# Changes in BNP, hs-CRP and TIMI risk index with addition of tirofiban during primary percutaneous coronary intervention for acute STEMI: a prospective observational cohort study

## *Akut STEMI'de primer perkütan koroner girişiminde tedaviye tirofibanın eklenmesi durumunda, TIMI risk indeksi, BNP ve hs-CRP değerlerindeki değişimi*

*İbrahim Halil Kurt, Sait Demirkol[1], İlker Ünal[2], Mustafa Kemal Batur[3]*

Clinic of Cardiology, Adana Numune Education and Research Hospital, Adana
[1]Clinic of Cardiology, Gülhane Medical School, Ankara
[2]Department of Biostatistics, Faculty of Medicine, Çukurova University, Adana
[3]Department of Cardiology, Acıbadem University, Adana-*Turkey*

## ABSTRACT

**Objective:** This study aimed to investigate the relationship of tirofiban, added to the treatment of acute ST-elevation myocardial infarction (STEMI) patients underwent primary percutaneous coronary intervention (PCI), with changes in the TIMI risk index (TRI) of TIMI flow, B-type natriuretic peptide (BNP) and high-sensitive C-reactive protein (hs-CRP) levels.

**Methods:** This single-center, prospective observational cohort study included 102 consecutive patients who were admitted with the diagnosis of acute STEMI (70 male; 54.9±10.4 years). Primary PCI was applied to all cases with STEMI, who applied to our hospital in the first 6 hours due to chest pain complaints. Tirofiban was administered to one group (n=55) (male: 36; 54.1±11.3 years), while the other group was not given tirofiban (n=47) (male: 34; 55.9±9.1 years). The primary end-point was TIMI flow 2 or 3 for reperfusion after primary PCI. Chi-square test, paired t-test or Wilcoxon signed rank test, Spearman correlation analysis and Kaplan-Meier survival analysis were used for statistical analysis where appropriate.

**Results:** BNP level remained the same in the tirofiban group, whereas a significant increase was observed in the group that was not treated with tirofiban (105.9±126.8 versus 261.3±202.3 pg/ml p<0.001). The hs-CRP level tended to rise significantly in both groups despite the treatment (tirofiban group - from 0.67±0.66 to 0.90±0.44 mg/L, p=0.015, non tirofiban group - from 0.51±0.43 to 1.08±0.74 mg/L, p<0.001). BNP and hs-CRP values remained the same in cases with TIMI 2 flow in the tirofiban group, whereas a significant increase was detected in the post-treatment BNP (before 97.8±122.3 after 281.6±217.3 pg/ml, p=0.011) and hs-CRP (before 0.65±0.69; after 1.33±0.80 mg/L, p=0.028) values in the group not treated with tirofiban. In patients with TIMI 3 flow, BNP (tirofiban group before 146.5±114.2; after 184.4±139.4 pg/ml, p=0.011, non tirofiban group before 172.1±297.9; after 295.9±384.9 pg/ml, p<0.001) and hs-CRP levels (tirofiban group before 0.66±0.58; after 0.92±0.65 mg/L, p=0.011, non tirofiban group before 0.81±0.74; after 1.45±1.23 mg/L, p<0.001) were found to be similarly reduced in both treatment groups p<0.05. Three patients with minor hemorrhage did not need blood transfusion.

**Conclusion:** It was concluded at the end of them PCI application in STEMI that the addition of tirofiban treatment in patients with ≥TIMI 2 flow and anterior location MI could decrease the expected rise in BNP and CRP values. *(Anadolu Kardiyol Derg 2012; 12: 107-14)*

**Key words:** Acute myocardial infarction, tirofiban, percutaneous coronary intervention, TIMI risk index, B-type natriuretic peptide, high-sensitive C-reactive protein

## ÖZET

**Amaç:** Bu çalışmada primer perkütan koroner girişim (PPCI) uygulanan akut ST elevasyonlu miyokart enfarktüslü olgularda (STEMI) tedaviye eklenen tirofibanın anjiyografik TIMI akım (The Thrombolysis in Myocardial Infarction), TIMI risk indeksi, serum B-tip natriüretik peptit, (BNP) ve yüksek-duyarlıklı C-reaktif protein (hs-CRP) düzeyleriyle ilişkisi araştırılmıştır.

**Yöntemler:** Bu tek merkezli, prospektif gözlemsel kohort'una akut STEMI tanısıyla kabul edilen ardışık 102 hasta [70 erkek, ort. yaş 54.9±10.4 yıl, (30-82 yaş), mediyan yaş 54 yıl] çalışmaya alındı. İlk 6 saat içinde başvuran tüm STEMI'lılara PPCI uygulandı. Hastaların bir grubuna tirofiban (n=55) (erkek: 36, 54.13±11.39 yıl) diğer gruba ise, standart tedavi (n=47) (erkek: 34, 55.98±9.16 yıl) uygulandı. Tüm hastaların TIMI indeksi ve TIMI akım dereceleri kayıt edildi. Reperfüzyon için TIMI 2 veya 3 akım sağlamak anjiyografik endpoint olarak kabul edildi. İstatistiksel analiz için Ki-kare, eşleştirilmiş t, Wilcoxon işaret sıralama ve Spearman korelasyon testleri ve Kaplan-Meier sağkalım analizi kullanıldı.

**Address for Correspondence/Yazışma Adresi:** Dr. İbrahim Halil Kurt, Adana Numune Eğitim ve Araştırma Hastenesi Kardiyoloji Kliniği, 01330 Adana-*Türkiye* Phone: +90 322 458 32 52 Fax: +90 322 459 51 63 E-mail: ibrahimhalilkurt@gmail.com

**Accepted Date/Kabul Tarihi:** 20.10.2011 **Available Online Date/Çevrimiçi Yayın Tarihi:** 26.01.2012


*doi:10.5152/akd.2012.035*

**Bulgular:** BNP seviyeleri tirofiban alan grupta aynı kalırken, tirofiban almayan grupta bu artış devam ettiği görüldü (105.9±126.8 karşı 261.3±202.3 pg/ml p<0.001). Buna karşın tirofiban tedavisi alan her iki grupta hs-CRP seviyeleri yükselme eğilimindeydi (tirofiban alan grup-0.67±0.66'dan, 0.90±0.44'e mg/L, p=0.015, tirofiban almayan grup - 0.51±0.43'den 1.08±0.74'e mg/L, p<0.001). TIMI 2 akıma sahip tirofiban alan grupta BNP and hs-CRP değerleri benzer kalırken, tirofiban almayan gruplarda tedavi sonrası BNP (öncesi, 97.8±122.3 sonrası, 281.6±217.3 pg/ml, p=0.011) ve hs-CRP (öncesi 0.65±0.69; sonrası 1.33±0.80 mg/L, p=0.028) değerlerinde yükselme eğilimi tespit edildi. TIMI 3 akıma sahip olgularda, BNP (tirofiban alan grup öncesi, 146.5±114.2; sonrası 184.4±139.4 pg/ml, p=0.011, tirofiban almayan grup öncesi 172.1±297.9; sonrası 295.9±384.9 pg/ml, p<0.001) ve hs-CRP seviyesi (tirofiban alan grup öncesi 0.66±0.58; sonrası 0.92±0.65 mg/L, p=0.011, tirofiban almayan grup öncesi 0.81±0.74; sonrası 1.45±1.23 mg/L, p<0.001) her iki grupta benzer azalmalar tespit edildi p<0.05. Üç hastada kan transfüzyonu gerektirmeyen minör kanama oldu
**Sonuç:** Çalışmamızda STEMI'de uygulanan PPCI sonucunda, ≥ anjiyografik TIMI 2 akıma sahip olgularda tirofiban tedavisinin eklenmesinin BNP ve CRP değerlerinde beklenen artışın tirofiban tedavisi ile bir miktar da olsa azaltabildiği görüşü ortaya çıkmıştır.
*(Anadolu Kardiyol Derg 2012; 12: 107-14)*
**Anahtar kelimeler:** Akut miyokart enfarktüsü, tirofiban, perkütan koroner girişim, TIMI risk indeksi, B-tip natriüretik peptit, yüksek-duyarlıklı C-reaktif protein

## Introduction

Today, primary percutaneous coronary intervention (PCI) is the most effective method of achieving epicardial TIMI 3 flow (The Thrombolysis in Myocardial Infarction) in patients with ST-elevation myocardial infarction (STEMI) (1). However, in acute STEMI cases, it does not always indicate an optimal result (2, 3). Therefore, adjuvant anti-aggregant agents are needed for the maintenance of epicardial and microvascular circulation during primary PCI (4, 5). Tirofiban, a glycoprotein (GP) IIb/IIIa receptor antagonist, is used recently for this purpose. A number of studies have investigated the relationship between the angiographic TIMI 3 flow and cardiac biomarkers (myocardial damage, inflammation markers and natriuretic peptides) (6-8). In acute STEMI, a relationship was found between the serum B-type natriuretic peptide (BNP) level, short and long- term mortality with post primary PCI angiographic success and reperfusion disorder (9, 10).

However, the addition of tirofiban treatment in the TIMI flow rate obtained in primary PCI was not investigated adequately in relation to the TIMI risk index. TIMI risk index mostly includes clinical and hemodynamic parameters (age, blood pressure and heart rate) and it is an easy formula to calculate.

This study aimed to investigate the relationship of tirofiban on TIMI risk index, BNP and high-sensitive C-reactive protein (hs-CRP) in STEMI patients undergoing primary PCI and to study whether these effects depend on MI localization and angiographic TIMI index.

## Methods

### Study design and population

This single-centre, prospective observational cohort study included 102 consecutive patients (70 male) who were admitted to the emergency department of Adana Numune Education and Research Hospital between April 2008 and March 2009 with the diagnosis of acute STEMI. Mean age of the patients was 54.9±10.4 years (range 30-82) (median 54 years). These patients were divided into two groups, and one group was treated with tirofiban (n=55) (mean age 54.13±11.39, male 36), while the other group was not given tirofiban (n=47) (mean age 55.98±9.16, male: 34). Primary PCI (angioplasty and stenting) was performed in the artery associated with infarction and control angiographies were performed in the sixth month. The patients included in the study were evaluated in terms of clinical features, vital functions, coronary risk factors, lipid panels, kidney functions, as well as electrocardiographic and angiographic assessments.

Exclusion criteria: Patients excluded from the study include those who previously had cardiogenic shock, those with left main coronary artery stenosis, those who previously underwent coronary by-pass and stent operation, those with spontaneous recanalized coronary arteries, those who previously had myocardial infarction, those with pericarditis, aortic dissection, chronic inflammation or renal insufficiency (serum creatinine >1.5 mg/dl), and those active infection, hs-CRP level of >10 mg/L, malignity and chest pain for more than 6 hours. Eight patients (4.2%) died and were excluded at the end of the study.

The procedure was executed upon the consent received from the patients as per the protocol followed by the approval of Ethics Committee of our hospital (Protocol number 3; date 28/01/2008).

### Study procedures

Acute STEMI diagnosis was confirmed by using ACC/AHA/ESC measures (11). Chest pain and/or discomfort lasting for at least 30 minutes, ST segment elevation exceeding 0.1 mm in at least two adjacent derivations and 0.2 mm in precordial derivations in the extremity derivations as determined by standard 12-derivation electrocardiography (ECG), the elevation of creatine kinase- MB (CK-MB) values more than two times the normal value and the presence of two of the criteria were defined as acute MI. In all cases with ST segment-elevation myocardial infarction, who were admitted in the first 6 hours with complaints of chest pain; 12-derivation ECG was taken and non-enteric 300 mg acetyl salicylic acid (ASA) was given during the admission.

### Biomarkers analysis

Peripheral blood samples for plasma BNP and hs-CRP determination were obtained at admission by direct venipuncture of an antecubital vein after the patient had been in the

supine position for 30 minutes. Blood samples were immediately centrifuged. High sensitive-CRP levels (normal range 0.53-0.95 mg/L) were measured by using immune nephelometric method (IMMAGE Immunochemistry Systems; Beckman Coulter, California, USA). BNP measurements (normal range 0-90 pg/ml was done using Triage Meter Plus equipment (Willich, Germany).

**Primary PCI procedure**

Post-treatment TIMI flow rates were detected by the post-procedure myocardium staining degree of the coronary artery. Angiographic data were calculated in the catheter laboratory and individual CD records were taken for each patient. The coronary angiographic procedure was performed by Shimadzu device (AUD 150 G-Digitex, Kyoto, Japan). Predefined grading system was used in determining the TIMI flow (12) (TIMI 0: No flow and perfusion in the occlusion distal; TIMI 1: penetration in the occlusion distal, but no perfusion; TIMI 2: partial perfusion; TIMI 3: full perfusion). Patients were given 600 mg clopidogrel and 10.000 units IV heparin bolus in addition to non-enteric ASA 300 mg administered before PCI. After the placement of femoral artery 6F sheath, stent (Ephesos, Nemed Corporation, Istanbul-Turkey) was implanted following the balloon predilatation to the suspicious lesion by means of 6 F guiding catheter. Complications during angiography, reocclusion, distal embolization, lateral protection, coronary dissection were defined according to the criteria of the National Heart, Lung, and Blood Institute (13).

Tirofiban (Aggrastat, Merck, USA) consecutively administration to patients was started during the PPCI procedure in the catheter laboratory. Tirofiban bolus was given at least 10 minutes before the lesion could be crossed with the guide wire tirofiban was initially administered as 10 µg/kg/min bolus dose per 3 minutes followed by 0.15 µg/kg/min infusion for 24 hours. Achieving TIMI 2 or 3 flow for reperfusion was accepted as the angiographic endpoint. PCI was considered inadequate in patients who achieved TIMI flow below 2 during the PCI. The patients, who received tirofiban after reperfusion, were given heparin, 300 mg ASA and 75 mg clopidogrel as infusion for 500 u/hour/24 hours. Initial and final TIMI flow rates were evaluated during the clinical and angiographic follow-ups up to the sixth month. Hospital complications, minor and major hemorrhage; mortality and late-stage restenosis rates were assessed. The definition of TIMI hemorrhage complication was taken as a basis for major and minor hemorrhage.

**Calculation of the TIMI Risk index**

The TIMI risk index of patients were calculated by the formula "Heart rate X $(age \div 10)^2 \div SBP$". This score is obtained by using the patient's pulse, systolic blood pressure and age, and it is reported to be a highly useful scoring system for risk stratification in STEMI cases, and that every 5 points increase in TIMI risk index for thirty days mortality leads to 43% risk increase (14).

**Statistical analysis**

The SPSS 16.0 (SPSS Inc., Chicago, USA) software package was used for statistical analysis of the data. Categorical analyses were expressed as numbers (n) and percentage (%), whereas continuous measurements were given as mean and standard deviation and as median and minimum-maximum where appropriate. The Chi-square test was used to compare categorical variables of treatment groups. For comparison of continuous variables obtained before and after the treatment in the groups, the t-test for dependent samples or Wilcoxon Signed Rank Test was used depending on whether the statistical assumptions were fulfilled or not; and the t-test for independent samples or Mann-Whitney U test for comparisons between groups. The correlation between certain variables of the treatment groups was performed using the Spearman Correlation Analysis. The statistical level of significance for all tests was considered to be 0.05.

## Results

**Baseline clinical characteristics (Table 1)**

The distribution of patients in terms of the chest pain duration at the time of their admission with the diagnosis of acute STEMI is as following: 33 (32.4%) for 1 hour and less, 37 (36.3%) for 1-3 hours and 32 (31.4%) for 3-6 hours, respectively, and there was no statistically significant difference between the patients. In patient groups, the distribution of chest pain duration of acute STEMI cases treated with and without tirofiban according to groups is: 1 hour and less (14/18), 1 to 3 hours (25/12), 3 to 6 hours (15/17), respectively; and there was no statistically significant difference between the groups ($p>0.05$).

No statistically significant difference was observed between the two groups also in terms of the demographic parameters (age, gender) and cardiovascular risk factors (hypertension, diabetes mellitus and smoking) ($p>0.05$). In the hemodynamic comparison between the groups treated with and without tirofiban, no difference was found between the groups with regard to systolic and diastolic blood pressures, pulse and lipid panel, kidney functions, BNP, hs-CRP and TIMI risk index values ($p>0.05$).

**The relationship of BNP, hs-CRP levels and TIMI risk index with tirofiban use and PCI parameters (Table 2)**

There was no significant difference in terms of heart rate, systolic and diastolic blood pressure measurements, lipid and kidney functions, Groups treated with and without tirofiban revealed no difference also in terms of the distribution of coronary artery in which primary PCI was applied, procedure period, number of stents, stent length, stent diameter and subacute occlusion, angiographically visible thrombus, distal emboli, heart failure, and side brunch protection. TIMI 2 and TIMI 3 flow rates were similar in both groups ($p>0.05$).

**Table 1. Demographic parameters, hemodynamic parameters and laboratory findings of groups**

| Variables | Tirofiban (n=55) | Non-tirofiban (n=47) | *p |
|---|---|---|---|
| **Demographics** | | | |
| Age, years | 54.1±11.4 | 56.0±9.2 | 0.373 |
| Gender, male/female, n | 36/19 | 34/13 | 0.524 |
| **Presence of cardiovascular risk factor** | | | |
| Diabetes, n (%) | 8 (14.5) | 6 (12.8) | 0.999 |
| Hypertension, n (%) | 17 (30.9) | 14 (29.8) | 0.999 |
| Smoking, n (%) | 26 (47.3) | 16 (34.0) | 0.227 |
| **Hemodynamic parameters and echocardiography findings** | | | |
| Systolic blood pressure, mmHg | 121.5±19.6 | 124.4±16.7 | 0.429 |
| Diastolic blood pressure, mmHg, mean±sd | 77.6±16.4 | 77.6±18.6 | 0.996 |
| Pulse, bpm | 79.8±16.1 | 79.3±13.5 | 0.856 |
| **Lipid profile** | | | |
| Total cholesterol, mg/dl | 199.8±40.9 | 193.6±49.5 | 0.490 |
| HDL | 38.0±7.5 | 38.9±8.1 | 0.558 |
| LDL | 129.2±35.1 | 122.5±43.1 | 0.387 |
| **Serum biochemistry** | | | |
| BUN, mg/dl | 32.3±8.8<br>31.2 (17-52) | 34.1±7.9<br>32 (21-57) | 0.270 |
| Serum creatinine, mg/dl | 0.99±0.20<br>1 (0.7-1.5) | 1.01±0.31<br>1 (0-2.3) | 0.742 |
| **Cardiac markers** | | | |
| BNP, pg/ml | 142.8±117.6<br>99.8 (12.2-500) | 157.9±273.6<br>110 (5-1794.1) | 0.190 |
| Hs-CRP, mg/L | 0.66±0.55<br>0.54 (0.04-2.88) | 0.78±0.72<br>0.57 (0.03-3.2) | 0.577 |
| TIMI risk index, points | 20.2±9.0<br>17.9 (5-46.2) | 20.8±8.5<br>19.7 (10.4-51.7) | 0.685 |
| **Chest pain, n** | | | |
| ≤1 hour | 15 | 18 | 0.113 |
| >1-3 hour | 25 | 12 | |
| >3-6 hour | 15 | 17 | |
| Angiotensin converting enzyme inhibitor, n | 24/31 | 21/26 | 0.999 |
| Beta-blocker, n | 41/14 | 36/11 | 0.999 |
| Acetyl salicylic acid, n | | | |
| Nitrate, n | 21/34 | 23/24 | 0.319 |
| Statin, n | 28/27 | 30/17 | 0.231 |

Data are presented as mean±SD, median (min-max) and number/percentage values
*-unpaired Student's t-test, Chi-square test, Mann-Whitney U test
BNP - Serum B - type natriuretic peptide, bpm - beats per minute, BUN - blood urea nitrogen, HDL - high-density lipoprotein, Hs-CRP - high-sensitive C - reactive protein, LDL - lower-density lipoprotein, n - number of patients, TIMI - the Thrombolysis in Myocardial Infarction

**Table 2. Primary PCI findings in tirofiban and non-tirofiban groups**

| Variables | Tirofiban (n=55) | Non-tirofiban (n=47) | *p |
|---|---|---|---|
| **Infarct-related artery, n** | | | |
| LAD | 35 | 19 | 0.060 |
| Cx | 6 | 7 | |
| RCA | 14 | 21 | |
| **Number of stents, n** | | | |
| 1 | 50 | 44 | 0.723 |
| 2 | 5 | 3 | |
| **Stent length, mm** | | | |
| 9-15 | 23 | 18 | 0.840 |
| 18-25 | 32 | 29 | |
| **Stent diameter, mm** | | | |
| 2.5-3 | 28 | 25 | 0.845 |
| 3.5-4 | 27 | 22 | |
| Stent (direct PTCA+stent), n | 14/41 | 13/34 | 0.825 |
| **Procedure period, min** | | | |
| 0-30 | 40 | 31 | 0.653 |
| 31-60 | 14 | 14 | |
| >60 | 1 | 2 | |
| Subacute occlusion, +/-, n | 4/51 | 5/42 | 0.729 |
| Thrombus, +/-, n | 32/23 | 27/20 | 0.999 |
| Distal emboli, +/-, n | 8/47 | 11/36 | 0.311 |
| Heart failure, +/-, n | 2/53 | 3/44 | 0.521 |
| Side branch protection, +/-, n | 41/14 | 38/9 | 0.485 |
| Restenosis, +/-, n | 13/42 | 14/33 | 0.508 |
| **Coronary artery, n** | | | |
| 1 | 11 | 19 | 0.48 |
| 2 | 21 | 10 | |
| 3 | 23 | 18 | |
| **TIMI flow, n** | | | |
| 2 | 7 | 9 | 0.422 |
| 3 | 48 | 38 | |

Data are presented as number values
* Chi-square test
Cx - circumflex artery, LAD - left anterior descending artery, MI - myocardial infarction, n - number of patients, PCI - percutaneous coronary intervention, PTCA - percutaneous transluminal coronary angioplasty, RCA - right coronary artery, TIMI - The Thrombolysis in Myocardial Infarction, + yes, - no

### Relationship between myocardial infarction localization and TIMI risk index, BNP, hs-CRP levels (Table 3)

MI localization (anterior and non-anterior) was comparable in both groups (p>0.05) (Table 4). In terms of the relationship between tirofiban use and MI localization, there was no significant difference in TIMI risk index levels in anterior and non-anterior localization before and after the treatment (p>0.05). BNP level did not show any

**Table 3. Relationship between myocardial infarction localization and TIMI risk index, BNP, hs-CRP levels before and after treatment in tirofiban and non-tirofiban groups**

| Variables | | Tirofiban (n=55) | | | Non-tirofiban (n=47) | | |
|---|---|---|---|---|---|---|---|
| | | Before treatment | After treatment | *p | Before treatment | After treatment | *p |
| Anterior MI | TRI | 21.7±10.3<br>17.9 (7.7-46.2) | 21.8±10.2<br>18.6 (10.1-48.1) | 0.761 | 20.0±8.6<br>18.5 (10.6-51.7) | 21.2±6.5<br>21.2 (8.1-37.3) | 0.101 |
| | BNP, mg/dl | 166.4±123.6<br>137.3 (21.6-438.3) | 199.7±133.4<br>141.0 (55-493.3) | 0.171 | 105.9±126.8<br>43.5 (5-500) | 261.3±202.3<br>202.5 (18.6-840) | <0.001 |
| | hs-CRP, mg/L | 0.67±0.66<br>0.49 (0.04-2.88) | 0.90±0.44<br>0.78 (0.34-2.17) | 0.015 | 0.51±0.43<br>0.41 (0.03-2) | 1.08±0.74<br>0.80 (0.09-2.80) | <0.001 |
| Non-anterior MI | TRI | 19.0±8.0<br>17.8 (5.0-44.9) | 20.1±7.8<br>18.8 (6-36.81) | 0.076 | 22.0±8.3<br>21.5 (10.4-34.5) | 22.6±9.8<br>19.7 (10.1-40.2) | 0.546 |
| | BNP, mg/dl | 125.9±111.9<br>93.5 (12.2-500) | 173.5±137.0<br>125.9 (24-599) | 0.007 | 234.5±396.0<br>137.7 (8.8-1794.1) | 340.1±510.1<br>234 (54-2389) | 0.008 |
| | hs-CRP, mg/L | 0.65±0.46<br>0.63 (0.10-1.84) | 0.92±0.75<br>0.78 (0.10-3.75) | 0.011 | 1.18±0.88<br>0.98 (0.11-3.20) | 1.95±1.44<br>1.40 (0.60-5.63) | 0.008 |

Data are presented as mean±SD and median (min-max) values
*Wilcoxon signed rank test
BNP - Serum B - type natriuretic peptide, hs-CRP - high-sensitive C - reactive protein, MI - myocardial infarction, TIMI - The Thrombolysis in Myocardial Infarction

**Table 4. Relationship between TIMI flow and TIMI risk index, BNP, hs-CRP levels before and after treatment in tirofiban and non-tirofiban groups**

| Variables | | Tirofiban (n=55) | | | Non-tirofiban (n=47) | | |
|---|---|---|---|---|---|---|---|
| | | Before treatment | After treatment | *p | Before treatment | After treatment | *p |
| TIMI 2 | TRI | 26.7±12.1<br>26.7 (14.2-44.9) | 26.1±11.8<br>27.1 (13.5-44.5) | 0.735 | 19.6±6.3<br>19.7 (11.9-32.3) | 20.9±4.9<br>21.3 (15.1-31.7) | 0.314 |
| | BNP, mg/dl | 118±146.2<br>57.1 (12.2-438.3) | 185±107.6<br>190.9 (70-359) | 0.176 | 97.8±122.3<br>31.7 (5-362.9) | 281.6±217.3<br>203.9 (156-840) | 0.011 |
| | hs-CRP, mg/L | 0.66±0.25<br>0.54 (0.41-1.10) | 0.85±0.49<br>0.75 (0.20-1.75) | 0.345 | 0.65±0.69<br>0.50 (0.03-2) | 1.33±0.80<br>1.48 (0.45-2.80) | 0.028 |
| TIMI 3 | TRI | 19.2±8.2<br>17.5 (5-46.2) | 20±8.2<br>18.6 (6-48.1) | 0.087 | 21.1±8.9<br>19.5 (10.4-51.7) | 22±8.5<br>20.6 (8.1-40.2) | 0.243 |
| | BNP, mg/dl | 146.5±114.2<br>103.8 (19.2-500) | 184.4±139.4<br>130.3 (24-599) | 0.011 | 172.1±297.9<br>129.5 (5-1794.1) | 295.9±384.9<br>225.3 (18.6-2389) | <0.001 |
| | hs-CRP, mg/L | 0.66±0.58<br>0.53 (0.04-2.88) | 0.92±0.65<br>0.89 (0.10-3.75) | 0.001 | 0.81±0.74<br>0.58 (0.06-3.20) | 1.45±1.23<br>1.00 (0.09-5.63) | <0.001 |

Data are presented as mean±SD and median (min-max) values
* Wilcoxon signed rank test
BNP - Serum B - type natriuretic peptide, Hs-CRP - high-sensitive C - reactive protein, TIMI -The Thrombolysis in Myocardial Infarction, TRI -The Thrombolysis in Myocardial Infarction risk index

change in the tirofiban group, while a significant increase was observed in the group not treated with tirofiban (p<0.001). On the other hand, hs-CRP level tended to rise significantly in both groups despite the treatment (p<0.01). In the non-anterior group, BNP and hs-CRP levels tended to rise in both treatment groups (p<0.05). In other cases, the observed increase was significant on the borderline.

### Inter-group relationship of post-treatment TIMI risk index, BNP and hs-CRP according to the angiographic TIMI assessment

According to the cut-off points determined for the angiographic TIMI flow rate, the assessment of all patients revealed no significant relationship between TIMI risk index, BNP and hs-CRP and these measurements before and after the treatment; and the pre- and post-treatment angiographic TIMI flows and TIMI risk index values of the cases were similar in both groups treated with and without tirofiban (p>0.05). In cases with angiographic TIMI 2 flow, pre- and post-treatment BNP and hs-CRP values remained the same in the group receiving tirofiban, whereas post-treatment BNP and hs-CRP values were detected to be significantly higher in the group not treated with tirofiban (p<0.05). In the cases with angiographic TIMI 3 flow, BNP and hs-CRP levels were found to be similarly high in both treatment groups (p<0.05).

**Table 5. Percentage change in pre- and post-treatment TIMI risk index, BNP and hs-CRP in studied groups**

| Percentage change | Tirofiban (n=55) | Non-tirofiban (n=47) | *p |
|---|---|---|---|
| TRI, % | 6.0±19.9<br>3.7 (-36.9-78.0) | 8.7±29.0<br>3.9 (-41.2-111.5) | 0.660 |
| BNP, % | 75.9±136<br>31.7 (-55.2-515.5) | 700.6±1268.0<br>80.3 (-65.5-5124.7) | 0.009 |
| hs-CRP, % | 121.8±209.8<br>54.6 (-81.8-940.5) | 298.7±579.6<br>50.0 (-55.6-2687.1) | 0.330 |

Data are presented as mean±SD and median (min-max) values
*Mann-Whitney U Test
BNP - Serum B - type natriuretic peptide, Hs-CRP - high-sensitive C - reactive protein, TIMI - The Thrombolysis in Myocardial Infarction, TRI - The Thrombolysis in Myocardial Infarction risk index

**Percentage change in pre and post-treatment TIMI risk index, BNP and hs-CRP levels in studied groups**

Value analysis of inter-group TIMI risk index, BNP and h-CRP in our study is summarized in Table 5. In this analysis, only percentage increase in post-treatment BNP value was statistically significantly different between groups when compared to pre-treatment value. While there was an increase of 32% in median BNP value in the group receiving tirofiban, 80% median increase is observed in the group not receiving tirofiban (p=0.009) (Table 5).

Although a significant decrease was detected in the pre- and post-treatment hematocrit (HCT) values (40.39±5.11; 38.25±3.90%, respectively, p<0.001) in the group treated with tirofiban, major hemorrhage was not observed in neither of the groups and minor hemorrhage rates were comparable (p>0.05). There was no significant difference in HCT values (38.81±5.47; 37.63±5.79%, respectively, p>0.05) in the group not treated with tirofiban. One case developed continuous ventricular tachycardia, and one case developed pulmonary edema. Three patients with minor hemorrhage did not need blood transfusion.

## Discussion

This study aimed to predict GP IIb/IIIa need by providing a simple and quick determination of the relationship between TIMI flow and TIMI risk index, BNP and hs-CRP for risk assessment in acute STEMI cases who underwent PPCI procedure. In our study, at the end of the PPCI procedure applied in STEMI cases, BNP and CRP values showed a significant increase compared to pre-treatment values in the group with TIMI 2 flow and treated without tirofiban, and in the group with TIMI 3 flow and treated with and without tirofiban. Accordingly, the addition of tirofiban treatment resulted in a lower increase in BNP and CRP values in patients with TIMI 2 or 3 flow and it was concluded that the expected increase in BNP and CRP values in this patient group could be reduced, even if to a small extent, by tirofiban treatment. PPCI is frequently used in the treatment of acute STEMI; yet, adjuvant pharmacological support is needed for obtaining an optimal result. It is known that GP IIb/IIIa receptor blockers with added primary PCI have a beneficial effect on microvascular perfusion (15). It is also reported that the positive effect of tirofiban on reperfusion is mainly related to anti-aggregation and has a positive contribution to endothelial dysfunction developing during PCI procedure (16). However, use of the aspiration system in patients presenting with acute coronary syndrome and visible thrombus provides no substantial benefit (17) and intracoronary administration of tirofiban was not associated with reduction in major adverse cardiac event (MACE) rates compared to intravenous administration in patients with STEMI who underwent primary PCI (18). In addition to using of high-dose tirofiban were reduced predictors of mortality in STEMI (19, 20).

It is still a clinical issue to predict the early-stage markers of mortality in acute STEMI. Considering that two third of the deaths in patients with acute myocardial infarction occur despite interventions, it becomes evident that a quick and simple method is required for risk assessment (21). TIMI risk index is a score obtained by the formulation of the three factors in the TIMI risk index (age, systolic blood pressure, pulse) by multi-regression analysis (22). In recently study thrombolytic therapy failed to decrease BNP, hs-CRP and TIMI risk index values in STEMI patients. The reason of failure is that enough TIMI 3 flow with thrombolytic therapy cannot be provided (23). But there are no adequate studies on the correlation of the numerical values of hemodynamic parameters in this index with biological markers using tirofiban in STEMI. In our study, TIMI risk index was preferred due to the convenience of obtaining the parameters included in the index and the good correlation established with the early hospital mortality (24). It was determined in this study that every 5 points increase in TIMI risk index for thirty days of mortality leads to 43% risk increase. This risk interval was classified as 5 different score systems, minimum risk being <12.5 and maximal risk being >30 (25). Our study revealed no difference between the total TRI averages of the risk stratification in both groups. In addition, when different cut-off values (between 12.5-30) were taken for TIMI risk index, it was observed that the addition of tirofiban at different TIMI flow rates did not change the early-stage TIMI risk index in cases achieving either partial reperfusion (TIMI 2) or total reperfusion (TIMI 3). This result may be associated with the statistical similarity of the systolic blood pressure, pulse and age parameters of the TIMI risk index mathematical formula in both groups. This, in turn, leads to a decrease in the TIMI risk index diagnostic value when these parameters are homogenous in both groups. In our study, no significant relationship was found between TIMI risk index and TIMI flow rates in terms of angiographic restenosis in long-term controls.

In our study, TIMI risk index was similar in both groups in terms of localization in patients with acute STEMI who underwent primary PCI procedure; therefore, TIMI risk index was found to be inadequate in localizing MI. On the other hand, BNP level was significantly lower in anterior localization in the group treated with tirofiban, whereas non-anterior localization showed a rising

tendency. It was reported in previous studies that plasma BNP level increased rapidly as from the first 24 hours of acute MI (26) and it provided significant and independent prognostic information in the long term with regard to non-fatal MI and mortality risk in patients who underwent primary PCI procedure (27). In our study, the BNP level, which was initially high in anterior localization, decreased in a short while in the tirofiban group, reflecting a reduction in myocardial ischemic load as a response to the limitation of the infracted area by tirofiban.

Serum hs-CRP also rises in the first days of acute MI as a response to myocardial necrosis (28). Plasma hs-CRP level and acute MI are noted to be the predictor of reperfusion failure in the short and long term (29). It is also reported that the combination of TIMI risk index and hs-CRP level provides additional information with regard to risk stratification and prognosis in cases with acute coronary syndrome (30). Several studies point at the predictive value of hs-CRP for risk assessment in cardiovascular cases (31, 32). In our study, no decrease was detected in the increase value of hs-CRP in both localizations in the acute period in the treatment group. Although a significant hematocrit decrease was observed in the group treated with tirofiban, there was no clinical need for blood transfusion.

### Study limitations

The major limitation of the present study is the small sample size. We did not provide mortality data because our primary aim was to determine TIMI risk index, BNP and hs-CRP values. We also did not measure infarct area and use high dose tirofiban with which we can reach to further conclusions.

## Conclusion

In our study, it was concluded at the end of the primary PCI application in STEMI that the addition of tirofiban treatment in cases with ≥ angiographic TIMI 2 flow and anterior location could decrease the expected rise in BNP, even if to a small extent. No difference was observed in the TIMI risk index.

### Clinical application of the study

Notwithstanding the successful mechanical reperfusion achieved at the end of primary PCI procedure, these data indicate that the addition of tirofiban in the treatment of STEMI produces positive results in prognostic markers.

**Conflict of interest**: None declared

**Authorship contributions:** Concept - İ.H.K.; Design - İ.Ü.; Supervision -M.K.B.; Resources - İ.H.K.; Material - İ.H.K.; Data collection&/or Processing: İ.H.K.; Analysis &/or Interpretation - İ.H.K., İ.Ü.; Literature Search - S.D., İ.H.K.; Writing - İ.H.K.; Critical review - S.D., M.K.B.

## References

1. Ochiai M, Isshiki T, Takeshita S, Oshima A, Toyoizumi H, Kondo K, et al. Relation of duration of ST re-elevation at reperfusion and improvement of left ventricular function after successful primary angioplasty of the left anterior descending coronary artery in anterior wall acute myocardial infarction. Am J Cardiol 1997; 79: 1667-70. [CrossRef]
2. Kobayashi N, Ohmura N, Nakada I, Yasu T, Iwanaka H, Kubo N, et al. Further ST elevation at reperfusion by direct percutaneous transluminal coronary angioplasty predicts poor recovery of left ventricular systolic function in anterior wall AMI. Am J Cardiol 1997; 79: 862-6. [CrossRef]
3. Miida T, Oda H, Toeda T, Higuma N. Additional ST-segment elevation immediately after reperfusion and its effect on myocardial salvage in anterior wall acute myocardial infarction. Am J Cardiol 1994; 73: 851-5. [CrossRef]
4. Nguyen CM, Harrington RA. Glycoprotein IIb/IIIa receptor antagonists: a comparative review of their use in percutaneous coronary intervention. Am J Cardiovasc Drugs 2003; 3: 423-36. [CrossRef]
5. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation1997; 96: 1445-53.
6. Giannitsis E, Muller-Bardorff M, Lehrke S, Wiegand U, Tolg R, Weidtmann B, et al. Admission troponin T level predicts clinical outcomes, TIMI flow, and myocardial tissue perfusion after primary percutaneous intervention for acute ST-segment elevation myocardial infarction. Circulation 2001; 104: 630-5. [CrossRef]
7. Grabowski M, Filipiak KJ, Karpinski G, Wretowski D, Rdzanek A, Huczek Z, et al. Serum B-type natriuretic peptide levels on admission predict not only short-term death but also angiographic success of procedure in patients with acute ST-elevation myocardial infarction treated with primary angioplasty. Am Heart J 2004; 148: 655-62. [CrossRef]
8. Kini AS, Lee P, Marmur JD, Agarwal A, Duffy ME, Kim MC, et al. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. Am J Cardiol 2004; 93: 18-23. [CrossRef]
9. Kuklinska AM, Sobkowicz B, Mroczko B, Sawicki R, Musial WJ, Knapp M, et al. Prognostic significance of the admission plasma B-type natriuretic peptide measurement in patients with first ST-elevation myocardial infarction in comparison with C-reactive protein and TIMI risk score. Clin Chim Acta 2007; 382: 106-11. [CrossRef]
10. Mega JL, Morrow DA, De Lemos JA, Sabatine MS, Murphy SA, Rifai N, et al. B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction: an ENTIRE-TIMI-23 substudy. J Am Coll Cardiol 2004; 44: 335-9. [CrossRef]
11. Krumholz HM, Anderson JL, Brooks NH, Fesmire FM, Lambrew CT, Landrum MB, et al. ACC/AHA clinical performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the ACC/AHA Task Force on Performance Measures (Writing Committee to Develop Performance Measures on ST-Elevation and Non-ST-Elevation Myocardial Infarction) Circulation 2006; 113: 732-61. [CrossRef]

12. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) Trial: phase I findings. N Engl J Med 1985; 312: 932-6. [CrossRef]
13. Holmes DR Jr, Holubkov R, Vlietstra RE, Kelsey SF, Reeder GS, Dorros G, et al. Comparison of complications during percutaneous transluminal coronary angioplasty from 1977 to 1981 and from 1985 to 1986: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. J Am Coll Cardiol 1988; 12: 1149-55. [CrossRef]
14. Morrow DA, Antman EM, Giugliano RP, Cairns R, Charlesworth A, Murphy SA, et al. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. Lancet 2001; 358: 1571-5. [CrossRef]
15. Neumann FJ, Blasini R, Schmitt C, Alt E, Dirschinger J, Gawaz M,et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998; 98: 2695-701.
16. Warnholtz A, Ostad MA, Heitzer T, Goldmann BU, Nowak G, Munzel T. Effect of tirofiban on percutaneous coronary intervention-induced endothelial dysfunction in patients with stable coronary artery disease. Am J Cardiol 2005; 95: 20-3. [CrossRef]
17. V Korn H, Ohlow M, Donev S, Yu J, Huegl B, Wagner A, et al. Export aspiration system in patients with acute coronary syndrome and visible thrombus provides no substantial benefit. Catheter Cardiovasc Interv 2007; 70: 35-42.
18. Erdim R, Erciyes D, Görmez S, Karabay KO, Catakoğlu AB, Aytekin V, et al. Comparison of intracoronary versus intravenous administration of tirofiban in primary percutaneous coronary intervention. Anadolu Kardiyol Derg 2010; 10: 340-5. [CrossRef]
19. Heestermans AA, Van Werkum JW, Hamm C, Dill T, Gosselink AT, De Boer MJ, et al. Marked reduction of early stent thrombosis with pre-hospital initiation of high-dose tirofiban in ST-segment elevation myocardial infarction. J Thromb Haemost 2009; 7: 1612-8. [CrossRef]
20. Heestermans AA, Hermanides RS, Gosselink AT, de Boer MJ, Hoorntje JC, Suryapranata H, et al. A comparison between upfront high-dose tirofiban versus provisional use in the real-world of non-selected STEMI patients undergoing primary PCI: Insights from the Zwolle acute myocardial infarction registry. Neth Heart J 2010; 18: 592-7. [CrossRef]
21. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol 2004; 44: 1-211. [CrossRef]
22. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarctiona convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000; 102: 2031-7.
23. Kurt IH, Batur MK, Unal I. The effect of Streptokinase therapy in STEMI and conventional therapy in NSTEMI patients on TIMI risk index, BNP, hs-CRP levels. Anadolu Kardiyol Derg; 2011; 11: 530-5.
24. Rathore SS, Weinfurt KP, Gross CP, Krumholz HM. Validity of a simple ST-elevation acute myocardial infarction risk index: are randomized trial prognostic estimates generalizable to elderly patients? Circulation 2003; 107: 811-6. [CrossRef]
25. Suzuki S, Yoshimura M, Nakayama M, Mizuno Y, Harada E, Ito T, et al. Plasma level of B-type natriuretic peptide as a prognostic marker after acute myocardial infarction: a long-term follow-up analysis. Circulation 2004; 110: 1387-91. [CrossRef]
26. de Winter RJ, Stroobants A, Koch KT, Bax M, Schotborgh CE, Mulder KJ, et al. Plasma N-terminal pro-B-type natriuretic peptide for prediction of death or nonfatal myocardial infarction following percutaneous coronary intervention. Am J Cardiol 2004; 94: 1481-5. [CrossRef]
27. Pietilä K, Harmoinen A, Pöyhönen L, Koskinen M, Heikkila J, Ruosteenoja R. Intravenous streptokinase treatment and plasma C-reactive protein in patients with acute myocardial infarction. Br Heart J 1987; 58: 225-9. [CrossRef]
28. Zairis MN, Manousakis SJ, Stefanidis AS, Papadaki OA, Andrikopoulos GK, Olympios CD. C-reactive protein levels on admission are associated with response to thrombolysis and prognosis after ST-segment elevation acute myocardial infarction. Am Heart J 2002; 144: 782-9. [CrossRef]
29. Foussas SG, Zairis MN, Lyras AG, Patsourakos NG, Tsirimpis VG, Katsaros K, et al. Early prognostic usefulness of C-reactive protein added to the Thrombolysis In Myocardial Infarction risk score in acute coronary syndromes. Am J Cardiol 2005; 96: 533-7. [CrossRef]
30. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Eng J Med 2005; 352: 20-8. [CrossRef]
31. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Eng J Med 2005; 352: 29-38. [CrossRef]
32. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. C-Reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836-43. [CrossRef]