











Bleeding risk with concomitant use of tirofiban and third-generation P2Y₁₂ receptor antagonists in patients with acute myocardial infarction: A real-life data

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ABSTRACT

Objective: Combination of dual antiplatelet therapy (DAPT) with glycoprotein (GP) IIb/IIIa inhibitors can increase bleeding risk. In this study, we aimed to investigate bleeding complications of different DAPTs with concomitant tirofiban use in patients with acute coronary syndrome (ACS).

Methods: This retrospective study included 224 consecutive ACS patients (mean age 56.6±11.1 years, 193 men) who were given conventional dose of tirofiban (25 µg/kg per 3 minutes followed by an infusion of 0.15 µg/kg/min for 24 hours) in addition to DAPT (300 mg aspirin followed by 100 mg/day + 600 mg clopidogrel followed by 75 mg/day or 180 mg ticagrelor followed by 90 mg twice daily or 60 mg prasugrel followed by 10 mg/day). Any intra-hospital bleeding complications were noted.

Results: Of the 224 patients, 115 were given ticagrelor and 32 were given prasugrel. Mean hemoglobin fall was similar between the patients taking ticagrelor/prasugrel and those taking clopidogrel. Ten patients taking ticagrelor and one patient taking prasugrel had hemoglobin fall ≥3 g/dL versus two patients in clopidogrel group (p=0.228). Gastrointestinal bleeding (two patients taking ticagrelor), hematoma at access site (three patients taking ticagrelor), and cardiac tamponade (two patients taking ticagrelor) rates were also similar. Creatinine levels were associated with hemoglobin fall ≥3 g/dL (p=0.032, Odds ratio 2.189, 95% confidence interval 1.070–4.479). There was no relation between hemoglobin fall ≥3 g/dL and antiplatelet agent, age, sex, hypertension, or diabetes.

Conclusion: Tirofiban may be given to patients receiving ticagrelor or prasugrel with a bleeding rate similar to clopidogrel. Close monitoring for bleeding risk is recommended, especially in patients with higher creatinine levels.

Keywords: acute coronary syndrome, bleeding, clopidogrel, prasugrel, ticagrelor, tirofiban

Cite this article as: Tigen MK, Özdil MH, Çinçin A, Gürel E, Sünbül M, Şahin A, et al. Bleeding risk with concomitant use of tirofiban and third-generation P2Y₁₂ receptor antagonists in patients with acute myocardial infarction: A real-life data. *Anatol J Cardiol* 2021; 25: 699-705.

Introduction

Intravenous glycoprotein (GP) IIb/IIIa inhibitors interferes with platelet aggregation by inhibiting fibrinogen binding to GP IIb/IIIa receptors on two adjacent platelets (1, 2). Glycoprotein IIb/IIIa inhibitors have been shown to reduce myocardial infarction (MI) and mortality in patients with acute coronary syndromes (ACS) (3-7).

Patients with ACS undergoing primary percutaneous coronary intervention (PCI) should receive a combination of aspirin and a P2Y₁₂ inhibitor. Current guidelines prefer the potent

P2Y₁₂ inhibitors, such as prasugrel and ticagrelor which have a more rapid onset of action and higher potency and superiority in clinical outcomes than clopidogrel (8, 9).

The combination of dual antiplatelet therapy (DAPT) with GP IIb/IIIa inhibitors may increase the risk of bleeding in patients with ACS. Although major studies on prasugrel and ticagrelor have shown the relative efficacy of these potent P2Y₁₂ inhibitors, irrespective of the use of GP IIb/IIIa inhibitors; the efficacy and safety of GP IIb/IIIa inhibitors along with these P2Y₁₂ inhibitors have not been prospectively addressed (10, 11). Current guidelines recommend the use of GP IIb/IIIa inhibitors for “bail-

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Accepted Date: 13.04.2021 **Available Online Date:** 27.09.2021

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DOI:10.5152/AnatolJCardiol.2021.27974



HIGHLIGHTS

- Glycoprotein IIb/IIIa inhibitors can increase bleeding risk.
- We retrospectively compared bleeding complications in 224 patients with acute coronary syndrome given the conventional dose of tirofiban in addition to dual antiplatelet therapy.
- Bleeding complications, including fall in hemoglobin, hematoma, and gastrointestinal bleeding were similar between the ticagrelor/prasugrel and clopidogrel groups.
- Creatinine levels were associated with fall in hemoglobin ≥ 3 g/dL, whereas no relation was found between fall in hemoglobin ≥ 3 g/dL and the antiplatelet agent used.

out therapy” in patients with high thrombotic burden or complications, including slow flow or no-reflow (8, 9).

In this study, we aimed to investigate bleeding complications of different DAPTs with the concomitant use of tirofiban in patients with ACS undergoing PCI.

Methods

This retrospective study was approved by Marmara University Faculty of Medicine Research Ethics Committee, which waived the need for obtaining informed consent for the investigation and presentation of de-anonymized medical data. The investigation conforms with the principles outlined in the Declaration of Helsinki.

The patients were retrospectively selected from among patients with ACS who underwent primary PCI and were given GP IIb/IIIa inhibitors because of high thrombotic burden or slow coronary flow. The diagnosis of ACS was based on symptoms, electrocardiography, and cardiac markers. ST segment elevation myocardial infarction (STEMI) was defined as the presence of chest pain with persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block. Patients with chest pain during the previous 48 hours with ST-segment and T wave changes on electrocardiography indicating ischemia and a positive troponin test were grouped as non-ST elevation myocardial infarction (NSTEMI). After the exclusion of patients who were already using DAPT and those with atrial fibrillation, known bleeding diathesis, low platelet count ($< 100000/\text{mm}^3$), advanced hepatic or renal disease, and known active malignancy; 224 consecutive patients aged 18 or older with ACS were included in the study.

Management of the patients was in accordance with the current guidelines. Patients with STEMI were immediately transferred to coronary angiography laboratory for primary PCI. Patients with NSTEMI underwent coronary angiography

within 24 hours. All the patients were given standard medical therapy, including beta-blocking agents, angiotensin converting enzyme inhibitor, and statin unless there was a contraindication. All the patients were given conventional dose of tirofiban (25 $\mu\text{g}/\text{kg}$ per 3 minutes followed by an infusion of 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 24 hours) in addition to DAPT; which consisted of 300 mg aspirin, followed by 100 mg/day and 600 mg clopidogrel, followed by 75 mg/day or 180 mg ticagrelor, followed by 90 mg twice daily or 60 mg prasugrel, followed by 10 mg/day. Tirofiban bolus injection was administered in the cardiac catheterization laboratory owing to high thrombotic burden or slow coronary flow during PCI, and the tirofiban infusion was continued in the coronary care unit. In patients with STEMI, loading doses of P2Y₁₂ inhibitors were given immediately on the diagnosis of STEMI. However, in patients with NSTEMI, loading doses of P2Y₁₂ inhibitors were given in the cardiac catheterization laboratory after diagnostic coronary angiography and directly before PCI.

All the patients underwent careful physical examination; and blood samples, including cardiac markers (high sensitive troponin T and creatine kinase MB), hemogram, hematocrit, platelet, and creatinine were obtained on admission. Bedside echocardiographic examination was performed with a portable echocardiographic device equipped with a 2.5 Mhz phased-array transducer with harmonic capability. Left ventricular ejection fraction was assessed with transthoracic echocardiography using the Simpson method.

The primary endpoint of the study was any intra-hospital bleeding complication, including gastrointestinal bleeding or hematoma in the access site and significant fall in the hemoglobin level (accepted as ≥ 3 g/dL) (12).

Statistical analysis

All statistical tests were performed with a commercially available software program (Statistical Package for the Social Science version 20.0 for Windows, Chicago, IL, USA). All the continuous variables were checked for normal distribution by the Kolmogorov-Smirnov test and presented as mean \pm standard deviation, whereas categorical variables were expressed as numbers or percentages. The chi-squared test was used to compare categorical variables, and Student's t test or Mann-Whitney U test was used to compare continuous variables. Binary logistics regression analysis and linear regression analysis were performed to explore associations with fall in hemoglobin level. $P < 0.05$ was considered statistically significant.

Results

Two hundred and twenty four consecutive patients were retrospectively included in the study. The mean age of the patients was 56.6 ± 11.1 (range 31–85) years, and 193 (86.2%) patients were men. One hundred and seventy-four (77.7%) patients presented with STEMI, and 50 (22.3%) patients had NSTEMI. Of the patients, 115 were treated with ticagrelor (95 patients with STEMI, 20 with NSTEMI), 32 with prasugrel (30

Table 1. Characteristics and laboratory parameters of the patients

	Prasugrel/ticagrelor + tirofiban group (n=147)	Clopidogrel + tirofiban group (n=77)	P-value
Age (years)	53.7±9.8	62.2±11.4	<0.001
Male sex (n, %)	133 (90.5)	60 (77.9)	0.010
Hypertension (n, %)	39 (26.5)	36 (46.8)	0.002
Diabetes (n, %)	29 (19.7)	21 (27.3)	0.198
STEMI (n, %)	125 (85.0)	49 (63.6)	<0.001
Hemoglobin (g/dL)	14.3±1.5	13.7±1.5	0.004
Hematocrit (%)	43.2±4.2	41.5±4.6	0.008
Platelet (10 ³ /mm ³)	249.8±71.3	234.4±63.8	0.112
Creatinine (mg/dL)	0.95±0.34	1.04±0.62	0.190
Left ventricular ejection fraction (%)	45±10	48±9	0.562
Peak Troponin T Median (25 th to 75 th percentile)	502 (91–3440)	713 (250–2420)	0.509
Peak creatine kinase MB Median (25 th to 75 th percentile)	40 (8–115)	24 (10–101)	0.919
Radial access (n, %)	40 (27.2)	10 (13.0)	0.015

STEMI - ST segment elevation myocardial infarction

Table 2. Complications seen in patients

	Prasugrel/ticagrelor + tirofiban group (n=147)	Clopidogrel + tirofiban group (n=77)	P-value
Mean hemoglobin fall (g/dL)	1.27±1.03	1.30±0.92	0.834
Hemoglobin fall ≥3 g/dL (n, %)	11 (7.5)	2 (2.6)	0.228
Gastrointestinal bleeding (n, %)	2 (1.4)	0	0.547
Pericardial tamponade (n, %)	2 (1.4)	1 (1.3)	1.00
Hematoma at the access site (n, %)	3 (2.0)	2 (2.6)	1.00
Stent thrombosis (n, %)	2 (1.4)	0	0.547
Death (n, %)	1 (0.7)	1 (1.3)	1.00

patients with STEMI, 2 with NSTEMI), and 77 with clopidogrel (49 patients with STEMI, 28 with NSTEMI). The loading doses of P2Y₁₂ inhibitors were given immediately on the diagnosis of STEMI during transport to coronary angiography laboratory. The patients with NSTEMI underwent diagnostic coronary angiography within 70±42 minutes after diagnosis, and loading doses of P2Y₁₂ inhibitors were given in the cardiac catheterization laboratory after visualization of coronary anatomy directly before PCI. Transfemoral access was performed in 174 patients and radial access in 50. The characteristics and laboratory parameters of the patients are shown in Table 1.

The complications of the patients are shown in Table 2. There were no significant differences in hemoglobin fall ≥3 g/dL, gastrointestinal bleeding, pericardial tamponade, and hematoma at the access site between the groups. Of the 11 patients with hemoglobin fall ≥3 g/dL in the ticagrelor/prasugrel group, 10 were taking ticagrelor. Gastrointestinal bleeding and hematoma

at the access site and cardiac tamponade developed in patients using ticagrelor. Stent thrombosis was seen in two patients taking prasugrel. Two deaths occurred, one in the prasugrel and one in the clopidogrel groups.

The characteristics of the patients with hemoglobin fall ≥3 g/dL are shown in Table 3. The patients with a hemoglobin fall ≥3 g/dL had significantly higher creatinine levels, although there were no significant differences in age, sex, and frequencies of hypertension and diabetes. Binary logistics regression analysis revealed a significant relation between hemoglobin fall ≥3 g/dL and creatinine levels (p=0.032, odds ratio 2.189, 95% confidence interval 1.070–4.479) with no significant relation being observed between hemoglobin fall ≥3 g/dL and antiplatelet agent, age, hypertension, or diabetes (Table 4). Linear regression analysis revealed no significant association between the amount of hemoglobin fall and the type of antiplatelet agent used, age, sex, hypertension, or diabetes.

Table 3. Characteristics of the patients with hemoglobin fall ≥ 3 g/dL

	Patients with ≥ 3 g/dL hemoglobin fall (n=13)	Patients with < 3 g/dL hemoglobin fall (n=211)	P-value
Age (years)	56.0 \pm 10.5	56.6 \pm 11.2	0.851
Male sex (n, %)	13 (100)	180 (85.3)	0.223
Hypertension (n, %)	4 (30.8)	71 (33.6)	1.00
Diabetes (n, %)	2 (15.4)	48 (22.7)	0.738
STEMI (n, %)	12 (92.3)	162 (76.8)	0.307
Baseline hemoglobin (g/dL)	15.3 \pm 1.2	14.0 \pm 1.5	0.004
Baseline hematocrit (%)	45.7 \pm 3.8	42.4 \pm 4.4	0.009
Platelet ($10^3/mm^3$)	233.8 \pm 58.2	245.1 \pm 69.7	0.591
Creatinine (mg/dL)	1.32 \pm 0.91	0.96 \pm 0.40	0.005
Radial access (n, %)	2 (15.4)	48 (22.7)	0.738
Antiplatelet agent used (n, %)			
Clopidogrel	2 (15.4)	75 (35.5)	
Ticagrelor	10 (76.9)	105 (49.8)	0.163
Prasugrel	1 (7.7)	31 (14.7)	

STEMI - ST segment elevation myocardial infarction

Table 4. Binary logistics regression analysis for hemoglobin fall ≥ 3 g/dL

	OR	95% CI	P-value
Age	0.995	0.946–1.046	0.840
Hypertension	0.876	0.261–2.945	0.831
Diabetes	0.617	0.132–2.882	0.540
Creatinine	2.189	1.070–4.479	0.032
Clopidogrel use	0.330	0.071–1.527	0.156
Ticagrelor use	3.365	0.901–12.573	0.071
Prasugrel use	0.484	0.061–3.855	0.493

OR - odds ratio; CI - confidence interval

Discussion

In our study, we evaluated the bleeding complications in patients with ACS who were given tirofiban infusion because of high thrombotic burden or slow coronary flow in addition to DAPT and found that patients given prasugrel or ticagrelor had a similar rate of bleeding complications, including significant fall in hemoglobin, gastrointestinal bleeding, and hematoma at the access site compared with the patients given clopidogrel.

There are concerns regarding bleeding risk with concomitant use of GP IIb/IIIa inhibitors with fast-acting highly active oral P2Y₁₂ inhibitors, namely prasugrel and ticagrelor. In the subanalysis of TRITON-TIMI 38 and PLATO studies, the effect of GP IIb/IIIa inhibitors on the efficacy and safety of prasugrel and ticagrelor were compared with clopidogrel (11, 13). Similar to our study, in these studies, the use of a GP IIb/IIIa inhibitor was at the physician’s discretion. Prasugrel significantly reduced MI, urgent revascularization, and stent thrombo-

sis in patients with ACS irrespective of GP IIb/IIIa inhibitor use, whereas the patients treated with GP IIb/IIIa inhibitor had greater rates of bleeding. TIMI major or minor bleeding risk was not significantly different between prasugrel and clopidogrel, and the investigators concluded that GP IIb/IIIa inhibitor use did not accentuate the relative risk of bleeding with prasugrel compared with that with clopidogrel. However, the PLATO study showed a higher rate of minor/major bleeding with a lower rate of stent thrombosis with ticagrelor compared with that with clopidogrel when GP IIb/IIIa inhibitors were not used, and no change was observed in the efficacy and safety of ticagrelor with GP IIb/IIIa inhibitor use. Similar to these results, in our study, bleeding complications including hemoglobin fall ≥ 3 g/dL, gastrointestinal bleeding, hematoma at access site, and cardiac tamponade were mostly observed in patients taking ticagrelor, and stent thrombosis was seen in two patients taking prasugrel. However, the rates of bleeding complications or stent thrombosis were not statistically different between the groups. Although non-randomized use of P2Y₁₂ inhibitors and GP IIb/IIIa inhibitor might limit the value of our study, our results showed that the use of GP IIb/IIIa inhibitors for bailout therapy in patients with ACS who were given potent P2Y₁₂ inhibitors was relatively safe.

A recent review has also discussed the efficacy of GP IIb/IIIa inhibitors in limiting early ischemic complications against the risk of increased bleeding complications in the contemporary PCI era and suggested the use of GP IIb/IIIa inhibitors in selective cases, including bailout administration for peri-procedural thrombotic complications, pointing out the relative efficacy and safety of GP IIb/IIIa inhibitors, largely irrespective of the use of more effective antiplatelet agents and interventional techniques (14). Similarly, a meta-analysis of pivotal studies found similar bleeding risk with the combination of GP IIb/IIIa

inhibitor and potent P2Y₁₂ inhibitor compared to a combination with clopidogrel and proposed that GP IIb/IIIa inhibitor use was the main reason of the increased bleeding risk and not the oral antiplatelet regimen (15). In our study, bleeding complications were less frequently observed compared with the mentioned studies, which might be explained by the non-randomized use of P2Y₁₂ inhibitors and GP IIb/IIIa inhibitor in our study as tirofiban or potent antiplatelet agents might not be preferred in patients with a high bleeding risk. However, our study suggested that concomitant use of tirofiban did not increase bleeding risk when used with ticagrelor or prasugrel or when used with clopidogrel, which were chosen according to patient comorbidities and bleeding risk. However, clopidogrel seems to be preferred more when tirofiban is to be administered. A recent meta-analysis, which recommended intracoronary administration of tirofiban combined with other conventional therapies as a valid option to prevent no-reflow, included 13 studies, all of which used clopidogrel and aspirin as oral DPAT (16).

The timing of P2Y₁₂ inhibitors loading may affect bleeding complications in patients who will also receive GP IIb/IIIa inhibitors. Pre-treatment with loading doses of P2Y₁₂ inhibitors given before diagnostic coronary angiography to patients with NSTEMI is associated with higher bleeding risk. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (17) showed that pre-treatment with ticagrelor, prasugrel, and clopidogrel was associated with a significantly increased risk of bleeding events, although there were no improved ischemic outcomes. Similarly, a prasugrel-based strategy with deferred loading after the coronary anatomy is known in patients with NSTEMI was found superior to a ticagrelor-based strategy that implied a routine pre-treatment strategy (18). Therefore, administering routine pre-treatment with a P2Y₁₂ inhibitor in patients with NSTEMI in whom coronary anatomy is not known, and an early invasive management is planned is not recommended. In our study, the loading doses of P2Y₁₂ inhibitors were given after diagnostic coronary angiography as early invasive management was planned in these patients. However, in patients with STEMI, the loading doses of P2Y₁₂ inhibitors were given immediately after the diagnosis of STEMI as early initiation of a P2Y₁₂ inhibitor is recommended in the guidelines (8). The time between the loading of P2Y₁₂ inhibitors and tirofiban infusion might have affected bleeding complications in our study. However, owing to the lack of exact timing between the loading of P2Y₁₂ inhibitors and tirofiban infusion, we could not evaluate the association of timing of P2Y₁₂ inhibitors loading on tirofiban associated bleeding complications.

Access site might be an important factor in evaluating bleeding complications. Hematoma at access site is a more common problem with femoral access (19). In our study, hematoma at the access site was noted in five patients, and femoral access was used in all these patients. Although the frequency of radial access was higher in prasugrel/ticagrelor group than in the clopidogrel group, there was no significant relation between the antiplatelet agent used and hematoma at access site. Similarly, the frequency of radial access was similar between the patients with and without significant hemoglobin fall.

Bleeding has been shown as the strongest associate of early mortality after PCI (20). Therefore, it is crucial to assess the factors associated with bleeding risk. As advanced age (21) and female sex (22) are associated with increased bleeding risk, primary physicians of these patients might prefer clopidogrel, which could explain the significant differences in age and male sex between the prasugrel/ticagrelor and clopidogrel groups. However, there was no correlation between hemoglobin fall ≥ 3 g/dL and age, sex, or antiplatelet agent used. Only creatinine levels were significantly associated with hemoglobin fall ≥ 3 g/dL. Abnormal renal function is associated with increased risk of bleeding and is included in the HAS-BLED bleeding score. Renal dysfunction is present in approximately 30%–40% of patients with ACS and is associated with a worse prognosis and increased risk of in-hospital complications (23). Patients with ACS with renal dysfunction were shown to receive excess dosing with is recommended to reduce the infusion rate of tirofiban by 50% (from 0.1 to 0.05 mg/kg/min) in patients with stage IV chronic kidney disease (eGFR 15–29 mL/min/1.73 m²). Although no patients in our study had stage IV chronic kidney disease and needed reduced tirofiban infusion rates, we found positive relation between creatinine levels and the risk of bleeding (24).

Study limitations

The major limitations of our study were the small sample size, retrospective design, and being a single center study. Another limitation was the non-randomized use of P2Y₁₂ inhibitors and GP IIb/IIIa inhibitor with a risk of unassessed confounding factors. Because of the non-randomized design, the clopidogrel and ticagrelor/prasugrel groups differed in age and sex. Although potent P2Y₁₂ inhibitors were preferred in patients with ACS at our center, clopidogrel might be preferred in patients with high bleeding risk, which might result in less bleeding complications than those in the TRITON-TIMI 38 and PLATO studies. Similarly, although GP IIb/IIIa inhibitor use was based on the current guidelines, the primary physician of the patients might decline the use of tirofiban in some patients owing to the high risk of bleeding. As only tirofiban was available in our hospital, our results could not be attributable to other types of GP IIb/IIIa inhibitor use. The time between the loading of P2Y₁₂ inhibitors and tirofiban infusion may affect the bleeding complications. We could not evaluate such an association in our study because of the lack of exact timing between the administration of loading of P2Y₁₂ inhibitors and tirofiban infusion. We evaluated the bleeding complications developed within the hospitalization and did not have the one-month or longer term follow-up data.

Conclusion

Despite concerns of higher major bleeding risk with a combination of GP IIb/IIIa inhibitor and oral P2Y₁₂ inhibitors, our study showed that in patients with ACS given tirofiban infusion, the bleeding complications including significant fall in hemoglobin levels were similar between patients using ticagrelor/prasugrel and clopidogrel. However, close monitoring for bleeding risk is recommended, especially in patients with higher creatinine levels.

Ethical standards statement: All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 and as revised in 2008.

Statement of informed consent: Informed consent was not obtained from the patients owing to the retrospective design of the study.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – M.K.T., N.S., B.Ö.; Design – M.K.T., N.S., B.Ö.; Supervision – M.K.T., N.S., B.Ö.; Fundings – None; Materials – M.K.T., M.H.Ö., A.Ç., E.G., M.S., A.Ş., T.G., Z.D.; Data collection &/or processing – M.K.T., M.H.Ö., A.Ç., E.G., M.S., A.Ş., T.G., Z.D.; Analysis &/or interpretation – M.K.T., A.Ş., T.G., Z.D., N.S., B.Ö.; Literature search – M.K.T., M.H.Ö., A.Ç., E.G., M.S., A.Ş., T.G., Z.D.; Writing – M.H.Ö., N.S., B.Ö.; Critical review – M.K.T., A.Ç., E.G., M.S., N.S., B.Ö.

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