIMI blood flow and TIMI myocardial perfusion grade before and after PCI are shown in Table 3. There is no significant difference between the two groups in TIMI flow grade, either before or after PCI. However, there was a significantly higher proportion of patients reaching TIMI myocardial perfusion grade 3 after PCI in the upstream group than in the downstream group (93.8% vs 87.2%, P=0.02). Similarly, the CTFC was significantly lower in the upstream group than in the downstream group (16.0 vs 18.0, P=0.002) (Figure 2). The Logistic regression analyses showed that upstream initiation of tirofiban was significantly associated with a higher proportion of TMPG grade 3 after PCI (OR=0.48, 95% CI: 0.24-0.97), and a lower value of CTFC (β=-0.143, P=0.003)

During the index hospitalization, MACEs occurred in 37 patients (16.8%) of the upstream group and 35 (13.6%) of the downstream group, which was not different significantly (P=0.32). Bleeding events occurred in 8.6% (2 major bleeding, 2 minor bleeding, 19 non-TIMI bleeding) in the downstream group and 9.0% (1 major bleeding, 5 minor bleeding, 12 non-TIMI bleeding) in the upstream group, yet without statistical difference (P=0.92) (Table 4).

Discussion

The present study, for the first time, in a relatively large Chinese population with mid to high-risk ACS, revealed that the upstream initiation of tirofiban, could improve the myocardial level of perfusion after PCI, compare to routine initiation in catheter lab after the decision of PCI.

The optimal timing of initiating GP IIb/IIIa antagonist has long been debatable. Large molecular weight of GPIIb/IIIa antagonist, like abciximab, is recommended only when PCI has been decided in the catheter lab, however, for small molecular weight GPIIb/IIIa antagonists, such as tirofiban and eptifibatide, the optimal timing remains unclear. Even though several studies have tried to explore this issue [14-22], the results were inconclusive. So the latest version of ESC guidelines on the management of the non-ST elevation ACS patients were published [2], the use of small molecular weight of GP IIb/IIIa receptor inhibitor (eptifibatideor tirofiban) in addition to dual antiplatelet therapy in high risk ACS patients was a class IIb recommendation and the level of evidence was C. Apparently such a recommendation is still lack of evidence.

A recent meta-analysis has shown that the upstream use of GP IIb/IIIa receptor inhibitors could lead to slightly lower ischemic events and slightly higher bleeding events [3]. We realized that studies enrolled in this meta-analysis investigated both eptifibatide and tirofiban and only a few studies investigated tirofiban, which the only commercially available GP IIb/IIIa receptor inhibitor in China currently. The EVEREST trial, aimed to compare the upstream use of tirofiban to downstream use of high-dose bolus tirofiban, and downstream use of abciximabin 93 high-risk ACS patients, found that the upstream use could result in improved tissue-level perfusion and less myocardial damage [13]. Liu and associates evaluated the upstream and downstream use of tirofiban in 160 high risk Chinese ACS patients and concluded that the early use of tirofiban was associated with attenuated myocardial damage [17]. Our study, again, showed that the upstream initiation of tirofiban could improve the tissue perfusion level shown by angiographic parameters, provided further evidence for early use of tirofiban in mid-to high-risk ACS patients receiving PCI.

There are two unique aspects of our study. First, the risk of the enrolled subjects is somewhat different from studies mentioned above: we use the TIMI grade score higher than 3 as the definition

of mid- to high-risk because it is practically easy to follow, compared to other definitions, such as the GRACE risk score. In this way, the results of the present study may be more clinically valuable. Second, the drug administration strategy and the dosage of tirofiban are different from other studies. However, this is the most widely used strategy now in China.

The present study did not show any benefits in clinical events of upstream use of tirofiban. This may result from the risk stratification of the study population. Some previous studies used the inclusion criteria such as the elevated myocardium marker, which means that all the study subjects were NSTEMI patients. In our study, only 58.4% of the study subjects had elevated baseline myocardium marker. So, in patients with such a risk profile, the statistical power is not high enough to evaluate difference in the clinical events, given the sample size of the present study.

In summary, in this randomized, open labeled, multicenter study, we found that upstream use of tirofiban was associated with improved tissue-level perfusion in ACS patients with TIMI risk score ≥3 receiving an early invasive strategy compared with those with a downstream use in the catheter lab. RCTs in large patient population are warranted to clarify the clinical benefits of this antiplatelet strategy.

Impact on Daily Practice

In this randomized, controlled, open labeled, multicenter study, we found that upstream use of tirofiban was associated with improved tissue-level perfusion in ACS patients with TIMI risk score ≥3 receiving an early invasive strategy compared than those with downstream use in the catheter lab. At the same time, the present study showed that upstream use of tirofiban did not lead to a significantly increased risk of bleeding. RCTs with larger sample size are warranted to clarify the clinical benefits of this an antiplatelet algorithm.

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