Original Article

Safety of Eptifibatide in Addition to Ticagrelor in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

Fatemeh Baharvand[1], Zeinab Hasani[1], Seifollah Jafari[2], Mohammad Ali Esfandiar[3,4], Arsalan Salari[1], Motahare Hatami[5], Hamed Vahidi[6], Niloofar Akbari Parsa[7], Mahboobeh Gholipour[7]*

[1] Department of Cardiology, Cardiovascular Diseases Research Center, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
[2] Department of Neurosurgery, Road Trauma Research Cenrer, Poursina hospital, School of Medicine, Guilan university of Medical Sciences, Rasht, Iran.
[3] Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
[4] Student Research Committee, Virtual School of Medical Education and Management, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[5] Tehran Heart Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran.
[6] Cardiology Department, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
[7] Department of Cardiology, Healthy Heart Research Center, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.

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Highlights

- In STEMI patients undergoing PCI, ticagrelor-based TAPT (with aspirin and eptifibatide) demonstrates significantly increased bleeding risk compared with clopidogrel-based TAPT.
- The ticagrelor group showed significantly higher rates of minor bleeding events, including gastrointestinal bleeding, hematuria, and epistaxis.
- No significant differences were observed between the groups in either major bleeding or procedure-related bleeding complications.

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* **Corresponding Author:**
Mahboobeh Gholipour
Department of Cardiology, Healthy Heart Research Center, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
Tel: +981333664282
E-mail: drmgholipur@gmail.com

ABSTRACT

Background: Primary percutaneous coronary intervention (PCI) is the gold-standard treatment for patients with ST-segment elevation myocardial infarction (STEMI). In some cases, glycoprotein IIb/IIIa inhibitors, considered part of triple antiplatelet therapy (TAPT), are administered. Most trials investigating the role of glycoprotein IIb/IIIa inhibitors in STEMI were conducted before the era of potent P2Y12 receptor inhibitors. It is, thus, reasonable to reevaluate the safety of eptifibatide, a widely used glycoprotein IIb/IIIa inhibitor, in patients treated with the latest generation of P2Y12 receptor inhibitors such as ticagrelor.

Methods: This cross-sectional study involved STEMI patients who underwent primary PCI and required adjunctive eptifibatide therapy during the procedure at Dr. Heshmat Educational and Remedial Center in Rasht, Iran, between December 22, 2021, and June 22, 2022. Patients were stratified into two groups according to their administered P2Y12 receptor inhibitor. All patients received eptifibatide, and its safety when used concomitantly with ticagrelor was assessed.

Results: The study included 241 patients with a mean age of 57.72 (SD:11.55) years. Procedure-related bleeding showed no significant difference between the groups (P=0.641), and no major bleeding events occurred in either group. Gastrointestinal bleeding and epistaxis rates were significantly higher in the ticagrelor-based TAPT group than in the clopidogrel-based group (P=0.033 and P=0.013, respectively). Among male patients, genitourinary bleeding was significantly more frequent in the ticagrelor-based TAPT subgroup than in the clopidogrel-based subgroup (P=0.035).

Conclusions: In STEMI patients undergoing primary PCI, ticagrelor-based TAPT is associated with a higher risk of minor bleeding than clopidogrel. Nevertheless, given its established clinical advantages over clopidogrel, ticagrelor should not be withheld from eligible STEMI patients. The decision to prescribe ticagrelor should remain at the interventionist's discretion, with careful consideration of individual benefit-risk profiles.

Keywords: ST-segment Elevation Myocardial Infarction; Percutaneous Coronary Intervention; Ticagrelor; Eptifibatide; Clopidogrel; STEMI

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) remains a leading cause of mortality worldwide, occurring when transmural myocardial ischemia leads to myocardial damage or necrosis.[1-3] Primary percutaneous coronary intervention (PCI) serves as the preferred treatment to restore coronary blood flow in STEMI patients.[4] Current guidelines emphasize that adjunctive antiplatelet therapy is essential for preventing ischemic events in acute MI. 5 Consequently, the combination of primary PCI with antiplatelet medications represents the optimal treatment strategy for STEMI.[6,7]

Achieving rapid and effective platelet inhibition represents a critical therapeutic objective in STEMI. Current standards for acute coronary syndrome (ACS), particularly in PCI-treated patients, involve dual antiplatelet therapy combining aspirin with P2Y12 receptor inhibitors.[8,9] Prior to 2018, clopidogrel served as the primary P2Y12 inhibitor, yet its variable response at standard dosing remains controversial in interventional cardiology, particularly for ACS.[10] This prodrug requires sequential hepatic metabolism, including cytochrome P450-dependent conversion, for activation, which results in delayed onset and suboptimal efficacy.[11,12] Studies have indicated reduced clopidogrel metabolic efficacy in Asian populations due to cytochrome P450 allele polymorphisms.[13] Reflecting this evidence, current guidelines strongly recommend potent P2Y12 inhibitors (ticagrelor or prasugrel) over clopidogrel for ACS management (Class I, Level of Evidence A).[14,15] Ticagrelor provides distinct pharmacological advantages as a direct-acting agent that bypasses hepatic activation, leading to a faster onset of action (30 minutes vs. 2 hours for clopidogrel), more potent platelet inhibition (80–90% vs. 40–50%), and greater effect stability.[16,17] These properties contribute to its demonstrated superiority over clopidogrel in improving cardiovascular outcomes in clinical trials.[18]

Glycoprotein IIb/IIIa inhibitors offer rapid platelet inactivation and reduced thrombotic risk in STEMI. Current evidence does not support routine pre-PCI administration due to a lack of clinical benefit and increased bleeding risk.[19,20] Be that as it may, glycoprotein IIb/IIIa inhibitors remain valuable as bailout therapy for procedural complications such as no-reflow phenomenon, slow coronary flow, or acute thrombotic events during primary PCI.[21,22] While novel P2Y12 inhibitors (with aspirin) are preferred over clopidogrel in STEMI patients undergoing primary PCI,[23] glycoprotein IIb/IIIa inhibitors retain a niche role in managing these high-risk scenarios.[21,22]

Notably, the efficacy and safety profile of triple antiplatelet therapy (TAPT) combining ticagrelor, aspirin, and glycoprotein IIb/IIIa inhibitors versus clopidogrel-based TAPT in primary PCI remains undefined. Given this evidence gap and the critical importance of bleeding risk assessment, we designed the present study to compare the safety profiles of ticagrelor-based versus clopidogrel-based TAPT in STEMI patients undergoing primary PCI.

Methods

This cross-sectional study was conducted from December 2021 through June 2022 and included STEMI patients undergoing primary PCI with coronary stenting who required glycoprotein IIb/IIIa inhibitors as rescue therapy for procedural complications (slow-flow, no-reflow, or thrombotic complications). Exclusion criteria included a history of anticoagulant or fibrinolytic drug use, bleeding disorders, second- or third-degree heart block, atrial fibrillation, prosthetic valve implantation, chronic kidney disease, and thrombocytopenia.

Data were collected using a standardized checklist documenting demographic characteristics, medical history, physical examination findings, and myocardial infarction type. Anthropometric measurements were obtained using calibrated instruments (Seca, Germany), with weight measured to the nearest 0.1 kg and height to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Patients were stratified into two treatment groups according to their administered P2Y12 receptor inhibitor: (1) clopidogrel (600 mg loading dose in the emergency department, followed by 75 mg daily maintenance) or (2) ticagrelor (180 mg loading dose, followed by 90 mg twice daily).

All patients received standardized eptifibatide therapy as bailout treatment (two 180 µg/kg bolus

doses administered 10 minutes apart, followed by continuous infusion of 2 µg/kg/min for 12 hours). The safety assessment compared in-hospital major and minor bleeding risks between the groups during the immediate postprocedural period.

All patients received identical aspirin therapy (325 mg loading dose administered immediately, followed by 80 mg daily maintenance). Following initial treatment, patients were transferred to the cardiac catheterization laboratory for primary PCI. Per protocol, all participants received weight-adjusted unfractionated heparin (70 U/kg bolus) at procedure initiation.

We categorized bleeding events using modified PLATO bleeding criteria 24 into three classifications: (1) major bleeding: hemoglobin decline > 3 g/dL, requirement of ≥ 2 units packed red blood cell transfusion, intracranial/intraocular / retroperitoneal hemorrhage, or fatal bleeding; (2) procedure-related bleeding: access site complications (hematoma or active bleeding at catheter insertion site); and (3) minor bleeding: all other clinically significant bleeding events. The cohort comprised 241 patients, with 72 (29.8%) undergoing radial access and 169 (70.2%) femoral access for angiography, as determined by operator preference. All bleeding events were monitored and documented throughout the hospitalization period (3-5 days post-procedure).

Statistical analysis

An appropriate formula for logistic regression was used with PASS11 software to estimate the sample size. Accordingly, considering a risk ratio of 2.46, a statistical power of 0.80, and an alpha of 0.5, a sample size of 62 patients per group was calculated. Nonetheless, due to the high number of patients referred, the study was conducted with a larger sample size to increase its accuracy.

In this study, categorical variables were presented as frequencies (percentages), and uantitative variables were presented as mean (SD) values. Shapiro-Wilk or Kolmogorov-Smirnov tests were employed to assess data normality. Levene's test was also utilized to assess the homogeneity of variances. An independent t-test (for normally distributed variables) and the Mann-Whitney U test (for non-normally distributed variables) were used for quantitative variables. The chi-square test (for normally distributed variables) and Fisher's exact test (for non-normally distributed variables) were drawn upon for qualitative variables. Data were analyzed using IBM SPSS Statistics, version 27. The significance level was set at $P<0.05$.

Results

A total of 241 patients who met the inclusion and exclusion criteria entered the study (from December 22, 2021, through June 22, 2022, at Dr. Heshmat Educational and Remedial Center, Rasht, Iran). Among these patients, 123 were in the clopidogrel group, and 118 were in the ticagrelor group. The baseline characteristics of the patients are shown in Table 1. The mean (SD) age of the study population was 57.72 (11.55) years; 82.2% were male and 17.8% were female. The mean (SD) BMI was 25.53 (3.68) kg/m², and 45.4% were smokers. Of the patients, 31.7% had hypertension and 28.3% had diabetes mellitus.

Comparison of demographic and clinical characteristics between the two groups

There was a significant difference in sex between the two groups (P=0.019). The number of females was higher in the ticagrelor-based TAPT group. There were no significant differences in age, BMI, hypertension, diabetes mellitus, or smoking status between the two groups (Table 1) .

Table 1. Baseline characteristics of the study population

Variables	Total	Clopidogrel-Based TAPT	Ticagrelor-Based TAPT	P-value
Age (y)	57.72 (11.55)	56.84 (10.89)	58.64 (12.25)	0.232*
Male (%)	82.2	87.8	76.3	0.019#
BMI (kg/m^2)	25.53 (3.68)	25.74 (3.88)	25.32 (3.48)	0.382*
HTN (%)	31.7	32.8	41.5	0.161#
DM (%)	28.3	23	33.9	0.06#
Smoking (%)	45.4	42.6	48.3	0.377#

Values are presented as mean (standard deviation) or as percentages.
clopidogrel-based TAPT: patients receiving aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitor (n=123), ticagrelor-based TAPT: patients receiving aspirin, ticagrelor, and glycoprotein IIb/IIIa inhibitor (n=118), BMI: body mass index, HTN: hypertension, DM: diabetes mellitus
P-values are the result of comparing the two study groups.
*: based on the independent samples test, #: based on Pearson's chi-square test

Comparison of bleeding complications between the two groups

Procedural bleeding rates showed no significant difference between the groups (P=0.641) (Table 2). Neither group experienced major bleeding events. Minor bleeding manifestations included three distinct types: gastrointestinal bleeding, genitourinary bleeding (hematuria), and epistaxis. Comparative analysis revealed significantly higher incidence rates in the ticagrelor-based TAPT group versus clopidogrel-based TAPT for both gastrointestinal bleeding (P=0.033) and epistaxis (P=0.013). Gender-stratified analysis demonstrated significantly increased hematuria among male patients receiving ticagrelor-based TAPT compared with clopidogrel-based TAPT (P=0.035). The ticagrelor group exhibited substantially higher rates of non-procedural bleeding overall (24 vs. 5 patients; P<0.001) (Table 2) (Figure 1).

Table 2. Determination and comparison of bleeding complications between the two study groups

Type of Bleeding		Sex	Clopidogrel-Based TAPT (n = 123)	Ticagrelor-Based TAPT (n = 118)	P-value*
Bleeding Related to the Procedure		Male	14 (13.1%)	13 (14.4%)	0.782
		Female	4 (25%)	7 (25%)	0.999
		Total	18 (14.8%)	20 (16.9%)	0.641
Major Bleeding		Male	0 (0%)	0 (0%)	
		Female	0 (0%)	0 (0%)	
		Total	0 (0%)	0 (0%)	
Minor Bleeding	gastrointestinal bleeding	Male	1 (0.9%)	6 (6.7%)	0.049
		Female	0 (0%)	1 (3.6%)	0.999
		Total	1 (0.8%)	7 (5.9%)	0.033
	genitourinary bleeding (hematuria)	Male	3 (2.8%)	9 (10%)	0.035
		Female	1 (6.7%)	2 (7.1%)	0.999
		Total	4 (3.3%)	11 (9.3%)	0.053
	epistaxis	Male	0 (0%)	5 (5.6%)	0.019
		Female	0 (0%)	1 (3.6%)	0.999
		Total	0 (0%)	6 (5.1%)	0.013

Values are presented as counts (percentages).
clopidogrel-based TAPT: patients receiving aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitor (n=123), ticagrelor-based TAPT: patients receiving aspirin, ticagrelor, and glycoprotein IIb/IIIa inhibitor (n=118)
*: Pearson's chi-square test

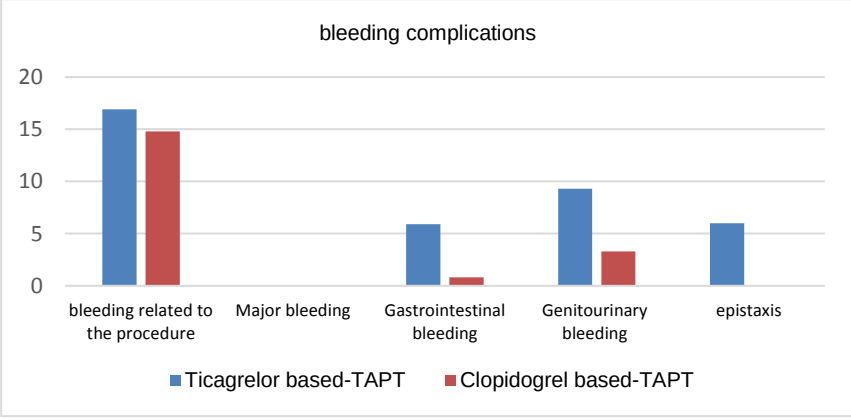

Figure 1. Comparison of bleeding complications between the two study groups. Values are presented as percentages; clopidogrel-based TAPT: patients receiving aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitor (n=123), ticagrelor-based TAPT: patients receiving aspirin, ticagrelor, and glycoprotein IIb/IIIa inhibitor (n=118). P-values are 0.641 for procedure-related bleeding, 0.033 for gastrointestinal bleeding, 0.053 for genitourinary bleeding, and 0.013 for epistaxis.

Discussion

This study compared the safety of TAPT with ticagrelor as the P2Y12 inhibitor versus clopidogrel-based TAPT in patients with STEMI undergoing primary PCI. We found that more patients in the ticagrelor group experienced procedure-unrelated bleeding than those in the clopidogrel group. There was no significant difference in procedure-related bleeding between the two groups. Overall, our results indicate that, for STEMI patients undergoing PCI, TAPT with

ticagrelor in combination with aspirin and eptifibatide may significantly increase the risk of bleeding events compared with clopidogrel-based TAPT.

The efficacy and safety of clopidogrel and newer, potent P2Y12 receptor inhibitors for patients with coronary artery disease have been compared previously in several studies. A meta-analysis by Tang et al.[25] reported that oral P2Y12 inhibitors significantly reduced the rate of ischemic events without causing a significant increase in major bleeding events in patients with coronary heart disease. Another meta-analysis comparing novel P2Y12 inhibitors with clopidogrel in non-ST-segment elevation ACS patients concluded that although novel P2Y12 inhibitors were associated with a decrease in the rate of major adverse cardiovascular events, they could significantly increase the risk of major and minor bleeding events.[26] On the other hand, Rafique et al.,[23] Serebruany et al.,[27] and Sun et al.,[28] in three different meta-analyses, reported that prasugrel and ticagrelor more effectively reduced the risk of major adverse cardiovascular events than clopidogrel in STEMI patients, with similar rates of bleeding events. A meta-analysis by Xie et al.[29] reported that ticagrelor and clopidogrel had similar efficacy, but ticagrelor dramatically increased the risk of bleeding events.

While current evidence strongly favors novel P2Y12 inhibitors (with aspirin) over clopidogrel-based dual therapy in STEMI patients undergoing primary PCI,[23] the safety and efficacy profile of ticagrelor-based TAPT, combining ticagrelor, aspirin, and glycoprotein IIb/IIIa inhibitors, remains incompletely characterized. A meta-analysis by Wang et al.[30] incorporating seven randomized controlled trials demonstrated that ticagrelor, or prasugrel-based TAPT significantly reduced major adverse cardiovascular events compared with clopidogrel-based TAPT in this population, with comparable bleeding risk between groups. These findings chime with another study showing equivalent bleeding rates between ticagrelor- and clopidogrel-based TAPT in ACS patients undergoing early PCI.[31]

In contrast to these studies,[30,31] our analysis demonstrated an increased risk of minor bleeding with ticagrelor-based TAPT compared with clopidogrel-based TAPT. This discrepancy may reflect our shorter follow-up duration or variations in glycoprotein IIb/IIIa inhibitor selection across studies. In agreement with our safety concerns, Tigen et al.[32] emphasized the need for close bleeding risk monitoring in such patients.

Xie et al.[33] concluded that in ACS patients using a glycoprotein IIb/IIIa inhibitor, ticagrelor increased the risk of major bleeding compared with clopidogrel. Tavenier et al. [34] also demonstrated that using ticagrelor and a glycoprotein IIb/IIIa inhibitor in a bailout situation increased the risk of major bleeding in STEMI patients who underwent primary PCI. In contrast to these studies, no major bleeding was observed in the present study.

Our study specifically evaluated three categories of minor bleeding: gastrointestinal bleeding, epistaxis, and hematuria. The ticagrelor-based TAPT group demonstrated significantly higher rates of both gastrointestinal bleeding and epistaxis than the clopidogrel-based group. Notably, male patients receiving ticagrelor-based TAPT exhibited increased hematuria incidence versus their clopidogrel-treated counterparts. This observed bleeding pattern may reflect ticagrelor's pharmacodynamic profile as a more potent, rapid-onset, and consistent platelet inhibitor compared with clopidogrel.[35]

Contrasting with our findings, Yuichi et al. [31] proposed that while ticagrelor monotherapy increased bleeding risk versus clopidogrel, concomitant glycoprotein IIb/IIIa inhibitor administration might equalize this differential through maximal platelet inhibition. Our results diverge from this hypothesis, suggesting the bleeding risk disparity between ticagrelor and clopidogrel persists even in the TAPT setting.

Nevertheless, our study has several limitations that should be considered. First, the current cross-sectional study had a small sample size and included a higher proportion of males than females. Thus, more randomized clinical trials with larger sample sizes are needed. Another limitation was the infrequent use of the transradial approach. Finally, most of our patients were within the normal BMI range, and our study included few patients with

BMIs at the extremes (high or low). It is suggested that this group of patients be considered in future studies.

With the use of potent antiplatelet agents such as ticagrelor, thrombotic complications and, consequently, the need for glycoprotein IIb/IIIa inhibitors during PCI have been substantially decreased. On the other hand, ticagrelor has proven benefits over clopidogrel,[12] and STEMI patients should not be deprived of these benefits. Therefore, drug prescriptions should be based on current evidence and the latest practice guidelines.

Different criteria exist to assess bleeding, such as the TIMI bleeding criteria or the PLATO bleeding criteria. Applying these criteria in future studies may facilitate more standardized comparisons of bleeding rates between the two drugs.

Conclusion

In STEMI patients undergoing primary PCI, ticagrelor-based TAPT demonstrates significantly higher risks of minor bleeding complications (gastrointestinal bleeding, hematuria, and epistaxis) than clopidogrel-based TAPT. Still, given ticagrelor's established therapeutic advantages, clinicians should not withhold its use in eligible STEMI patients. The optimal antiplatelet regimen should be individualized, with interventionists carefully weighing each patient's bleeding risk against potential cardiovascular benefits when selecting therapy.

Declarations:
Ethical Approval

The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (Approval Code: IR.GUMS.REC.1400.504; Date: May 8, 2021). Written informed consent was obtained from all participants after full explanation of study procedures and potential risks.

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Conflict of Interest

All the authors declare that they have no competing interests relevant to this study.

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