The effects of tirofiban infusion on clinical and angiographic outcomes of patients with STEMI undergoing primary PCI

Cihangir Kaymaz, Nurşen Keleş, Nihal Özdemir, İbrahim Halil Tanboğa, Hacer C. Demircan, Mehmet M. Can, Fatih Koca, İbrahim Akın İzgi, Alper Özkan, Muhsin Türkmen, Cevat Kırma, Ali M. Esen

Department of Cardiology, Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital; İstanbul-*Turkey*

ABSTRACT

Objective: The present study was designed to determine the effects of tirofiban (Tiro) infusion on angiographic measures, ST-segment resolution, and clinical outcomes in patients with STEMI undergoing PCI. Glycoprotein (GP) IIb/IIIa inhibitors are beneficial in ST-segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI), while the most effective timing of administration is still under investigation.

Methods: A total of 1242 patients (83.0% males, mean (standard deviation; SD) age: 54.7 (10.9) years) with STEMI who underwent primary PCI were included in this retrospective non-randomized study in four groups, composed of no tirofiban infusion [Tiro (-); n=248], tirofiban infusion before PCI (pre-Tiro; n=720), tirofiban infusion during PCI (peri-Tiro; n=50), and tirofiban infusion after PCI (post-Tiro; n=224). In all Tiro (+) patients, bolus administration of Tiro (10 µg/kg) was followed by infusion (0.15 µg/kg/min) for a mean (SD) duration of 22.4±6.8 hours.

Results: The pre-PCI Tiro group was associated with the highest percentage of patients with TIMI 3 flow (99.4%; p<0.001), the lowest corrected TIMI frame count [21(18-23.4); p<0.001], the highest percentage of patients with >75% ST-segment resolution (78.1%; p<0.001), and the lowest rate of in-hospital sudden cardiac death and in-hospital all-cause mortality (3.2%, p<0.05, 3.3%, p=0.01). Major bleeding was reported in 18 (1.8%) patients who received tirofiban.

Conclusion: Use of standard-dose bolus tirofiban in addition to aspirin, high-dose clopidogrel, and unfractionated heparin prior to primary PCI significantly improves myocardial reperfusion, ST-segment resolution, in-hospital mortality rate, and in-hospital sudden cardiac death in patients with STEMI with no increased risk of major bleeding. *(Anatol J Cardiol 2015; 15: 899-906)*

Keywords: tirofiban, myocardial infarction, percutaneous coronary intervention, angiography, treatment outcome

Introduction

Primary percutaneous coronary intervention (PCI) is the preferred method for early restoration of blood flow in the infarct-related vessel in patients with ST-segment elevation myocardial infarction (STEMI) (1-3), and adjunctive anti-platelet therapy is found to be associated with clinical outcomes following primary PCI (4, 5). In addition to the standard dual anti-platelet therapy consisting of aspirin and clopidogrel, further measures to inhibit platelet aggregation, such as addition of a glycoprotein IIb/IIIa inhibitor (GPI), have been shown to reduce thrombotic complications and the composite incidence of death, myocardial infarction, and the need for target vessel revascularization after PCI (6).

Current data on the timing of GPIs in relation to clinical benefit from pre-treatment with GPIs prior to hospital arrival or administration of the drug in the catheterization laboratory are controversial (7, 8). In this regard, tirofiban (Tiro), given in the ambulance, was shown to result in an improvement in ST-segment resolution as a marker for myocardial perfusion in patients with STEMI undergoing primary PCI (5). Based on the ongoing debate considering the efficacy and timing of optimal GPI therapy for patients with STEMI undergoing primary PCI (8), the present study was designed to determine the effects of pre-, peri-,and post-intervention tirofiban infusion on angiographic measures, ST-segment resolution, and clinical outcomes in patients with STEMI undergoing primary PCI.

Address for Correspondence: Dr. Cihangir Kaymaz, Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kartal, İstanbul-*Türkiye*
Phone: +90 216 459 44 40 Fax: +90 216 500 15 00 E-mail: cihangirkaymaz2002@yahoo.com
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Methods

Study population

This retrospective non-randomized study included 1242 patients [83.0% males, mean (SD) age: 54.7(10.9) years], presenting with chest pain and no contraindication for primary PCI and diagnosed with acute STEMI, based on clinical and electrocardiographic (ECG) measures, upon their admission to Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital between January 2005 and March 2008. All patients meeting the inclusion criteria were included into the study consecutively. The patient data were obtained from patient file archives and catheter laboratory records. Medical history, risk factors, duration of chest pain, and medications were recorded for each patient. Data concerning the physical examination and myocardial infarction-related basal risk evaluation were performed.

Coronary angiography and PCI

Coronary angiography and PCI procedures were performed via the femoral percutaneous approach using a Siemens Angiocore (Germany) by experienced interventional cardiologists, performing at least 75 interventional procedures annually. Patients in the emergency service were directly transferred to the catheter laboratory. Prior to the procedures, all patients were administered aspirin (300 mg, oral), clopidogrel (600 mg, oral), and heparin (10,000 U, intravenous). Blood flow in the coronary epicardial arteries was evaluated by two blinded interventional cardiologists, according to the Thrombolysis in Myocardial Infarction (TIMI) Coronary Flow Classification (9) and Corrected TIMI Frame Count (10). PCI was performed in patients who were identified to have target vessel occlusion with TIMI 0-1 flow during coronary angiography. Angiographic coronary thrombus burden was scored based on TIMI thrombus grade. Patients with a thrombus burden of grade 4 or 5 were defined as having high thrombus burden, ad patients with thrombus burden < grade 4 was defined as having low thrombus burden (11). No thrombolytic therapy or thrombectomy was administered before or after the procedures. A coronary stent was implanted in all patients.

Tirofiban administration and study groups

In the tirofiban-treated study groups, depending on the decision of the interventional cardiologist, intravenous tirofiban was administered as a bolus dose of tirofiban (10 μg/kg), followed by infusion therapy (0.15 μg/kg/min), for a mean (SD) duration of 22.4± 6.8 hours. Tirofiban was used before PCI in patients with a high TIMI risk score by the primary operator's discretion (12). Since there was no recommendation of a standard dose of tirofiban for STEMI at the time of the study, tirofiban was used in doses established for PCI patients. The study population was divided into four subgroups with reference to timing and administration of tirofiban: (a) patients without tirofiban infusion (Tiro (-) group; n=248), (b) Tiro administration immediately after the initial diagnosis in the emergency department before PCI (pre-Tiro group; n=720, mean (SD) duration 16.0± 6.8 min before PCI), (c) Tiro administration prior to balloon inflation of a totally occluded target artery during PCI (peri-Tiro group; n=50); and (d) tirofiban infusion in the coronary intensive care unit after PCI (post-Tiro group; n=224; mean (SD) duration 38.0±18.5 min after PCI).

ECG evaluation

ECG was performed at the initial admission and 90 minutes after PCI, with 12-hour intervals afterwards. Percent resolution in ST-segment elevation was determined by comparison of the lead with maximum ST elevation on the post-PCI 90-min ECG with the baseline ST elevation leading consideration of complete benefit (>75% resolution), partial benefit (50%-75% resolution), and no benefit (<50% resolution) (3).

End points

Angiographic (TIMI flow grade, corrected TIMI frame count) and electrocardiographic (ST-segment resolution 90 minutes after primary PCI) endpoints were the primary endpoints, while the clinical outcomes (sudden cardiac death, all-cause mortality, acute stent thrombosis, and recurrent MI during hospitalization) were the secondary endpoints evaluated in each study group.

Peak creatine kinase and peak troponin were defined as the highest creatine kinase and troponin I serum concentrations within the first 48 h. Safety endpoints were major bleeding. Bleeding was evaluated in terms of TIMI criteria as major (intracranial hemorrhage, ≥5 g/dL decrease in the hemoglobin concentration, ≥15% absolute decrease in hematocrit), minor (observed blood loss 3 to <5 g/dL in hemoglobin concentration and ≥10% decrease in hematocrit, and no observed blood loss with ≥4 g/dL decrease in hemoglobin concentration and ≥12% decrease in hematocrit), and minimal (any clinically overt sign of hemorrhage associated with a <3-g/dL decrease in hemoglobin concentration or <9% decrease in hematocrit) bleeding (9).

Statistical analysis

Statistical analyses were performed using SPSS software, version 16 (SPSS Inc., Chicago, Illinois, USA). The distribution of continuous variables for normality was tested with one-sample Kolmogorov-Smirnov test, and data are presented as mean and standard deviation (SD) or median and interquartile ranges, as appropriate. Categorical variables are reported as frequencies and group percentages. Differences among patients in normally and non-normally distributed variables were evaluated by ANOVA and Kruskal-Wallis test, respectively, as appropriate. A p value of less than 0.05 was considered a statistically significant result.

Multiple binary logistic regression analysis was performed for parameters considered to affect in-hospital all-cause mortality and in-hospital sudden cardiac death. Data were expressed as "mean (standard deviation; SD)" and/or percent (%). $p<0.05$ was considered statistically significant.

Table 1. Comparison of demographic and clinical features according to study group

	pre-PCI (n=720)	peri-PCI (n=50)	post-PCI (n=224)	Tiro (-) (n=248)	*P*
Age, years					
Median	54 (48-61)*	56 (50-64)*	56 (49-65)*	56 (49-65)*	0.08
Male gender					
Count	618 (86.2)	45 (90)	181 (81.2)	184 (74.2)	<0.001
Diabetes mellitus					
Count	129 (18)	9 (18)	41 (18.4)	61 (25.4)	0.08
Baseline ECG					
Anterior MI					
Count	330 (63.7)	20 (3.9)	86 (16.6)	82 (15.8)	0.003
Multiple-vessel disease					
Count	390 (54.2)	23 (46)	123 (54.9)	140 (56.5)	0.09
Cardiogenic shock					
Count	14 (1.9)	2 (4)	1 (0.4)	4 (1.6)	0.34
Culprit lesion					
LAD					
Count	395 (55)	26 (52)	105 (47)	112 (45)	0.03
Door-to-balloon time, min					
Median	30 (30-30)*	30 (25-30)*	30 (30-30)*	30 (30-30)*	0.16
Pain-to-balloon time, min					
Median	185 (120-300)*	210 (150-390)*	180 (120-285)*	210 (150-358)*	0.007
Troponin-I peak, ng/mL					
Median	6.4 (0.5-56)*	3.4 (0.9-27)*	5.8 (0.4-52)*	6.9 (0.5-67)*	0.78
High thrombus burden					
Count	316 (44)	1 (2)	74 (33)	66 (26.7)	<0.001

MI - myocardial infarction; Tiro - tirofiban treatment,
p<0.05 significance level; Kruskal-Wallis test; *interquartile range

Results

Clinical and demographic features of the patients

Tirofiban was administered to 80% of the patients (pre-Tiro 58%; peri-Tiro 4%; post-Tiro 18%). The ages of patients in all study groups were similar. The percentage of males was significantly lower in the Tiro(-) group (p<0.001) (Table 1).

The frequency of anterior MI in the pre-PCI group was the highest (p=0.003); on the other hand, the frequencies of patients with cardiogenic shock were similar among the study groups (p=0.34) (Table 1).

Door-to-balloon time (min) was not significantly different among the study groups (p=0.16), and pain-to-balloon time (min) in the peri-PCI and Tiro (-) (p=0.007) groups was significantly± longer than in pre-Tiro and post-Tiro patients (Table 1).

Patients with Killip Class I-II accounted for 90.8% of the study population. There was no significant difference among the study groups in terms of clinical features, including the incidence of diabetes mellitus and multiple vessel disease and troponin-I peak levels (Table 1).

A TIMI risk score above 8 was noted in 54.7% in the pre-tiro group and 22.1%, 16.8%, and 6.3% in the post-Tiro, Tiro (-), and peri-Tiro groups, respectively (Fig. 1).

Angiographic parameters

Comparison of TIMI flow grade in infarction-related arteries immediately following PCI revealed TIMI 3 flow in 99.4%, 98%, and 77.7% of patients in the pre-, peri-, and post-Tiro groups and in 94.4% of patients in the Tiro (-) group, respectively. The frequency of patients with TIMI 3 flow was the highest in the pre-Tiro group (p<0.001) (Fig 2).

The corrected TIMI frame count was the lowest in the pre-Tiro group [21(18-23.4)] and the highest in post-Tiro group [41.55(34-61.82)] as compared to those in the peri-Tiro [26(25-29.2)] and Tiro (-) [36(24-51)] groups (p<0.001; Fig. 3). The frequency of patients that had a high thrombus burden was the highest in the pre-Tiro group [316 (44%)] and the lowest in the peri-Tiro [2(1%)] group (p<0.001) (Table 1). The frequency of patients with a high thrombus burden was statistically higher in the pre-Tiro, peri-Tiro, and post-Tiro groups [392 (39%)] than in the Tiro (-) [66 (27%)] group [(p<0.001)] (Table 2).

Electrocardiographic parameters

The 90-minute ST-segment resolution (>75%) was most frequent in the pre-Tiro group (78.1%) and least frequent in the Tiro (-) (30.2%) group, compared with the peri-Tiro (54%) and post-Tiro (38.8%) groups (p<0.001; Fig. 4).

In-hospital sudden cardiac death, in-hospital mortality, and total mortality

The rate of in-hospital sudden cardiac death in the pre-Tiro group (3.2%) was lower than in the post-Tiro (8%) group (p<0.05) but similar to that in the peri-Tiro (8%) and Tiro (-) (5.2%) groups (Fig. 5). Multiple binary logistic regression analysis showed that tirofiban use before PCI (OR: 0.49, 95% CI: 0.3-0.83, p=0.007) or after (OR: 1.88, 95% CI: 1.1-3.2, p=0.02) PCI and baseline Killip status (IV) (OR: 6.39, 95% CI: 3.8-10.6, p=0.000) were independent predictors of the decrease in SCD.

The pre-Tiro group had the lowest rate of in-hospital all-cause mortality (3.3%), and the rate of in-hospital all-cause was significantly different as compared to the other study groups (p=0.01) (Fig. 6).

Multiple binary logistic regression analysis showed that age (OR: 1.09, 95% CI: 1.0-1.1, p=0.001) and baseline Killip status (IV) (OR: 4.01, 95% CI: 1.7-9.5, p=0.002) were independent predictors of in-hospital all-cause mortality.

Safety endpoint

There was no significant difference between tirofiban-treated and Tiro(-) patients with respect to major and minor bleeding incidence (p=NS). Major bleeding was reported in 18

Table 2. Association between thrombus burden and tirofiban use

	High thrombus burden (n=458)	Low thrombus burden (n=784)	*P*
Tirofiban (+), n (%)	392 (39)	603 (61)	<0.001
Tirofiban (-), n (%)	66 (27)	181 (73)	

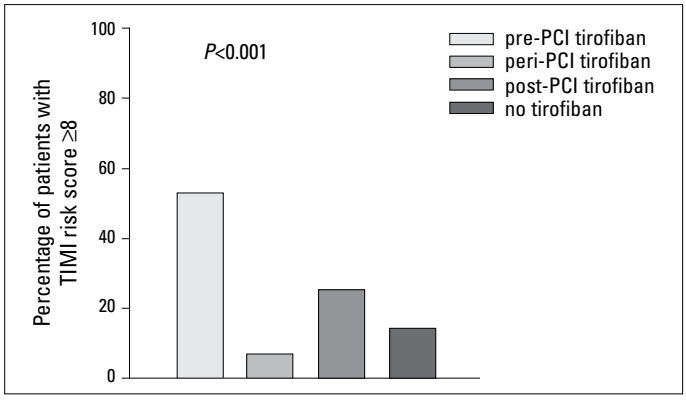

Figure 1. High TIMI Risk Score: Percentage of patients with a TIMI risk score above 8 in the study groups
Chi-square test

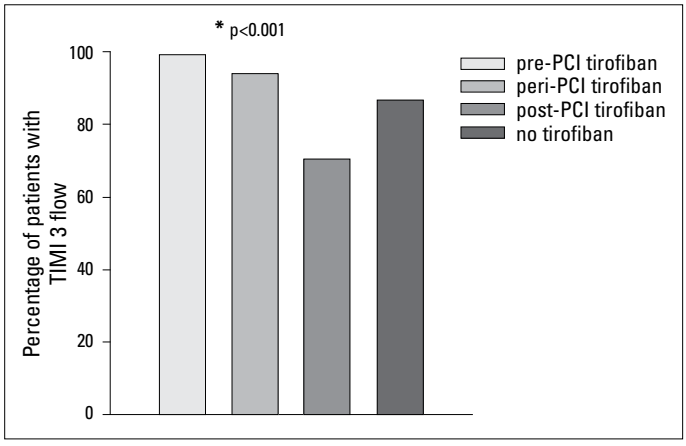

Figure 2. TIMI 3 flow: Percentage of patients with TIMI 3 flow in the study groups
*p<0.001 among all groups
Chi-square test

patients (1.8%) who received tirofiban and in 4 patients (1.6%) without tirofiban therapy. Likewise, minor bleeding was reported in 35 patients (3.5%) following the administration of tirofiban and in 4 patients (1.6%) without tirofiban therapy.

Discussion

Our findings revealed that administration of a GPI, tirofiban, in addition to aspirin, heparin, and high-dose clopidogrel, prior to primary PCI (upstream Tiro) was associated with better angiographic measurements and greater ST-segment resolution in patients with STEMI when compared to groups with peri-interventional or post-interventional administration of tirofiban and PCI without tirofiban, despite the high TIMI risk scores and high

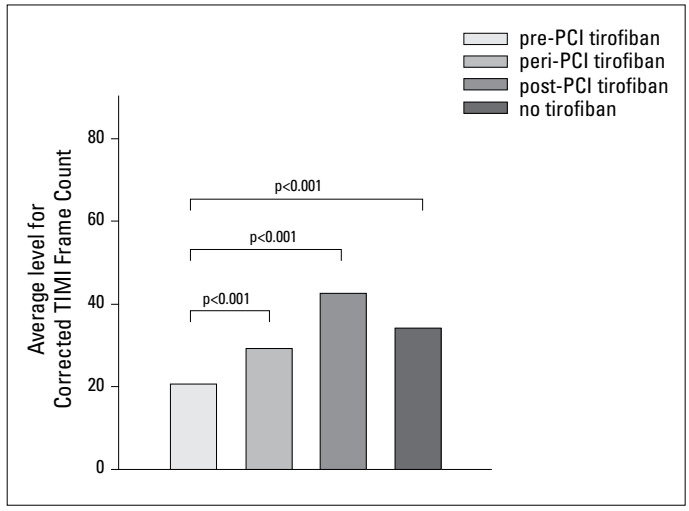

Figure 3. Corrected TIMI frame count: Average level for Corrected TIMI Frame Count in the study groups
Mann-Whitney U test

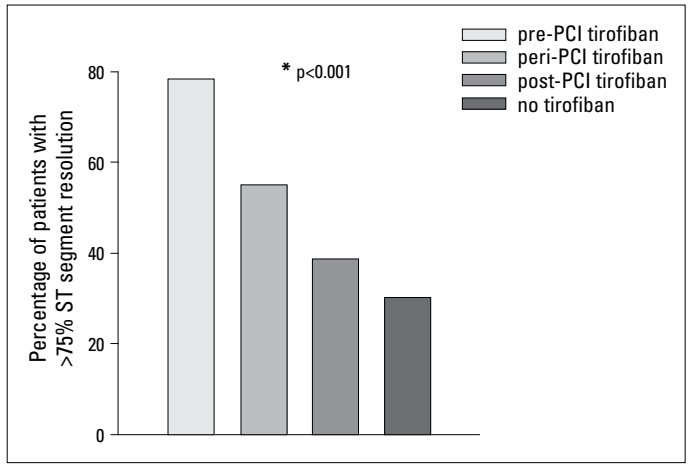

Figure 4. ST-segment resolution: Percentage of patients with >75% ST-segment resolution in the study groups
*p<0.001 among all groups
Chi-square test

thrombus burden in patients in whom tirofiban was administrated before primary PCI.

The patients in our study were recorded between 2005 and 2008. In both the 2007 Focused Update of the 2004 ACC/AHA STEMI Guidelines and 2004 ACC/AHA STEMI Guidelines, the authors reported that quantitative analysis showed no advantage for pretreatment with a GP IIb/IIIa inhibitor; on the other hand, it did not document any major disadvantage, either. In the 2004 ACC/AHA STEMI Guidelines, facilitated PCI was recommended as a reperfusion strategy in higher-risk patients. Because of this recommendation and the absence of any documented major disadvantage of GP IIb/IIIa inhibitors, we used tirofiban in patients with STEMI that had higher risk in our clinics.

Current opinions for adjunctive use of a GPI in STEMI remain inconclusive. The retrospective analysis of the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial provided an opportunity to assess early versus late or non-use

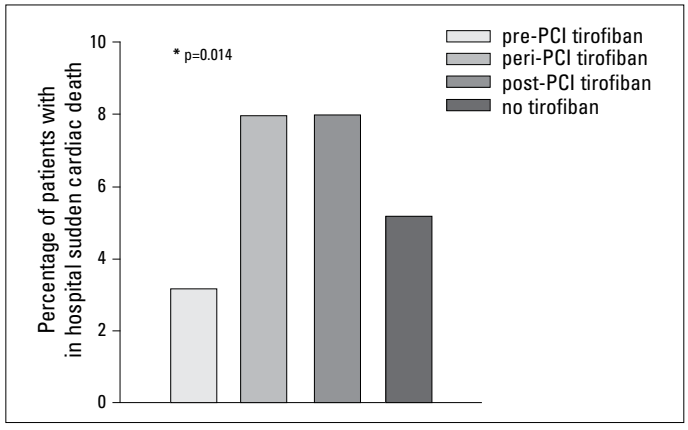

Figure 5. In-hospital sudden cardiac death: Percentage of patients with in-hospital sudden cardiac death in the study groups
*p=0.014 among all groups
Chi-square test

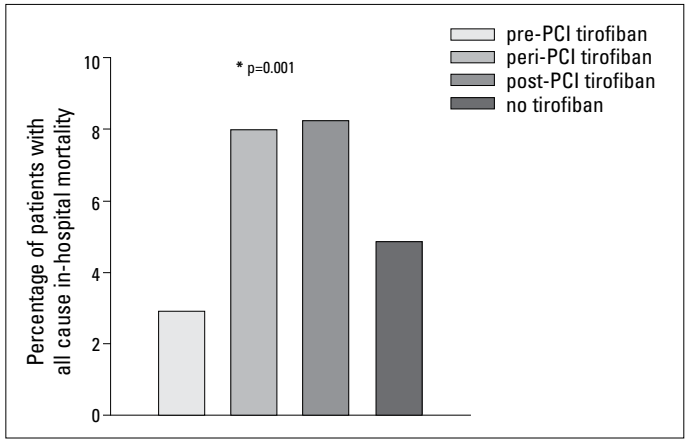

Figure 6. In-hospital all-cause mortality: Percentage of patients with in-hospital mortality in the study groups
*p=0.01 among all groups
Chi-square test

of GPIs in a large STEMI cohort treated with PCI, indicating that pre-treatment with GPIs, particularly abciximab, was associated with significantly lower occurrence of 90-day clinical outcomes (13). However, the recommendations and level of evidence were different for abciximab (IIa, A), eptifibatide (IIa, B), Tiro (IIb, B), and upstream GPIs (III, B) in the 2010 European Society of Cardiology Guidelines on Myocardial Revascularization for adjunctive GPI use in STEMI (14).

In a recent meta-analysis, GPI use was associated with a 62% reduction in 30-day re-infarction, a 42% reduction in 30-day repeat PCI, a 53% reduction in short-term mortality, and a 62% reduction in long-term mortality, with a non-significant increase in major bleeding (15) Likewise, in a recent systematic review and meta-analysis of 10 studies comparing the outcomes of tirofiban/eptifibatide and abciximab treatments in 7349 patients with STEMI treated with primary PCI, the non-inferiority of tirofiban/eptifibatide treatment was documented in terms of ST-segment resolution and the short-term rate of all-cause mortality plus nonfatal reinfarction, without an increase of major bleeding (16).

Although Tiro has been extensively studied in a variety of clinical settings over the last 10 years, the selection of the appropriate dose regimen and protocols in patients undergoing PCI are still not well defined (6). Current data derived from a meta-analysis of six randomized controlled trials suggest that routine and early tirofiban before primary PCI is related to a better corrected TIMI frame count and a lower rate of major adverse cardiovascular events but no significant differences in post-PCI TIMI 3 flow and TIMI myocardial perfusion/blush grade 3, TIMI major bleeding, or mortality rates (17). Adjunctive tirofiban therapy was reported to improve reperfusion measures and ST-segment resolution in the infarct area and clinical outcomes at the 30-day and 6-month follow-up, without increased risk of hemorrhage. Multivariable analysis revealed that tirofiban therapy, age >65 years, and LVEF<0.50 were independent predictors of major adverse cardiac events at the 6-month clinical follow-up, with a more significant improvement with upstream compared to downstream tirofiban administration (18).

In this respect, our findings correlate with improved angiographic reperfusion measures and ST-segment resolution, reported by means of routine upstream initiation of GP IIb/IIIa inhibitors, in addition to aspirin, heparin, and high-dose clopidogrel, in the literature (19).

In fact, while GPIs were shown to reduce the composite incidence of death, myocardial infarction, and the need for target vessel revascularization after PCI (6), the use of tirofiban (10-mcg/kg bolus followed by a 0.15-mcg/kg/min infusion) during PCI was related to controversial results in large multicenter trials (20-22). As a result, since sub-therapeutic inhibition of glycoprotein IIb/IIIa binding activity was considered to be responsible for the greater incidence of peri-procedural complications (6), using a high bolus dose of tirofiban, 25 mcg/kg, followed by an 18-h infusion of 0.15 μg/kg/min, was suggested to obtain higher blood tirofiban concentrations soon after the start of treatment (23).

Although a standard bolus dose of tirofiban was reported to fail to achieve early sufficient platelet aggregation inhibition after administration in previous studies (24), the use of the standard bolus dose of tirofiban (10 μg/kg) instead of a high-bolus dose (2 μg/kg) in our study population was associated with significant angiographic, electrocardiographic, and clinical improvement if administered prior to PCI.

The systematic use of GPIs in STEMI was also questioned by the negative findings of the Bavarian Reperfusion AlternatiVes Evaluation (BRAVE 3) (25) and Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) (26) studies and the ambivalent results of the On-TIME2 study (19). In fact, administration of abciximab fairly late (>200 min) after the onset of symptoms was considered to have a role in the lack of benefit of early versus late administration of abciximab, as well as the failure to reduce infarction size in patients who were already pretreated with 600 mg clopidogrel (19, 25, 26). However, the Abciximab before Direct Angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) study (27) showed the significance of the adminis-

tration of a GPI in the ambulance, well in advance of arrival to the PCI center.

Notably, in relation to the reported higher efficacy of upstream tirofiban administration in cases of a shorter time period between the onset of symptoms of acute myocardial infarction and the administration of the study drug (19), the mean door-to-balloon time was 30.5 minutes, and the pain-to-balloon time was 231.1 minutes in our population. The average door-to-balloon time of our patients (Table 1) is much better than the 90-min target for optimal primary PCI outcomes (28), whereas the total ischemic time was beyond the goal of 120 min, according to the latest STEMI guidelines of the American Heart Association and American College of Cardiology (8, 28).

While its remarkably short time period presents a challenge for a comparison to prior randomized studies, the shorter door-to-balloon time in our study emphasizes the compensatory role of tirofiban administration, even when used in a lower dose indicated for PCI patients, achieving anti-platelet activity during balloon operation, since thienopyridines only act 2 hours after administration, with a peak level at 4-6 hours. On the other hand, the shorter door-to needle time in our study prevented us from observing the proper effect of tirofiban on high thrombus burden at the beginning of the coronary angiography; so, higher thrombus burden was recorded in the pre-Tiro group. The proper effect of tirofiban infusion emerged after PCI.

Similarly, in the ICT-AMI study, an additional intracoronary tirofiban bolus administration following upstream intravenous treatment was reported to significantly improve myocardial reperfusion and left ventricular function, as well as 6-month MACE-free survival, for STEMI patients undergoing primary PCI (28). Additionally, in correlation to the previously reported 15-min delay between angiography and PCI (7), the average time from angiography to restoration of coronary blood flow was 16 min in our study, indicating that most patients in the upstream tirofiban group had GPIs on board at least 20 min before PCI, which was documented to allow adequate platelet inhibition (7). In our study, this delay in door-to-balloon time seems to be associated with significant differences in quantitative measures of angiographic success and ST-segment resolution between the pre- and peri-PCI tirofiban subgroups. The post-Tiro group had worse angiographic outcomes expectedly; furthermore, ST-segment resolution was better than in the Tiro (-) group. It might be mentioned that late administration of tirofiban also has beneficial effects on patients with STEMI undergoing primary PCI.

The significant benefit of upstream administration of tirofiban in our patients is in line with the results of the Assessment of the Safety and Efficacy of a New Treatment strategy with percutaneous coronary intervention (ASSENT) 4 study (30), which showed a benefit in ST-segment resolution before PCI, which totally disappeared after PCI. Indeed, the lack of success in angiographic, electrographic, and clinical endpoints in the tirofiban-untreated group in our population is worth noting, given that GPIs are given to only 25%-30% of patients with STEMI, often for bail-out situations in real-world practice (19). Accordingly, the worse ST-segment resolution in the placebo or no-Tiro arm that was reported in the On-TIME 2 trial may be associated with insufficient inhibition of platelet aggregation with aspirin and clopidogrel alone, especially during the first hours, when platelet activation is highest (31).

A role for an early high loading dose of clopidogrel on the blunted difference in patency rate and ST-segment resolution success between the early and late groups was indicated in the recent On-TIME2 (19) and AGIR-2 (7) studies. Likewise, although many studies shown a beneficial effect of routine GPIs before PCI, the results of the BRAVE-3 study suggest less benefit of initiation in the catheterization laboratory in patients treated with high-dose clopidogrel (25).

Owing to the reported benefit of improved ST resolution on survival amongst STEMI patients (19), the ST resolution achieved in the upstream tirofiban group in our population might also be the reason for the lower incidence of in-hospital mortality rate, in-hospital sudden cardiac deaths, and in-hospital total mortality rate in this group.

Besides, the lack of a significant difference in our tirofiban-treated and -untreated patients in terms of major or minor bleeding incidence seems to be in accordance with the indication that triple antiplatelet therapy, with high-dose tirofiban, in addition to high-dose clopidogrel and aspirin pretreatment, is not associated with an increased risk of major bleeding (19).

Additionally, despite the significantly higher percentage of patients with poor prognostic factors, such as anterior MI in the pre-Tiro group, angiographic and electrocardiographic improvements were significantly better in this group.

It is unclear whether intracoronary bolus administration of GPIs during primary PCI is superior to intravenous administration. A meta-analysis of 10 randomized controlled trials revealed that the intracoronary bolus group was more likely to have complete perfusion without the expense of increased bleeding, lower short-term target vessel revascularization, and short-term mortality risks. However, data regarding mid-/long-term outcomes remain inconclusive (32).

An additional intracoronary tirofiban bolus following upstream intravenous tirofiban treatment was reported to decrease coronary platelet activation and inflammatory processes and improve myocardial reperfusion and left ventricular function, as well as 6-month MACE-free survival, for STEMI patients undergoing primary PCI. A recent pilot study comparing intracoronary bolus-only tirofiban with standard intravenous bolus plus maintenance infusion of tirofiban in patients who underwent primary PCI showed no difference in terms of corrected TIMI frame count, myocardial blush grade, microvascular resistance, coronary flow reserve, infarct size, and left ventricular function at 6 months (33, 34). In our study, the association between pre-Tiro use and reduction in in-hospital all-cause mortality rate and in-hospital sudden cardiac death seems unclear and should be interpreted cautiously. Given the likely roles of underlying baseline differences and Killip class and age but not tirofiban timing in predicting death after multivariable adjustments.

Although the patients in the Tiro (-) group had lower TIMI risk scores, they had similar in-hospital all-cause mortality rates as the other study groups using tirofiban. This surprising result may be associated with a possible compensatory benefit of tirofiban.

Study limitations

The limitations of the current study originate mainly from the intrinsic nature of retrospective and observational studies, unequal group sizes, and risk of selection bias with the groups. Major limitations are the inclusion of the in-hospital period without long-term follow-up and the non-randomized distribution of patients according to the timing of tirofiban treatment. The lack of subgroup comparisons among tirofiban protocols in terms of standard intravenous pretreatment with and without additional intracoronary tirofiban administration or intracoronary tirofiban without pretreatment may be considered another important limitation.

Conclusion

In conclusion, our findings indicate that the use of standard-dose bolus tirofiban, in addition to aspirin, high-dose clopidogrel, and unfractionated heparin, prior to primary PCI significantly improves myocardial reperfusion, ST-segment resolution, in-hospital sudden cardiac death, and in-hospital mortality and total mortality rates in patients with STEMI without increased risk of major bleeding. These results emphasize the crucial role of subsequent initiation of potent antithrombotic therapy very early after the onset of symptoms, considering the limited or lack of benefit obtained with the administration of tirofiban during or after PCI.

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