ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

In-Hospital Bleeding and Mortality in Acute Coronary Syndrome Patients Treated with Tirofiban and Potent P2Y12 Inhibitors

Tirofiban ve Güçlü P2Y12 İnhibitörleri ile Tedavi Edilen Akut Koroner Sendrom Hastalarında Hastane İçi Kanama ve Mortalite

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: In this study, we aimed to determine whether potent agents affect in-hospital bleeding and mortality compared to clopidogrel in patients with the acute coronary syndrome in whom tirofiban and P2Y12 inhibitor are used together.

Methods: Patients who were treated interventionally between 2015 and 2020 and were using tirofiban were retrospectively screened. Clinical, laboratory, and angiographic findings were obtained from the hospital database. Patients were analyzed by dividing them into clopidogrel and prasugrel/ticagrelor groups.

Results: Acute coronary syndrome patients (n = 227) who were treated interventionally were included in this retrospective study. Clopidogrel was given to 93 (41%), ticagrelor to 112 (49.3%), and prasugrel to 22 of the patients (9.7%). Compared to the ticagrelor/prasugrel group, the clopidogrel group was older and more were women, and the history of hypertension and previous coronary artery disease was higher (*P*, respectively: <.001; .001; .008; .0045). The creatinine value was higher, the basal hemoglobin was lower, and the GRACE (Global Registry of Acute Coronary Events) and CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) scores were higher (*P*, respectively: .026; .002; .002; <.001). The in-hospital bleeding rate was significantly higher in the clopidogrel group ($P < .001$). Although the in-hospital mortality rate was higher, it was not statistically significant ($P = .07$). Regression analysis showed that GRACE score and gender were associated with in-hospital mortality ($P < .001$; $P = .031$, respectively), and only age was associated with in-hospital bleeding ($P < .001$). No relationship was found with P2Y12 inhibitor.

Conclusion: In our study, we found that the combined use of potent P2Y12 inhibitor with tirofiban in acute coronary syndrome patients treated interventionally was not different from the use of clopidogrel in terms of in-hospital bleeding and mortality.

Keywords: Acute coronary syndrome, bleeding, mortality, p2y12 receptor antagonist, tirofiban

ÖZET

Amaç: Bu çalışmada, merkezimizde tirofiban ve P2Y12 inhibitörünün (P2Y12i) birlikte kullanıldığı akut koroner sendromlu (AKS) hastalarda güçlü ajanların klopidogrel ile karşılaştırıldığında hastane içi kanamayı ve mortaliteyi etkileyip etkilemediğini belirlemeyi amaçladık.

Yöntemler: 2015-2020 yılları arasında girişimsel olarak tedavi edilen ve tirofiban kullanan hastalar geriye dönük olarak tarandı. Klinik, laboratuvar ve anjiyografik bulgular hastane veri tabanından elde edildi. Hastalar klopidogrel ve prasugrel/tikagrelor gruplarına ayrılarak analiz edildi.

Bulgular: Bu retrospektif çalışmaya girişimsel olarak tedavi edilen 227 AKS hastası dahil edildi. Hastaların 93'üne (%41) klopidogrel, 112'sine (%49,3) tikagrelor ve 22'sine (%9,7) prasugrel verildi. Tikagrelor/prasugrel grubu ile karşılaştırıldığında, klopidogrel grubu daha yaşlıydı, kadın oranı daha yüksekti ve hipertansiyon ve koroner arter hastalığı öyküsü daha yüksekti (*P*, sırasıyla: <,001; ,001; ,008; ,0045). Kreatinin değeri daha yüksek, bazal hemoglobin daha düşük ve GRACE ve CRUSADE skorları daha yüksekti (*P*, sırasıyla: ,026; ,002; ,002; <,001). Hastane içi kanama oranı klopidogrel grubunda anlamlı olarak daha yüksekti ($P < ,001$). Hastane içi ölüm oranı daha yüksek olmasına rağmen istatistiksel olarak anlamlı değildi ($P = ,07$). Regresyon analizi, GRACE skoru ve cinsiyetin hastane içi mortalite ile ilişkili olduğunu (*P*, sırasıyla <,001; ,031) ve sadece yaşın hastane içi kanama ile ilişkili olduğunu ($P < ,001$) gösterdi. P2Y12i ile ilişki bulunamadı.

Sinan Akıncı, M.D.[1]
Ali Çoner, M.D.[1]
Ertan Akbay, M.D.[1]
Adem Adar, M.D.[1]
Haldun Müderrisoğlu, M.D.[2]

[1]*Department of Cardiology, Başkent University School of Medicine, Alanya Application and Research Center, Antalya, Turkey*
[2]*Department of Cardiology, Başkent University School of Medicine, Ankara, Turkey*

Corresponding author:
Sinan Akıncı
✉ akincisinan@gmail.com

Received: December 20, 2021
Accepted: April 14, 2022

Cite this article as: Akıncı S, Çoner A, Akbay E, Adar A, Müderrisoğlu H. In-hospital bleeding and mortality in acute coronary syndrome patients treated with tirofiban and potent P2Y12 inhibitors. *Turk Kardiyol Dern Ars.* 2022;50(5):320-326.

DOI:10.5543/tkda.2022.21311

Sonuç: Çalışmamızda girişimsel olarak tedavi edilen ACS hastalarında potent P2Y12i lerin tirofiban ile kombine kullanımının hastane içi kanama ve mortailte açısından klopidogrel ile kullanıma göre farklı olmadığını saptadık.

Anahtar Kelimeler: Akut koroner sendrom, kanama, mortalite, p2Y12 reseptör antangonist, tirofiban

Platelet activity has an important role in the pathogenesis of acute coronary syndromes (ACS). Therefore, antiplatelet therapies are used extensively in the treatment of ACS.[1] These agents are effective in dissolving thrombotic material and preventing thrombus formation after interventional therapies. However, intensive use of these treatments creates a risk of bleeding, and insufficient use causes a decrease in the success of the procedure and recurrent ischemic events.[2]

Aspirin, clopidogrel and GpIIb/IIIa inhibitors (GPI) have been used for a long time in ACS. It has been shown that adding tirofiban to the standard treatment in ACS without ST elevation significantly reduces the outcome of death and myocardial infarction (MI).[3] However, after the widespread use of interventional treatments, the routine use of GPIs was abandoned and the guidelines recommended their bailout use only in cases of heavy thrombus load or no-reflow during the intervention.[4]

After interventional treatments, the use of aspirin and a P2Y12 inhibitor (P2Y12i), clopidogrel, was found to be significantly superior to placebo in preventing ischemic events.[5] Later, the use of aspirin and clopidogrel became standard in interventional treatments. However, new antiplatelet agents were needed due to the slow emergence of the efficacy of clopidogrel and the observation of clopidogrel resistance in some patients.[6] In the following years, P2Y12i's with potent antiplatelet effects have emerged. It was observed that ticagrelor and prasugrel significantly reduced the risk of cardiovascular death, MI, and stent thrombosis compared to clopidogrel, but they caused a slight increase in major bleeding.[7,8] These agents have taken their place in the guidelines and their use is recommended over clopidogrel in the treatment of ACS.[4]

Combined use of potent P2Y12i and GPIs may cause an increase in the risk of bleeding, but in subgroup analyses of large studies, these agents did not cause an increase in bleeding compared to clopidogrel when used together with GPIs.[9,10] In this study, we aimed to examine the effects of using different P12Y12is together with tirofiban, a GPI, on in-hospital mortality and bleeding rates in patients undergoing interventional treatment for ACS, using real-life data from our center.

ABBREVIATIONS

ACS	Acute coronary syndrome
BP	Blood preesure
CAD	Coronary artery disease
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines
EF	Ejection fraction
GPI	Glycoprotein IIb/IIIa inhibitor
GRACE	Global Registry of Acute Coronary Events
NSTEMI	Non-ST elevated myocardial infarction
P2Y12i	P2Y12 inhibitor
PLATO	PLATelet inhibition and patient Outcomes
STEMI	ST-elevated myocardial infarction
TRITON-TIMI	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
USAP	Unstable angina pectoris

Methods

The records of Başkent University Alanya Application and Research Center patient database were retrospectively scanned. Patients with insufficient records and missing follow-up data were excluded from the study. A total of 227 patients with ACS who were treated with tirofiban and underwent interventional therapy between 2015 and 2020 were included in the study. Myocardial infarction was defined as the presence of at least one of the criteria for myocardial ischemia-related symptoms, ischemic electrocardiogram changes, or demonstration of myocardial damage by imaging methods, together with elevated troponin. Unstable angina pectoris was defined as myocardial ischemia findings at rest or with minimal effort, without troponin elevation.

Coronary angiography and interventional procedures of all patients were performed on a 7F sheath placed through the femoral artery. Coronary interventions of all patients were performed in the same session with coronary imaging. During the procedure, patients were given unfractionated heparin at a dose of 50-70 IU/kg. Before or during the procedure, prasugrel was given 10 mg once daily after a 60 mg loading dose, ticagrelor 90 mg twice daily after a 180 mg loading dose, and clopidogrel 75 mg once daily after a 600 mg loading dose. According to our clinical protocols, patients were given 25 µg/kg of tirofiban as a loading dose and intravenous (IV) infusion was given at a dose of 0.15 µg/kg/min after loading, and the tirofiban infusion dose was halved in patients with GFR less than 60 mL/min. If tirofiban was started during the procedure, the loading dose was administered intracoronally. If tirofiban was started before the patient was taken to the catheter laboratory, it was classified as pretreatment, and if it was used during the procedure in conditions such as heavy thrombus load, slow-flow, or no-reflow, it was classified as bailout use.

Demographic findings, medical histories, physical examination findings, hemogram, biochemical parameters, and echocardiographic findings were obtained from the records of the patients at the time of admission. Using the data obtained, the GRACE (Global Registry of Acute Coronary Events) ACS and CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) risk scores of all patients were calculated.[11,12] All bleeding events that caused hemodynamic deterioration, were life-threatening, caused a decrease in hemoglobin of more than 3 g/dL, required transfusion, and required surgical or interventional treatment were detected. In addition, deaths due to

intra-hospital bleeding or acute coronary syndrome after interventional treatment were examined.

Statistical Analysis

Statistical analyzes were performed using SSPS 25.0 (IBM Corp., Armonk, NY, USA) statistical analysis software. Due to the small number of patients given prasugrel and both agents are the new generation potent P2Y12is, the patient groups given prasugrel and ticagrelor were combined and compared with clopidogrel. Categorical variables were expressed as percentages, normally distributed continuous variables as mean and standard deviation, and non-normally distributed ones as median and 25/75 quartiles. Whether the distribution of continuous variables was normal or not was evaluated with the Kruskal–Wallis test. Categorical variables were compared with the chi-square test, normally distributed continuous variables were compared with the Student's *t*-test and those not normally distributed with the Kolmogorov–Smirnov test. Binary logistic regression analysis with conditional forward method was performed to determine the factors affecting in-hospital bleeding and mortality. Among the parameters affecting bleeding and mortality, those with a *P*-value below .1 was included in the regression analysis. Among the continuous variables included in the regression analysis, those that were not normally distributed were normally distributed by applying a 2-step approach.[13] Due to the inhomogeneity of the patient groups, the relationship between P2Y12i and in-hospital bleeding and mortality was analyzed using inverse propensity score weighting. All analyzes were 2-way and statistical significance was accepted as $P < .05$.

Results

A total of 227 patients aged between 31 and 100 were included in the study. The mean age of the patients was 62 years and 72.7% were male. Clopidogrel was given to 93 (41%) of the patients, ticagrelor to 112 (49.3%), and prasugrel to 22 of them (9.7%). Compared to the ticagrelor/prasugrel group, the clopidogrel group was older, the ratio of women was higher, and the history of hypertension and coronary artery disease were higher (*P*, respectively: <.001; .001; .008; .0045). The creatinine value was higher, the basal hemoglobin was lower, and the GRACE and CRUSADE scores were higher in the clopidogrel group (*P*, respectively: .026; .002; .002; <.001). There was no significant difference between the groups in terms of other clinical and laboratory findings (Table 1). The rate of MI with ST-elevation was higher in the prasugrel/ticagrelor group, and accordingly, the rate of total occlusion and rate of early angiography (<2 hours) were higher (*P*, respectively: .001; .006; .004). The culprit artery, use of balloon and stent, and use of tirofiban before intervention or bailout were not significantly different between the groups (Table 2).

Table 1. Baseline Characteristics of the Study Population in Accordance to Antiplatelet Agent

Variable	Clopidogrel	Ticagrelor + Prasugrel	Total	*P*
Number (%)	93 (41)	134 (59)	227 (100)	-
Age, Years	66.7 ± 11.7	58.8 ± 10.9	62 ± 11.9	<.001
Male/Female, N (%)	56 (60.2)/37 (39.8)	109 (81.3)/25 (18.7)	165 (72.7)/62 (27.3)	.001
Hypertension, N (%)	52 (55.9)	51 (38.1)	103 (45.4)	.008
Diabetes, N (%)	37 (39.8)	40 (29.9)	77 (33.9)	.120
Active smoking, N (%)	24 (25.8)	50 (37.3)	74 (32.6)	.069
History of CAD, N (%)	39 (41.9)	39 (29.1)	78 (34.4)	.045
Systolic BP, mm Hg	130 (110/150)	130 (120/140)	130 (110/150)	.527
Diastolic BP, mm Hg	80 (70/90)	80 (70/90)	80 (70/80)	.960
Heart rate, bpm	78 (70(87)	80 (72/88)	80 (70/88)	.433
Ejection fraction, %	45 (35/50)	45 (40/50)	45 (35/50)	.620
Glucose, mg/dL	141 (105/182)	138 (113/208)	139 (111/201)	.223
Creatinine, mg/dL	1 (0.8/1.4)	0.93 (0.8/1.1)	0.96 (0.8/1.2)	.026
Hemoglobin, g/dL	13.8 (14.5/15.2)	13.4 (14.5/15.6)	14.2 (12.7/15.4)	.002
Leucocyte, $\times 10^3/\mu L$	11.4 (9.4/14.2)	11.9 (9.9/14.9)	11.8 (9.6/14.3)	.143
Platelet, $\times 10^3/\mu L$	252 (202/299)	256 (217/307)	256 (209/304)	.513
Total cholesterol, mg/dL	190 (142/217)	191 (149/230)	191 (148/224)	.221
HDL cholesterol, mg/dL	37 (30/43)	37 (31/43)	37 (31/43)	.984
LDL cholesterol, mg/dL	123 (82/137)	116 (89/142)	117 (86/140)	.470
Triglyceride, mg/dL	153 (103/198)	155 (108/232)	153 (108/217)	.399
GRACE ACS score	117 (90/135)	102 (85/120)	106 (87/128)	.002
CRUSADE score	36 (24/49)	24 (18/33)	27 (19/38)	<.001

BP, blood preesure; CAD, coronary artery disease.

Table 2. Comparison of Clinical and Angiographic Findings and Outcomes According to Antiplatelet Agents

Variable	Clopidogrel	Ticagrelor+Prasugrel	Total	*P*
Diagnosis				
STEMI	46 (49.5)	88 (65.7)	134 (59)	.001
NSTEMI	30 (32.3)	41 (30.6)	71 (31.3)	
USAP	17 (18.3)	5 (3.7)	22 (9.7)	
Timing of intervention				
<2 hour	41 (44.1)	84 (62.7)	125 (55.1)	.006
>2 hour	52 (55.9)	50 (37.3)	102 (44.9)	
Culprit artery				
LAD	38 (40.9)	67 (50)	105 (46.3)	.554
Cx	18 (19.4)	20 (14.9)	38 (16.7)	
RCA	31 (33.3)	38 (28.4)	69 (30.4)	
Graft	6 (6.5)	9 (6.7)	15 (6.6)	
Total occlusion, N (%)	46 (49.5)	92 (68.7)	138 (60.8)	.004
PTCA	83 (89.2)	128 (95.5)	211 (40.5)	.069
Stent	82 (88.2)	119 (88.8)	201 (88.5)	.883
Tirofiban use, N (%)				
Pretreatment	21 (22.6)	23 (17.2)	44 (19.4)	.310
Bailout				
Slow-flow	41 (56.9)	79 (71.2)	120 (65.6)	
No-reflow	17 (23.6)	19 (17.1)	36 (19.7)	
Heavy thrombus	14 (19.4)	13 (11.7)	27 (14.8)	
In-hospital bleeding	15 (16.1)	5 (3.7)	20 (8.8)	.001
In-hospital mortality	12 (12.9)	8 (6.0)	20 (8.8)	.070

Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; NSTEMI, non-ST elevated myocardial infarction; RCA, right coronary artery; STEMI, ST-elevated myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; USAP, unstable angina pectoris.

In-hospital bleeding occurred in 20 patients (8.8%) and death in 20 patients (8.8%). The in-hospital bleeding rate was significantly higher in the clopidogrel group ($P < .001$). Although the in-hospital mortality rate was higher in the clopidogrel group, it was not statistically significant ($P = .07$). Patients who had in-hospital death were older than those who did not, and the female gender was higher (*P*, respectively:.002; .007). Ejection fractions (EF) and hemoglobin were low, creatinine value and GRACE and CRUSADE scores were higher (*P*, respectively: .001; .019; .014; <.001; .002). On the other hand, patients with in-hospital bleeding were older, had lower hemoglobin, and had higher GRACE and CRUSADE scores (*P*, respectively: <.001; .031; .003; .003). There was no significant difference between the patients with and without bleeding and death in other parameters (Table 3).

In binary regression analysis, GRACE score ($P < .001$) and sex ($P = .031$) were found to be significantly associated with in-hospital mortality. In-hospital bleeding was found to be significantly associated only with age ($P < .001$) (Table 4). Inverse propensity score weighting showed that P2Y12i used was not associated with in-hospital mortality (odds ratio (OR): 0.636, CI: 0.146-2.767) and in-hospital bleeding (OR: 0.560, CI: 0.177-2.555).

Discussion

In ACS patients treated with tirofiban during interventional therapy, we observed higher bleeding and mortality in patients using clopidogrel compared to patients using potent P2Y12i. However, when the patient groups were examined, we found that those using clopidogrel were older, had lower hemoglobin and EF, and had higher creatinine values. We also found that the GRACE risk score and the CRUSADE bleeding risk score were higher. In the binary regression analysis, in-hospital bleeding and mortality were not associated with the antiplatelet agent used, while bleeding was associated with age and mortality with gender and GRACE score. Although there are similar studies on this subject, our study provides an additional contribution as it is based on real-life data.

In the publications comparing the combination of GPIs with the new-generation potent P2Y12i's and clopidogrel, no difference was observed in terms of bleeding in general, but different results were obtained in terms of ischemic events. These studies mostly consist of subgroup analyzes and real-life data. In the subgroup analysis of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) study, it was

Table 3. Comparison of Clinical and Angiographic Findings of Patients According to In-hospital Mortality and Bleeding

	In-hospital Mortality			In-hospital Bleeding		
	Yes (n=20)	No (n=197)	*P*	Yes (n=20)	No (n=197)	*P*
Age, Years	69.9 ± 13.5	61.2 ± 11.4	.002	71.8 ± 12.8	61 ± 11.3	<.001
Male/Female, N (%)	9 (45)/11 (55)	156 (75.4)/51 (24.6)	.007	11 (55)/9 (45)	154 (74.4)/53 (25.6)	.071
Hypertension, N (%)	10 (50)	93 (44.9)	.815	11 (55)	92 (44.4)	.481
Diabetes, N (%)	4 (20)	73 (44.9)	.219	5 (25)	72 (34.8)	.464
CAD history, N (%)	6 (30)	72 (34.8)	.807	5 (25)	73 (35.3)	.463
Systolic BP, mm Hg	110 (80/140)	130 (120/150)	.057	130 (110/157)	130 (110/145)	.792
Heart rate, bpm	78 (71/99)	80 (70/86)	.403	76 (67/88)	80 (70/88)	.747
Ejection fraction, %	35 (30/40)	45 (40/50)	.001	42 (35/50)	45 (35/50)	.978
Glucose, mg/dL	148 (127/212)	138 (110/201)	.251	146 (109/203)	138 (111/201)	.863
Creatinine, mg/dL	1.19 (0.9/1.35)	0.95 (0.8/1.1)	.014	1.05 (0.87/1.47)	0.95 (0.8/1.12)	.076
Hemoglobin, g/dL	12.1 (11.3/14.8)	14.3 (13.1/15.4)	.019	13 (10.9/15)	14.3 (13/15.4)	.031
Leucocyte, $\times 10^3/\mu L$	12.4 (9.4/15.1)	11.8 (9.6/14.3)	.746	11.8 (9.5/14.1)	11.8 (9.5/14.5)	.704
GRACE ACS score	140 (118/197)	103 (85/123)	<.001	129 (107/147)	105 (85/125)	.003
CRUSADE score	49 (20/61)	27 (19/37)	.002	42 (25/56)	27 (18/38)	.003
Diagnosis, N (%)						
STEMI	13 (65)	121 (58.5)	.814	10 (50)	124 (59.9)	.595
NSTEMI	51 (25)	66 (31.9)		7 (35)	64 (30.9)	
USAP	2 (10)	20 (9.7)		3 (15)	19 (9.2)	
Tirofiban use, N (%)						
Pretreatment	2 (10)	42 (20.3)	.379	3 (15)	41 (19.8)	.772
Bailout	18 (90)	165 (79.7)		17 (85)	166 (80.2)	
Time to CAG						
<2 hours	15 (75)	110 (53.1)	.097	9 (45)	116 (56)	.358
>2 hours	5 (25)	97 (46.9)		11 (55)	91 (44)	

BP, blood pressure; CAD, coronary artery disease; CAG, coronary angiography; NSTEMI, non-ST elevated myocardial infarction; STEMI, ST-elevated myocardial infarction; USAP, unstable angina pectoris.

observed that prasugrel did not increase bleeding events compared to clopidogrel but provided a significant reduction in cardiovascular events when used together with GPIs.[10] In the PLATO (PLATelet inhibition and patient Outcomes) study, patients receiving ticagrelor had less stent thrombosis and MI compared to clopidogrel, but ticagrelor was associated with more bleeding.[9] However, when the patients using GPI were examined, no difference was observed in terms of bleeding or cardiovascular events. In our study, in-hospital bleeding was found to be consistent with this study. Our study did not look at long-term mortality rates, but in-hospital mortality was not different between groups, similar to the subgroup analysis of the PLATO study. This finding may be since ticagrelor was used predominantly in the potent P2Y12i group in our study.

Table 4. Binary Logistic Regression Analysis for Covariates of In-hospital Mortality and Bleeding

Variable	Beta	Standard Error	Significance
In-hospital mortality*			
Sex (male)	−1.133	0.526	.031
GRACE ACS score	0.41	0.1	<.001
In-hospital bleeding**			
Age	0.086	0.024	<.001

*Variables included in the model: P2Y12i, age, sex, hemoglobin, systolic blood pressure, creatinine, ejection fraction, GRACE ACS score, CRUSADE score; **Variables included in the model: P2Y12i, age, sex, hemoglobin, creatinine, GRACE ACS score, CRUSADE score.

Holmes et al[14] prospectively investigated the effects of using different GPIs and different P2Y12i in ACS in 83 patients. There was no difference between clopidogrel and ticagrelor/prasugrel in terms of 30-day bleeding and major cardiovascular events. Wang et al[15] reviewed 7 large randomized-controlled trials using P2Y12i loading and GPI in ST-elevated MI patients. In their metanalysis with over 10 000 patients, they found similar bleeding rates with clopidogrel as well as a lower rate of major cardiovascular events in the group receiving prasugrel and ticagrelor. In the metanalysis of Roule et al,[16] 3 major studies of clopidogrel, prasugrel, and ticagrelor were investigated. Researchers have seen that patients who do not use GPIs have fewer ischemic events with strong P2Y12 inhibitors compared to clopidogrel, and they also have

more bleeding events. However, they observed that when GPI was used in patients, the difference between the groups in terms of bleeding disappeared and the difference in ischemic events continued. The researchers thought that the use of GPI increased bleeding more than P2Y12i, and therefore, bleeding rates were not different in all groups. In the PRISM PLUS (Platelet-Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) study, although there was no significant difference in major bleeding in patients receiving tirofiban, a significant increase was observed in all bleedings.[3]

Tigen et al[17] examined real-life data of 224 ACS patients using tirofiban and P2Y12i, and they did not find a significant difference in hospital bleeding between the clopidogrel and prasugrel/ticagrelor groups. They found a significant relationship between bleeding events and only creatinine elevation. Similar to our study, the group given clopidogrel was older and more female in their study. This seems to be due to the operators' preference for clopidogrel in the patient group with a high risk of bleeding. Mohamed et al[18] retrospectively reviewed over 500 000 ACS patients in the United Kingdom. They found that in patients with high GRACE and CRUSADE scores, and especially in women, the treatments with guideline recommendations were applied less, as less invasive treatment, higher major cardiovascular events, death, bleeding, and less dual antiplatelet therapy.

Although the new generation P2Y12is have a faster antiplatelet effect than clopidogrel, it takes 2-4 hours for full efficacy to emerge.[19] The effectiveness of GPIs, on the other hand, starts much faster. In the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) study, sufficient antiplatelet effect appeared for at least 2 hours after prasugrel loading in ST-elevation MI patients, and this effect appeared rapidly when tirofiban was loaded, and its effectiveness was maintained for 2 hours.[20] In patients who were loaded with clopidogrel, infusion should be given in addition to the tirofiban loading to maintain the efficacy. In our study, the infusion was given to all patients after tirofiban loading. Therefore, similar bleeding and mortality rates may have been observed.

Limitations

Although our research was conducted to reveal real-life data, its most important limitations are retrospective design and small sample size. The treating physicians used different antiplatelet agents according to the clinical condition of the patients. This causes the patient groups to be heterogeneous. Clopidogrel is especially preferred in patients with a high risk of bleeding. In addition, minor bleeding could not be evaluated because it could not be detected in the patient records. Therefore, less bleeding than expected may have been observed with strong P2Y12i's. Although we tried to improve the accompanying variables with regression analysis, there may be other variables that we could not determine.

Conclusion

In our study, we found that the combined use of ticagrelor and prasugrel, the new generation potent P2Y12i, and tirofiban in interventionally treated ACS patients did not increase in-hospital bleeding rates compared to clopidogrel. We also observed that it did not create a difference in in-hospital mortality rates. These findings suggest that the combination of potent P2Y12i and tirofiban is effective and safe in patients with ACS treated interventionally, but the findings need to be supported by larger, prospective randomized studies.

Ethics Committee Approval: This study was approved by the Baskent University Medicine and Health Sciences Research Board with the decision numbered 94603339-604.01.02/26321 on September 15, 2020 (Project no: KA20/348). Informed consent was not required according to the ethics committee decision.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.A., A.Ç., E.A., A.A.; Design – S.A., A.Ç., E.A., A.A.; Supervision – H.M.; Materials – S.A.; Data Collection and/or Processing – S.A., A.Ç., E.A., A.A.; Analysis and/or Interpretation – S.A., A.Ç., E.A., A.A., H.M.; Literature Review – S.A.; Writing – S.A., A.Ç., E.A.; Critical Review – H.M.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This study was supported by Başkent University Research Fund (Project no: KA20/348).

References

1. Jourdi G, Lordkipanidzé M, Philippe A, Bachelot-Loza C, Gaussem P. Current and novel antiplatelet therapies for the treatment of cardiovascular diseases. *Int J Mol Sci*. 2021;22(23):13079. [CrossRef]
2. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J*. 2019;40(31):2632-2653. [CrossRef]
3. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms (PRISM-PLUS) study investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and Non–Q-wave myocardial infarction. *N Engl J Med*. 1998;338(21):1488-1497. [CrossRef]
4. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40(2):87-165. [CrossRef]
5. Mehta SR, Yusuf S, Peters RJG, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527-533. [CrossRef]
6. O'Donoghue M, Wiviott SD. Clopidogrel response variability and future therapies: clopidogrel: does one size fit all? *Circulation*. 2006;114(22):e600-e606. [CrossRef]
7. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2009;361(11):1045-1057. [CrossRef]
8. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2007;357(20):2001-2015. [CrossRef]
9. Shimada YJ, Bansilal S, Wiviott SD, et al. Impact of glycoprotein IIb/IIIa inhibitors on the efficacy and safety of ticagrelor compared with clopidogrel in patients with acute coronary syndromes: analysis from the Platelet Inhibition and Patient Outcomes (Plato) Trial. *Am Heart J*. 2016;177:1-8. [CrossRef]

10. O'Donoghue M, Antman EM, Braunwald E, et al. The efficacy and safety of prasugrel with and Without a glycoprotein IIb/IIIa inhibitor in patients With acute coronary syndromes undergoing percutaneous intervention: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) analysis. *J Am Coll Cardiol*. 2009;54(8):678-685. [CrossRef]
11. Fox KAA, FitzGerald G, Puymirat E, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open*. 2014;4(2):e004425. [CrossRef]
12. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009;119(14):1873-1882. [CrossRef]
13. Templeton GF. A two-step approach for transforming continuous variables to normal: implications and recommendations for IS research. *Commun Assoc Inf Syst*. 2011;28(1):41-58. [CrossRef]
14. Holmes LE, Gupta R, Rajendran S, Luu J, French JK, Juergens CP. A randomized trial assessing the impact of three different glycoprotein IIb/IIIa antagonists on glycoprotein IIb/IIIa platelet receptor inhibition and clinical endpoints in patients with acute coronary syndromes. *Cardiovasc Ther*. 2016;34(5):330-336. [CrossRef]
15. Wang Z, Zhou DY, Su Y, Si LY, Xu Q. Prasugrel or ticagrelor relative to clopidogrel in triple-antiplatelet treatment combined with glycoprotein IIb/IIIa inhibitor for patients with STEMI undergoing PCI: a meta-analysis. *BMC Cardiovasc Disord*. 2020;20(1):130. [CrossRef]
16. Roule V, Agueznai M, Sabatier R, et al. Safety and efficacy of IIb/IIIa inhibitors in combination with highly active oral antiplatelet regimens in acute coronary syndromes: a meta-analysis of pivotal trials. *Platelets*. 2017;28(2):174-181. [CrossRef]
17. Tigen MK, Özdil MH, Çinçin A, et al. Bleeding risk with concomitant use of tirofiban and third-generation P2Y12receptor antagonists in patients with acute myocardial infarction: a real-life data. *Anatol J Cardiol*. 2021;25(10):699-705. [CrossRef]
18. Mohamed MO, Rashid M, Timmis A, et al. Sex differences in distribution, management and outcomes of combined ischemic-bleeding risk following acute coronary syndrome. *Int J Cardiol*. 2021;329:16-22. [CrossRef]
19. Wallentin L. P2Y12 inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J*. 2009;30(16):1964-1977. [CrossRef]
20. Valgimigli M, Tebaldi M, Campo G, et al. Prasugrel Versus tirofiban bolus with or Without short post-bolus infusion with or Without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. *JACC Cardiovasc Interv*. 2012;5(3):268-277. [CrossRef]