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Original article

Influence of Tirofiban maintenance duration on patients with acute myocardial infarction treated by percutaneous coronary intervention

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Abstract

Objective: To evaluate the efficacy and short term prognosis of Tirofiban in different treatment duration in patients with acute ST segment elevation myocardial infarction (STEMI) and percutaneous coronary intervention (PCI) combined with intracoronary injection.

Methods: A total of 125 patients with acute STEMI were enrolled in this study. They were randomly divided into two groups: control group ($n = 61$) and Tirofiban group ($n = 64$). The Tirofiban was used by intracoronary and intravenous administration in Tirofiban group which was randomly divided into three sub-groups according to the duration of Tirofiban by persistent intravenous injection for 12 hours, 24 hours or 36 hours. Thrombolysis in myocardial infarction flow and myocardial perfusion grades were recorded immediately after PCI. The adverse cardiac events and cardiac death within 180 days of PCI, and the adverse effects (hemorrhage and thrombocytopenia) were compared between the two groups and within Tirofiban sub-groups.

Results: Grade 3 in myocardial perfusion was significantly better in Tirofiban group than control group (85.94% *vs.* 72.13%, $P = 0.03$) after PCI. There was one cardiac death in control group in 180 days after PCI. The adverse cardiac event rates between two groups was significant difference (16 patients in control group and only 8 in Tirofiban group, $P = 0.047$). There was no significant difference in incidence of hemorrhage complications and platelet counts between two groups. Nevertheless, hemorrhage complications in the 12- and 24-hour subgroups were less than 36-hour subgroup ($P = 0.01$).

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Conclusions: Intravenous Tirofiban treatment reduced the adverse cardiac events and improved short term prognosis without increasing the adverse reactions of the drugs in patients undergoing PCI. The less rate of hemorrhage complication can be achieved in short-duration of Tirofiban by intravenous injection after PCI.

Keywords: Platelet glycoprotein IIb/IIIa inhibitor; Acute ST segment elevation myocardial infarction; Coronary artery; Percutaneous coronary intervention

Introduction

Percutaneous coronary intervention (PCI) is an important and the effectivest method used to revascularize the target vessel and to save the life of patients with ST-segment elevation myocardial infarction (STEMI).[1,2] Clinical randomized trials and observational studies have demonstrated that adjunctive infusion of glycoprotein (GP) IIb/IIIa inhibitors (intravenous and intracoronary bolus administration) is associated with improved clinical outcomes and further reduced mortality of the patients with STEMI.[3−5] Standard Tirofiban regimen consists of an intravenous (IV) bolus followed by an intracoronary (IC) bolus administration and 12−72 h IV infusion.[6,7] However, whether longer duration of Tirofiban IV infusion would result in improved clinical outcomes and decrease the incidence of complications or not is unknown. The aim of this study was to compare the efficacy and prognosis of intracoronary bolus followed by different duration of IV maintenance infusion of Tirofiban with respect to improvement in outcomes and complications after PCI.

Methods

Patient selection

125 patients with STEMI and age <80 years admitted to The First Hospital of Hebei Medical University and The Third Hospital of Shijiazhuang City from April 2010 to February 2012 were enrolled in this study. Inclusion criteria: ST-segment elevation of two adjacent leads >0.1 mV, presenting within 12 hours of symptom onset and admission. All the patients underwent primary PCI by the right radial approach with Thrombolysis In Myocardial Infarction (TIMI) flow grade in the infarction related artery (IRA) which was described as grade 0 or 1. Only IRA underwent intervention. Patients who had any one of the following conditions were excluded from the study: (1) cardiac function class III and IV (Killip classification); (2) definite resistance or allergy to anti-platelet drugs; (3) severe hypertension (blood pressure >180/110 mmHg, 1 mmHg = 0.133 kPa); (4) previous history of cerebral hemorrhage or cerebral infarction in the last six months or visceral hemorrhage in recent one month; (5) blood coagulation disorders and platelet count $<100 \times 10^9$/L; (6) serum creatinine >177 μmol/L, hemodialysis patients; (7) history of heparin-caused thrombocytopenia and heparin allergy; (8) left main artery stenosis >50% or severe triple vessel lesion; (9) unable to complete the procedure by radial artery and not willing to participate in the study; (10) Non-STEMI or undergoing PCI or coronary artery bypass grafting procedure in six-month.

After initial evaluation and coronary artery angiography (CAG), a total of 125 eligible patients were randomly (simple randomization) divided into two groups: control group (intracoronary saline, $n = 61$) and study group (intracoronary Tirofiban, $n = 64$) with maintenance infusion for 12 h, 24 h or 36 h. All the patients gave a written informed consent and institutional ethics committee approved the study.

Medication scheme

All the patients received pre-treated with aspirin (300 mg) and clopidogrel (600 mg) immediately before CAG with heparin 3000 IU via the radial artery. After the diagnostic CAG was performed, an initial intravenous bolus dose of 100 IU/kg and a maximal dose of 10000 IU was given. The maintenance dosage was adjusted according to the values of activated clotting time (ACT) which were closely monitored during PCI for a total of 250−300 seconds. Primary PCI was performed according to routine procedures. Tirofiban bolus (study groups) or saline (control group) was administered after successful passage of guidewire with/without predilatation by a balloon immediately after the first restoration of antegrade flow. The patients in Tirofiban group received a bolus dose of Tirofiban 10 μg/kg via IC through the guiding catheter in the IRA over a period of 30 s, followed by a 12 hours (12 h

subgroup), 24 hours (24 h subgroup) or 36 hours (36 h subgroup) of IV infusion at 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. As the final step, stenting (Everolimus Eluting Coronary Stent) was performed. Heparin with 500–700 U/h was given for 12 h after PCI by IV according to ACT. All the patients routinely took aspirin 100 mg, clopidogrel 75 mg, beta-blocker, statin and an angiotensin-converting enzyme inhibitor, unless contraindicated. A low-molecular-weight heparin, enoxaparine, was given for 3–5 days after the procedure unless contraindicated.

Electrocardiogram (ECG) analysis

A 12-lead ECG was acquired before PCI and 60 minutes after PCI. ST-segment elevation was measured 60 ms from the J-point. The sum of ST-segment elevations (sigmaSTE), ST resolution (STR) and the rate of STR (STR%) was assessed by comparing the ST-segment elevation in the infarct-related area on the ECG before PCI with the post-interventional ECG with the minimum elevation.[8] All ECG recordings were analyzed by an experienced physician.

Angiographic analysis

The following were recorded from the offline angiographic analysis of the whole procedure. TIMI flow grades,[9] TIMI myocardial perfusion (TMP) grade in the culprit vessel which was described as grade 0 =Failure of dye to enter the microvasculature, 1 =Dye slowly enters but fails to exit the microvasculature, 2 = Delayed entry and exit of dye from the microvasculature, and 3 = Normal entry and exit of dye from the microvasculature.[10] All the visual assessments were performed offline by an experienced blinded interventionalist.

Left ventricular function

Echocardiography was performed by two cardiology specialists using IE33 instruments (Philips Medical Systems, Milwaukee, WI, USA), with a 2.5-MHz transducer. The left ventricular ejection fraction (LVEF) was assessed using the modified biplane Simpson's method after the seventh day and thirtieth day of PCI.

Clinical end-points

Clinical follow-up of each patient was obtained from hospital records and interviews.

Adverse cardiac events and cardiac death

Adverse cardiac events and cardiac death were defined as acute myocardial infarction, repeat revascularization, cardiac death, angina pectoris, heart failure and malignant arrhythmias which occurred duration of hospitalization or within 6 months after primary PCI.

Hemorrhage events and thrombocytopenia

Bleeding events from the beginning of Tirofiban administration to the discharge of patients were categorized by the change in hemoglobin using the TIMI criteria.[11] Major hemorrhage required a decrease in hemoglobin of more than 50 g/L or intracranial or pericardial bleeding. Minor hemorrhage consisted of a decrease in hemoglobin between more than 30 g/L and 50 g/L with a documented site or between more than 40 g/L and 50 g/L without an identified site or hematuria, hematochezia, or hematemesis. Insignificant hemorrhage complications which were defined as blood loss insufficient to meet major or minor criteria were also included in the minor bleeding. Thrombocytopenia is defined as mild when the platelet count is below 100×10^9/L, severe when it falls below 50×10^9/L, and profound when it is below 20×10^9/L.

Statistical analysis

STATA version 12.0 (STATA Corp., College Station, TX, USA) was used for all statistical analyses. Continuous data were presented as mean values ± standard deviation (SD) or as counts or proportions (%). Categorical data were compared using the χ^2 test or Fisher's exact test when expected cell values were less than 5. Continuous data were compared using the t test or one-way analysis of variance (ANOVA) method and differences between groups were compared with Scheffe test. A survival analysis (Kaplan–Meier method) was applied to examine the adverse cardiac events during 180-day of PCI and bleeding events after PCI. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

There were 125 patients (81 male, 44 female) enrolled into the study. Baseline characteristics were well balanced between the control group (61 patients) and Tirofiban group (64 patients, Table 1). The ages varied from 38 to 78 (58.70 ± 9.26) years. There were

Table 1
Baseline characteristics.

Items	Control ($n = 61$)	Study ($n = 64$)	P value
Age (year)	59.05 ± 10.09	58.36 ± 8.47	0.68
Male (%)	43	38	0.19
Risk factors, No.			
Current smoking	28	33	0.53
Hypertension	23	39	0.88
Hypercholesterolaemia	46	41	0.17
Diabetes	17	16	0.72
Prior myocardial infarction	8	7	0.71
Time from symptom-onset to arrival PCI centre (min)	116.07 ± 65.58	119.84 ± 98.03	0.72
Systolic pressure (mmHg)	118.31 ± 22.68	122.66 ± 20.57	0.26
Diastolic pressure (mmHg)	70.41 ± 12.05	73.13 ± 14.02	0.25
Heart rate (beats/min)	74.41 ± 12.05	71.39 ± 16.45	0.33
Characteristics of IRA			
Single-vessel disease, n	46	48	0.96
Stent diameter (mm)	3.14 ± 0.39	3.14 ± 0.41	0.94
No. of stent placement	1.07 ± 0.25	1.06 ± 0.24	0.61
Length of stent (mm)	17.84 ± 7.43	17.19 ± 7.78	0.63
IRA			0.19
LAD	19	30	0.07
LCX	12	9	0.40
RCA	30	25	0.26

PCI: percutaneous coronary intervention; RCA: right coronary artery; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; IRA: infarct-related artery.

Table 2
Angiographic data during percutaneous coronary intervention (PCI).

Items	Control group n (%)	Study group n (%)	P value
TIMI 0 or 1 at baseline	61(100)	64(100)	>0.05
TIMI 3 after PCI	55(90.16)	60(93.75)	>0.05
TMP 0 at baseline	61(100)	64(100)	>0.05
TMP 3 after PCI	44(72.13)	55(85.94)	0.03

TIMI: thrombolysis in myocardial infarction flow grade; TMP: TIMI myocardial perfusion grade; PCI: percutaneous coronary intervention.

21 patients in the maintenance intravenous infusion for 12 h, 22 patients for 24 h and 21 patients for 36 h in the Tirofiban group.

Coronary angiography

Baseline TIMI flow was grade 0 or 1 and TMP was grade 0 in all patients (control group and Tirofiban group) before the PCI. Final TIMI 3 flow after PCI was not significantly different in control group and study group. TMP grade 3 were different in the study group compared to the control group after PCI (Table 2). There was no significant difference in TIMI flow ($P = 0.75$, $\chi^2 = 0.57$) and TMP grade ($P = 0.88$, $\chi^2 = 0.26$) among 3 sub-groups in the study group.

Left ventricular function

LVEF (%) after 7 days (50.75 ± 5.65 vs. 50.94 ± 4.79, $P = 0.84$, $t = 0.20$) and 30 days (52.31 ± 5.43 vs. 52.95 ± 4.41, $P = 0.47$, $t = 0.73$) of PCI was a similar between control group and Tirofiban group (Table 3). However, there was significant difference in the changes of LVEF between 7 days and 30 days after PCI in control ($P = 0.01$, $t = 4.26$) or Tirofiban group ($P = 0.01$, $t = 6.52$). There were no

Table 3
LVEF and ST-segment changes between control group and Tirofiban groups.

Items	Control group	Study group			$P1$	$P2$
		12 h	24 h	36 h		
LVEF (%) at 7 days	50.75 ± 5.65	50.52 ± 5.75	50.18 ± 4.57	52.14 ± 3.89	>0.05	>0.05
LVEF (%) at 30 days	52.31 ± 5.43	52.81 ± 5.17	52.23 ± 4.00	53.86 ± 4.04	>0.05	>0.05
SigmaSTE (mV) before PCI	9.52 ± 3.58	9.57 ± 5.36	9.50 ± 4.79	9.57 ± 5.01	>0.05	>0.05
SigmaSTE (mV) after PCI	4.62 ± 3.45	2.86 ± 2.29	2.59 ± 2.06	2.86 ± 2.29	>0.05	>0.05
STR (%)	51.95 ± 28.09	70.54 ± 19.66	72.31 ± 22.67	72.50 ± 13.31	<0.01	>0.05

$P1$ = P-value between control group and study group, $P2$ = P-value in Tirofiban groups.

significant difference in Tirofiban groups in 7 days or 30 days.

ST-segment changes in ECG

The sum of ST-segment elevations (sigmaSTE) and STR% was shown in Table 3. The rate of complete STR was considerably higher in Tirofiban group than control group (P <0.01). However, there was no significant difference in tirofian groups.

Cardiac adverse events

Total cardiac adverse event were 16 patients in the control group vs. 8 patients in Tirofiban group at six months. The individual components of the events in patients were shown as follows in control group vs. Tirofiban group: death − 1 vs. 0; recurrent angina pectoris − 8 vs. 3; recurrent myocardial infarction − 4 vs. 1; heart failure − 3 vs. 4. However, as shown in Fig. 1, there was significant difference in free-event survive rate between the 2 groups at six months after PCI by survive analysis ($P = 0.047$, $\chi^2 = 3.93$). The cardiac adverse event rate in the Tirofiban group was lower than in control group. There was no significant difference in the sub-groups of Tirofiban group ($P = 0.87$, $\chi^2 = 0.29$).

Hemorrhage complications and platelet reduction

Minor hemorrhage was developed in 22 patients (control: 9 vs. Tirofiban: 13). No major hemorrhage was observed in control group. 3 patients developed major hemorrhage in Tirofiban group (gastrointestinal hemorrhage). The difference in hemorrhage complications was not significant between two groups ($\chi^2 = 1.80$, $P = 0.18$). It showed Kaplan–Meier curves for hemorrhage survive rate during the first 7 days for patients in two groups in Fig. 2. It showed the curves for free-hemorrhage survive rate among study subgroups during the first 7 days ($\chi^2 = 8.66$, $P = 0.01$) in Fig. 3. More hemorrhage complication was developed in 36-hour group than other two sub-groups.

The changes in the platelet count were not significant in no matter whether control group and Tirofiban group or subgroups.

Discussion

This study demonstrates that intracoronary administration of high dose bolus of Tirofiban with maintenance infusion for short duration (only for 12 h) leads to improve myocardial reperfusion and clinical outcomes at 180 days, and does not increase hemorrhage events in STEMI patients undergoing PCI. It may suggest that the more hemorrhage events relate to the dosage and administration duration of the GP inhibitors. The beneficial effects of intravenous GP IIb/IIIa antagonists may be somewhat offset by their associated increased risk of minor hemorrhage though that the agent do not have a significant impact on major hemorrhage except for heparin infusion was continued after the procedure in which major hemorrhage was

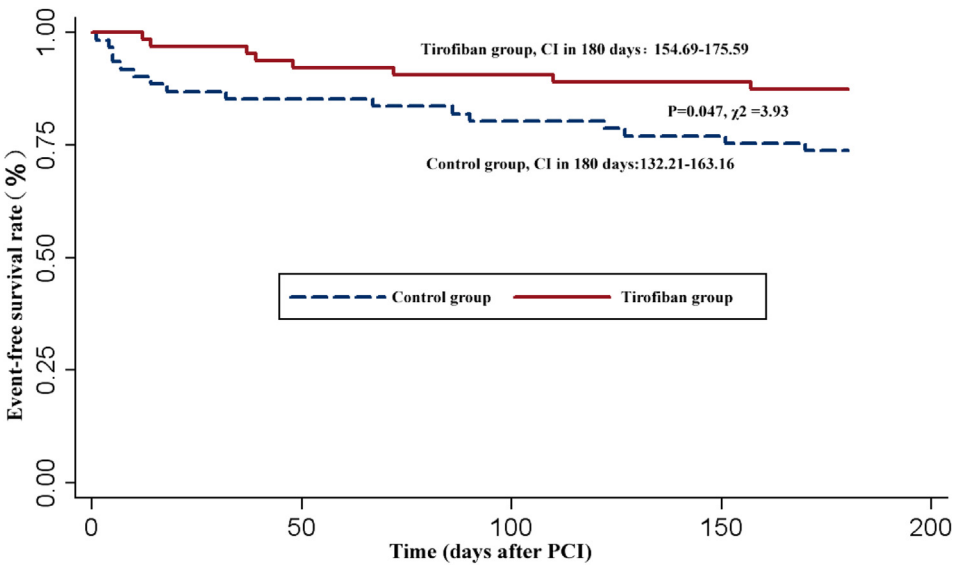

Fig. 1. Kaplan–Meier estimates of event-free rate during the first 180 days between control group and Tirofiban group. PCI: percutaneous coronary intervention, CI: confidence interval (95%).

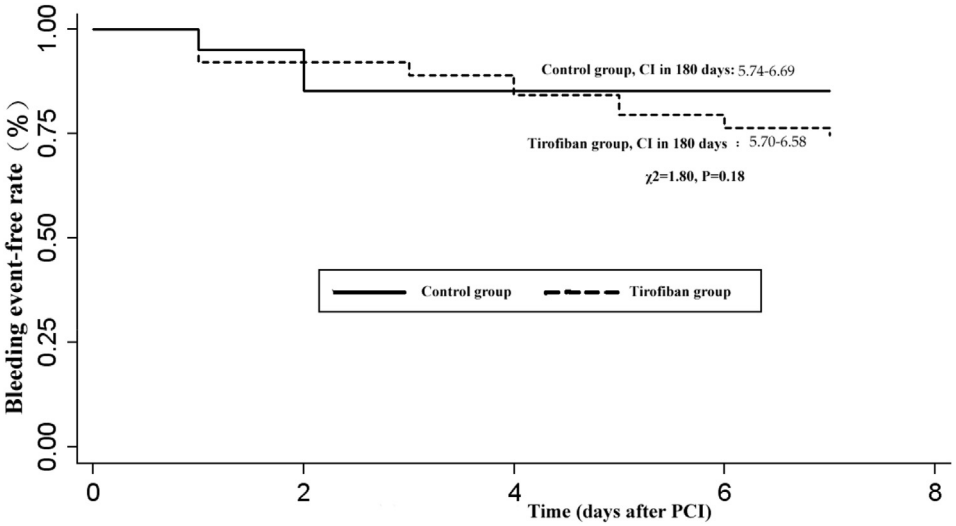

Fig. 2. Kaplan–Meier estimates of bleeding event-free rate during the first 7 days between control group and Tirofiban group. PCI: percutaneous coronary intervention, CI: confidence interval (95%).

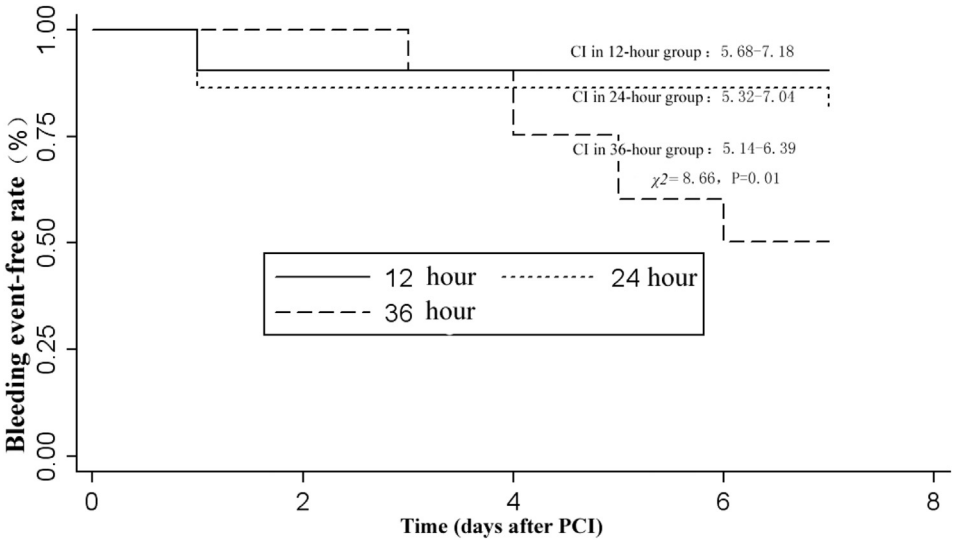

Fig. 3. Kaplan–Meier estimates of bleeding event-free rate during the first 7 days within Tirofiban sub-groups. PCI: percutaneous coronary intervention, CI: confidence interval (95%).

significantly increased and did have a significant impact on long-term outcomes.[12] More interesting that recent study reported the efficacy of even intracoronary high-dose bolus-only strategy was similar as a standard high dose intravenous bolus plus infusion strategy.[13]

There was no thrombocytopenia in the GP IIb/IIIa-treated group and control group in this study. Likely, this result was driven by a reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor and short-term administration of Tirofiban.[14] Tirofiban, a non-peptide molecule, is a reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. Platelet aggregation inhibition is reversible following cessation of the infusion of Tirofiban. Tirofiban has been demonstrated benefit in optimizing the clinical outcome of STEMI patients undergoing primary PCI.[14,15] Our results suggests that not only clinical outcomes were compared between control group and study group but analyzed the effectiveness and adverse effect in different duration of Tirofiban groups.

A previous meta-analysis of 10 randomized controlled trials demonstrated that IC administration of GP inhibitors can yield superior clinical outcomes compared to IV administration in short-term (1 month−3 months) in STEMI patients undergoing primary PCI. No significant difference was observed in the frequency of short-term hemorrhage events with IC administration or IV administration.[16] A similar study with our study including a total of 453 eligible STEMI patients had shown that an additional intracoronary Tirofiban bolus administration following upstream intravenous treatment reduced coronary circulatory platelet activation and inflammatory process, and significantly improved myocardial reperfusion and left ventricular function as well as 6-month major adverse cardiac events-free survival for STEMI patients undergoing primary PCI.[17] Our randomized clinical pilot demonstrated that in patients with STEMI undergoing primary PCI, IV administration with an additional IC bolus administration of Tirofiban did not significantly improve cardiac function at 1 month of PCI compared with control group. However, coronary angiography after PCI had shown that the number of TMP grade 3 was more in Tirofiban group than control group. There was no significant difference in TIMI flow and TMP grade among Tirofiban 3 sub-groups.

In our study, STR was higher in the intracoronary than in the intravenous group (70%−72% vs. 51.95%). This result is similar to the results by TMP. STR and TMP represent different pathophysiological phenomena. TMP reflects mechanical patency of the microvasculature, whereas STR may reflect the functional status of the myocardial cells.[18,19] Both markers are widely accepted as surrogate end points of clinical outcome and independent prognostic value in predicting long-term mortality. The two markers are assessed at different time points after primary PCI: TMP directly after PCI and STR at 30−60 minutes after PCI. The beneficial effect of intracoronary administration on myocardial reperfusion may be present directly after PCI.

GP inhibitors such as abciximab, eptifibatide, and Tirofiban has been shown to exhibit dose-dependent activity to dissolve platelet aggregates[20] and higher levels of platelet receptor occupancy was associated with improved myocardial perfusion among patients with ST-elevation myocardial infarction.[21] Aside from GP inhibitor-dependent improved disaggregation of newly formed platelet aggregates, some experimental studies shown that GP inhibitors (GPIs) exert additional antiplatelet, antithrombotic, and anti-inflammatory effects when local drug concentrations are higher.[22] These reports eventually gave rise to the logical hypothesis of choosing the intracoronary route for GP inhibitors aiming increased local concentrations with higher levels of platelet GP inhibitor receptor occupancy leading to more rapid dissolution of thrombus with improved disaggregation of newly formed platelet aggregates, which might be eventually associated with improved myocardial perfusion.[23−25]

Although our results shown that short time-duration of IV administration with an additional IC bolus administration of Tirofiban significantly improves clinical outcome at 6 month of PCI and does not increase the hemorrhage events compared with control group in patients with STEMI underwent primary PCI, this study was a pilot study with a relatively small sample size, and the follow-up was limited to 180 days. Longer time research and more patients will be needed to further demonstrate the above results.

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