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ORIGINAL ARTICLE

Efficacy and Safety of Glycoprotein IIb/IIIa Inhibitors Used Concomitantly with Cangrelor in Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background: Cangrelor, an intravenous and reversible P2Y12 receptor antagonist, is approved for use in patients undergoing primary and non-primary percutaneous coronary intervention (PCI).

Aim: To evaluate the efficacy and safety of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors initiated during PCI in patients with acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) receiving cangrelor therapy.

Study Design: Retrospective, multicenter study.

Methods: This subgroup analysis of previously reported real-world data on cangrelor use in Türkiye evaluated the effects of GP IIb/IIIa inhibitors on bleeding, ischemic events, and mortality during follow-up in patients receiving cangrelor.

Results: A total of 411 patients were included (mean age: 63.8±12.7 years; 76% male). Of these, 44 patients (10.7%) received GP IIb/IIIa inhibitors in addition to cangrelor (mean age: 68.0±11.3 years; 79% male). Kaplan-Meier analysis showed no significant difference in 12-month overall survival between coronary artery disease groups (log-rank p=0.392). In Firth penalized logistic regression analysis adjusting for age, sex, cardiogenic shock, chronic kidney disease, and femoral vascular access, GP IIb/IIIa inhibitor use was identified as an independent and significant predictor of 48-hour bleeding (odds ratio: 8.44, 95% confidence interval: 3.54-20.18, p<0.001).

Conclusion: This study represents the first large-scale, multicenter retrospective analysis in Türkiye to examine the concomitant use of GP IIb/IIIa inhibitors with cangrelor in a high-risk population of patients with ACS and CCS. The findings suggest that combining GP IIb/IIIa inhibitors with cangrelor does not improve clinical outcomes but significantly increases the incidence of mild-to-moderate bleeding events.

Keywords: Cangrelor, glycoprotein IIb/IIIa inhibitors, percutaneous coronary intervention, acute coronary syndrome, chronic coronary syndrome

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INTRODUCTION

Cardiovascular diseases remain the leading cause of mortality and morbidity worldwide, with acute coronary syndrome (ACS) often representing the first clinical manifestation.[1,2] Current European guidelines emphasize that early percutaneous coronary intervention (PCI) with stent implantation significantly reduces mortality and limits the development of heart failure (HF) in patients with ACS.[3] Achieving rapid and adequate platelet inhibition before coronary intervention is therefore critical for preventing early stent thrombosis, recurrent myocardial infarction, and associated mortality.

Oral P2Y12 inhibitors, including clopidogrel, ticagrelor, and prasugrel, are widely used for this purpose. However, their pharmacokinetic profiles depend on gastrointestinal absorption, which may delay the onset of action and limit their ability to provide rapid and predictable platelet inhibition, particularly in patients at high thrombotic risk.[4,5] Moreover, several conditions frequently encountered in patients with ACS—such as hemodynamic instability, hypotension, nausea and vomiting, the need for endotracheal intubation, delayed gastric emptying, intestinal hypoperfusion, hypothermia, and opioid use—can further impair the bioavailability and pharmacodynamic effectiveness of oral agents, resulting in delayed or inadequate clinical responses.[6,7]

Cangrelor, an intravenously administered, rapidly acting, and reversible P2Y12 receptor antagonist, has been approved for use during PCI and provides potent and predictable platelet inhibition, particularly in clinical scenarios in which oral agents may have delayed or insufficient effects.[8] The safety and efficacy of cangrelor have been evaluated in three randomized controlled trials comparing cangrelor with clopidogrel or placebo in patients undergoing PCI for stable or acute indications who had not previously received a P2Y12 inhibitor. Pooled analyses of these studies demonstrated that cangrelor administration during PCI significantly reduced the composite endpoint of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis within 48 hours. However, this ischemic benefit was accompanied by an increased incidence of minor bleeding events, without a corresponding rise in life-threatening or fatal bleeding.[9-11]

Glycoprotein IIb/IIIa (GP IIb/IIIa) receptor inhibitors are parenteral agents that prevent platelet aggregation by blocking the binding of fibrinogen or von Willebrand factor to the GP IIb/IIIa receptor, thereby inhibiting platelet cross-linking. Their use has become more selective and is now largely limited to adjunctive therapy during PCI in patients with a high thrombus burden or as "rescue" or "bailout" therapy in the presence of PCI-related complications, such as no-reflow or persistent or recurrent intralesional thrombus.[12]

We recently published the first multicenter study evaluating real-world cangrelor use in Türkiye.[13] In this predefined subgroup analysis, we aimed to assess the efficacy and safety of GP IIb/IIIa inhibitors initiated during PCI in patients with ACS or chronic coronary syndrome (CCS) receiving cangrelor therapy.

METHODS

Study Design and Population

Data were collected between January 20, 2025, and April 1, 2025, from 14 high-volume PCI centers in Türkiye that maintain 24/7 cangrelor administration programs. This retrospective observational study evaluated the records of patients who received cangrelor, with or without concomitant GP IIb/IIIa inhibitors, during the preceding five years. All patients who received cangrelor therapy within the specified period were included in the analysis, regardless of whether GP IIb/IIIa inhibitors were administered.

A total of 411 patients aged ≥18 years with a diagnosis of ACS or CCS who received cangrelor prior to PCI, in accordance with approved indications, were included. Patients with myocardial infarction with non-obstructive coronary arteries or Takotsubo syndrome identified on coronary angiography, and therefore not undergoing PCI, were excluded from the study.[14,15]

Data Collection and Clinical Definitions

Collected data included indications for cangrelor administration, demographic and clinical characteristics, pre- and postprocedural laboratory parameters, procedural details, and in-hospital ischemic events, bleeding events, and mortality outcomes. According to European Society of Cardiology guidelines, patients were categorized into four clinical groups: ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), unstable angina (UA), and CCS.[3]

Stent thrombosis (acute, subacute, or late) was defined as definite, probable, or possible events confirmed either angiographically or clinically.[16] Bleeding events were evaluated at 48 hours and 1 month after the procedure. Bleeding severity was classified using the Bleeding Academic Research Consortium (BARC) and Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria.

According to the BARC classification, type 1 bleeding refers to events not requiring unscheduled diagnostic evaluation, hospitalization, or treatment. Type 2 bleeding includes events requiring non-surgical medical intervention, hospitalization, or escalation of care. Type 3 bleeding is subdivided into three categories: type 3a, overt bleeding associated with a hemoglobin decrease of 3-5 g/dL or requiring transfusion; type 3b, bleeding with a hemoglobin decrease ≥5 g/dL, cardiac tamponade, bleeding requiring surgical intervention (excluding dental, nasal, cutaneous, or hemorrhoidal bleeding), or bleeding requiring intravenous vasoactive therapy; and type 3c, intracranial or intraspinal hemorrhage or intraocular bleeding causing vision loss. Type 4 bleeding refers to coronary artery bypass graft-related bleeding, including perioperative intracranial bleeding, reoperation after sternotomy closure, or significant transfusion requirements. Type 5 bleeding refers to fatal bleeding, with type 5a indicating probable fatal bleeding without confirmatory autopsy or imaging and type 5b indicating definite fatal bleeding confirmed by autopsy or imaging.[17] In the present analysis, BARC type 1-2 bleeding events were classified as minor bleeding, whereas BARC type ≥3 events were considered major bleeding.

According to the GUSTO classification, severe or life-threatening bleeding includes intracranial hemorrhage or bleeding causing hemodynamic compromise requiring intervention; moderate bleeding includes bleeding requiring blood transfusion without hemodynamic deterioration; and mild bleeding includes events not meeting the criteria for severe or moderate bleeding.[18]

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, a prior diagnosis of hypertension, or current use of antihypertensive medication.[19] Diabetes mellitus was defined as a fasting plasma glucose level >126 mg/dL, a prior diagnosis of diabetes, or use of glucose-lowering medication.[20] HF was defined as the presence of characteristic symptoms accompanied by objective evidence of cardiac dysfunction resulting in reduced cardiac output and/or elevated intracardiac pressure.[21]

Contrast-induced acute kidney injury (CI-AKI) was defined according to Kidney Disease: Improving Global Outcomes guidelines as an increase in serum creatinine ≥0.3 mg/dL within 48 hours after contrast administration, an increase to ≥1.5 times the baseline value within the prior 7 days, or urine output <0.5 mL/kg/h for at least 6 hours.[22]

Procedural Details

Standard coronary angiography was performed using either the transradial or transfemoral approach, according to the operator's preference, using the Seldinger technique. In all patients, a low-osmolar, non-ionic contrast agent, iohexol (350 mg iodine/mL; 755 mOsm/kg H_2O) (Omnipaque-350; GE Healthcare, Rydalmere, Australia), was used.

Following primary PCI (pPCI), saline infusion (0.9% NaCl) was administered according to institutional protocol to reduce the risk of CI-AKI. Patients without HF received isotonic saline at 1 mL/kg/h for 12 hours, whereas those with HF received 0.5 mL/kg/h for 12 hours. The duration of hydration was adjusted by the treating interventional cardiologist based on individual patient risk assessment.

Cangrelor was administered according to current guideline recommendations as an intravenous bolus of 30 µg/kg, followed by a continuous infusion of 4 µg/kg/min. The infusion was maintained for at least 2 hours or for the duration of the procedure, whichever was longer. After discontinuation of cangrelor, transition to an oral P2Y12 inhibitor was performed according to guideline-based recommendations.[3] In patients receiving GP IIb/IIIa inhibitor therapy, tirofiban was administered according to standard practice. A high-dose bolus of 25 µg/kg was given intravenously over 3 minutes, followed by a continuous infusion of 0.15 µg/kg/min. The infusion was typically continued for up to 18 hours at the discretion of the interventional cardiologist.[3] Unfractionated heparin was administered according to current guideline recommendations. An initial intravenous bolus of 70-100 IU/kg was given at the start of the procedure. In patients receiving concomitant GP IIb/IIIa inhibitors, a reduced initial bolus of 60 IU/kg was used. Anticoagulation was monitored using activated clotting time (ACT), when available, and additional boluses were administered as needed to maintain a target ACT of 250–300 seconds (or 200–250 seconds in patients receiving GP IIb/IIIa inhibitors).

Data Management and Follow-up

All numerical variables were cross-checked across participating centers prior to analysis to ensure consistency, and data audits were performed to verify the accuracy of procedural and outcome variables. In-hospital data were retrieved from existing patient records, whereas long-term follow-up data were obtained from hospital databases, telephone interviews, and the national electronic health record system.[23]

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Trakya University School of Medicine (aproval number: TUTF-GOBAEK-2024/560, date: 20.01.2025).

Statistical Analysis

Continuous variables were summarized as mean±standard deviation or median [interquartile range (IQR)], depending on data distribution. Categorical variables are presented as frequencies and percentages. Event rates were calculated with 95% confidence intervals (CIs) using the Wilson method.

Bleeding rates according to the BARC and GUSTO classifications were summarized based on coronary artery disease presentation (STEMI, NSTEMI, or UA). Time intervals were defined according to the first occurrence of an event, including 48-hour and 30-day intervals with a ±2-day tolerance window. Given the low number of bleeding events relative to the number of predictors (events-per-variable ratio=4.3), Firth's penalized logistic regression was used to identify independent predictors of 48-hour bleeding. The multivariable model included age, sex, cardiogenic shock (Killip class IV), chronic kidney disease, and femoral vascular access. Results are reported as odds ratios (ORs) with profile likelihood-based 95% CIs. As a sensitivity analysis, inverse probability of treatment weighting (IPTW) was performed to assess the robustness of the primary findings. Propensity scores for GP IIb/IIIa inhibitor use were estimated using logistic regression, including age, sex, chronic kidney disease, femoral vascular access, Killip class, diabetes mellitus, hypertension, STEMI presentation, and left ventricular ejection fraction (LVEF) as covariates. The average treatment effect on the treated was estimated using IPTW, with weights trimmed at the 99th percentile to minimize the impact of extreme values. Covariate balance was assessed using standardized mean differences, with <0.1 indicating adequate balance. Weighted outcome analysis was performed using the survey package with robust variance estimation. A two-sided p value <0.05 was considered statistically significant. All analyses were performed using R software version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 411 patients included in the study, the median ages of patients in the STEMI, NSTEMI, UA, and CCS groups were 64, 70, 66, and 59 years, respectively. Patients in the STEMI group presented with higher Killip classes, higher heart rates, and lower systolic and diastolic blood pressures at admission. The prevalence of hypertension was high across all groups. Chronic kidney disease was more prevalent in the STEMI group, whereas diabetes mellitus was more common

in the NSTEMI group. The lowest median LVEF was observed in the STEMI group. Cangrelor was most frequently administered in clinical scenarios involving cardiogenic shock, endotracheal intubation, and nausea or vomiting with impaired oral intake. A total of 44 patients (10.7%) received GP IIb/IIIa inhibitors in addition to cangrelor. The most common indication for GP IIb/IIIa inhibitor use was high thrombus burden in the culprit coronary artery and impaired distal coronary flow [thrombolysis in myocardial infarction (TIMI) 0-1] at the end of the procedure. All patients received aspirin and heparin. In all cases, oral P2Y12 inhibitor therapy was initiated immediately after completion of cangrelor infusion, with clopidogrel being the most frequently used agent (57%). Baseline characteristics, including age, sex, type of coronary artery disease, Killip class, LVEF, diabetes mellitus, and hypertension, were comparable between patients who received GP IIb/IIIa inhibitors and those who did not (all $p>0.05$) (Table 1).

Although femoral access was more frequently used in patients receiving GP IIb/IIIa inhibitors, median stent diameter (3.0 mm), total stent length (34.3±19.7 mm), median procedural time [39 minutes (IQR: 26-55)], contrast volume [150 mL (IQR: 110-220)], and the rate of complex bifurcation procedures were comparable between the groups (Table 2).

In firth penalized logistic regression analysis adjusting for age, sex, cardiogenic shock, chronic kidney disease, and femoral vascular access, GP IIb/IIIa inhibitor use was the only independent predictor of 48-hour bleeding, corresponding to an approximately eightfold increased risk (OR: 8.44; 95% CI: 3.54-20.18; $p<0.001$). Notably, neither chronic kidney disease (OR: 0.82; 95% CI: 0.26-2.27; $p=0.708$) nor femoral access (OR: 1.05; 95% CI: 0.37-3.33; $p=0.926$) was independently associated with bleeding after adjustment. The remaining covariates also did not reach statistical significance (all $p>0.05$) (Table 3). In the IPTW sensitivity analysis, adequate covariate balance was achieved after weighting, with all standardized mean differences <0.1. The IPTW-adjusted analysis yielded consistent results, confirming a significant association between GP IIb/IIIa inhibitor use and 48-hour bleeding (OR: 7.97; 95% CI: 3.24-19.62; $p<0.001$).

When hemodynamic and procedural parameters associated with the decision to use GP IIb/IIIa inhibitors were analyzed, arrhythmia was significantly more common in patients receiving GP IIb/IIIa inhibitors than in those who did not ($p=0.011$). However, inotropic support, mechanical circulatory support, cardiopulmonary arrest, admission systolic and diastolic blood pressure, heart rate, and number of culprit lesions did not differ significantly between the groups (all $p>0.05$) (Table 4).

Within 48 hours, the incidence of any bleeding event, major bleeding (BARC ≥3), and blood transfusion was significantly higher in patients receiving GP IIb/IIIa inhibitors compared with those not receiving them (28% vs. 3.8%, $p<0.001$; 7.0% vs. 1.1%, $p=0.028$; and 12% vs. 2.7%, $p=0.014$, respectively) (Table 3) (Figure 1). All major bleeding events were gastrointestinal in origin, whereas minor bleeding events were predominantly related to vascular access sites and the genitourinary system. Regarding bleeding risk indicators and potential contraindications influencing the decision to use GP IIb/IIIa inhibitors, all categories of BARC and GUSTO bleeding scores at 48 hours, chronic kidney disease, and the need for blood transfusion were significantly more frequent in the GP IIb/IIIa inhibitor group than in the non-GP IIb/IIIa group (Table 5).

DISCUSSION

In this study, we evaluated the impact of concomitant use of GP IIb/IIIa inhibitors with the parenteral P2Y12 inhibitor cangrelor on clinical outcomes and bleeding complications in patients undergoing PCI for acute or CCS. The principal finding of our analysis is that the addition of GP IIb/IIIa inhibitors to cangrelor therapy was associated with an approximately eightfold increase in bleeding risk, independent of baseline clinical risk factors, including chronic kidney disease and femoral vascular access, whereas no significant difference in in-hospital mortality was observed.

Cangrelor, currently the only available intravenous P2Y12 inhibitor, has an established role in the management of ACS.[24,25] Although the CHAMPION series of randomized clinical trials demonstrated the efficacy and safety of cangrelor in controlled settings, data reflecting its performance in real-world clinical practice remain limited. In this context, the retrospective multicenter study by Altay et al.[13] provided important real-world evidence regarding cangrelor use in Türkiye, showing that the drug is predominantly used in high-risk patients with ACS and CCS, and describing its indications and clinical outcomes during follow-up.[26,27]

Similarly, real-world data regarding the efficacy and safety of concomitant use of cangrelor and GP IIb/IIIa inhibitors remain scarce. In a meta-analysis by Sethi et al.,[28] which included 20 randomized controlled trials and 7,404 patients with STEMI undergoing pPCI, the effects of GP IIb/IIIa inhibitors on clinical outcomes were compared between patients who did or did not receive preprocedural thienopyridines. The analysis showed that in patients not receiving thienopyridines before PCI, GP IIb/IIIa inhibitors significantly reduced 30-day mortality and target vessel revascularization. In contrast, these benefits were not statistically significant in patients who had received thienopyridines prior to the procedure. However, safety outcomes related to GP IIb/IIIa inhibitors were not reported in detail in this meta-analysis.

In another meta-analysis, Jeremias et al.[29] evaluated 2,937 STEMI patients undergoing pPCI and compared abciximab, a GP IIb/IIIa inhibitor, with placebo in patients who had received preprocedural thienopyridine therapy. The authors reported that abciximab did not reduce mortality or reinfarction rates, either at 30 days or during long-term follow-up. Similar to the previous analysis, safety data were limited.

Importantly, the patient populations included in these meta-analyses differ from those in our study, as all patients in the referenced studies received oral P2Y12 inhibitors, whereas our cohort consisted of patients who could not receive oral P2Y12 inhibitors due to various clinical conditions and were therefore treated with the intravenous P2Y12 inhibitor cangrelor. Among patients receiving GP IIb/IIIa inhibitors in our study, 32 (74%) presented with STEMI. When comparing patients who received GP IIb/IIIa inhibitors with those who did not, no statistically significant differences were observed in

Table 1. Patient risk profile by GP IIb/IIIa use

Characteristic	Overall n=411	GP IIb/IIIa (-) n=367	GP IIb/IIIa (+) n=44	p value[1]
Age, median (Q1, Q3)	64 (56, 73)	64 (56, 73)	69 (53, 77)	0.35
Sex, n (%)				0.58
Male	313 (76)	278 (76)	35 (80)	
Female	98 (24)	89 (24)	9 (20)	
CAD type, n (%)				0.11
CCS	33 (8.0)	33 (9.0)	0 (0)	
NSTEMI	100 (24)	88 (24)	12 (27)	
STEMI	268 (65)	236 (64)	32 (73)	
UA	10 (2.4)	10 (2.7)	0 (0)	
Cardiogenic shock (Killip 4), n (%)				0.54
Yes	111 (30)	97 (29)	14 (34)	
No	259 (70)	232 (71)	27 (66)	
Killip class, n (%)				0.35
1	185 (50)	169 (51)	16 (39)	
2	52 (14)	45 (14)	7 (17)	
3	22 (5.9)	18 (5.5)	4 (9.8)	
4	111 (30)	97 (29)	14 (34)	
LVEF (%), median (Q1, Q3)	40 (30, 53)	40 (30, 55)	37 (30, 50)	0.090
Diabetes, n (%)	188 (46)	171 (47)	17 (39)	0.31
Hypertension, n (%)	255 (62)	227 (62)	28 (64)	0.83

[1]Wilcoxon rank sum test; Pearson's chi-squared test; Fisher's exact test
If "Shock" or "Killip" class is not significantly higher in this group, the drug may have been administered for procedural complications rather than clinical severity
STEMI: ST-segment elevation myocardial infarction, CCS: Chronic coronary syndrome, Killip classification (risk assessment of patients after STEMI), Killip class I: Patients without any clinical signs of heart failure; Killip class II: Patients with rales or crackles in the lungs, elevated jugular venous pressure, and S3 gallop; Killip class III: Patients with frank acute pulmonary edema; Killip class IV: Patients with cardiogenic shock or hypotension (systolic blood pressure <90 mmHg) and signs of low cardiac output
LVEF: Left ventricular ejection fraction, NSTEMI: Non-ST-segment elevation myocardial infarction, CAD: Coronary artery disease, UA: Unstable angina, GP IIb/III: Glycoprotein IIb/IIIa. Data are summarized as mean±standard deviation, median (25th percentile; 75th percentile), or n (%)

Killip class, cardiopulmonary arrest, mortality, or recurrent myocardial infarction, findings that are broadly consistent with those reported in the aforementioned studies.

In the three phase III CHAMPION trials, a total of 24,902 patients undergoing elective or non-elective PCI were randomized to receive cangrelor or clopidogrel, and both clinical efficacy and safety outcomes were assessed.[8] In these studies, 12.7% of patients also received GP IIb/IIIa inhibitors. Among them, abciximab or eptifibatide was administered in 89.2%, whereas tirofiban was used in the remaining 10.8%. The use of GP IIb/IIIa inhibitors was more frequent in the NSTEMI population. Baseline comorbidities, including hypertension, dyslipidemia, diabetes mellitus, prior stroke, HF, and previous myocardial infarction, were more prevalent in patients not receiving GP IIb/IIIa inhibitors. The primary endpoint of the CHAMPION trials was a composite of all-cause mortality, myocardial infarction, ischemia-driven revascularization, or stent thrombosis within 48 hours after randomization. Although the primary endpoint was numerically lower in the cangrelor group compared with the clopidogrel group among patients receiving GP IIb/IIIa inhibitors, this difference did not reach statistical significance.

Regarding safety outcomes, three bleeding classification systems were used: the GUSTO, TIMI, and Acute Catheterization and Urgent Intervention Triage Strategy criteria. Across all three scoring systems, mild and moderate bleeding events were more frequent in patients receiving GP IIb/IIIa inhibitors compared with those who did not, whereas the incidence of severe bleeding was similar between the groups.

In our study, GP IIb/IIIa inhibitors were administered to 44 patients (74% STEMI), primarily in the context of high thrombus burden or as bailout/rescue therapy rather than routine use. Unlike the CHAMPION trials, tirofiban was the only GP IIb/IIIa inhibitor used in our cohort. Baseline characteristics, including age, sex, hypertension, diabetes mellitus, LVEF, and cardiogenic shock, were comparable between patients who did and did not receive GP IIb/IIIa inhibitors.

The clinical outcomes observed in our study were consistent with those reported in the CHAMPION trials, showing no significant differences in major clinical outcomes between patients receiving cangrelor with or without GP IIb/IIIa inhibitors. This study was conducted across 14 high-volume PCI centers in Türkiye, where the femoral approach was used in most procedures. Although radial access is recommended in current

Table 2. Procedural details and complexity indicators

Characteristic	GP IIb/IIIa (-) n=367	GP IIb/IIIa (+) n=44	p value[1]
Vascular access, n (%)			0.003
Femoral	257 (70)	40 (91)	
Radial	110 (30)	4 (9.1)	
Bifurcation procedure (complex), n (%)			0.31
Yes	61 (17)	10 (23)	
No	306 (83)	34 (77)	
Number of stents, n (%)			0.71
0	10 (2.7)	1 (2.4)	
1	227 (62)	23 (55)	
2	99 (27)	14 (33)	
3	22 (6.0)	3 (7.1)	
4	5 (1.4)	1 (2.4)	
5	1 (0.3)	0 (0)	
Total stent length (mm), median (Q1, Q3)	29 (20, 44)	36 (20, 56)	0.29
Procedure duration (min), median (Q1, Q3)	39 (25, 55)	35 (30, 55)	0.72
Contrast volume (mL), median (Q1, Q3)	150 (105, 220)	190 (120, 250)	0.20

[1]Pearson's chi-squared test; Fisher's exact test; Wilcoxon rank sum test
Increased bifurcation, stent length, or procedure duration supports "bail-out" (rescue) use
GP IIb/III: Glycoprotein IIb/IIIa

Table 3. Firth penalized logistic regression for independent predictors of bleeding within 48 hours

Variables	OR (95% CI)	p value
GP IIb/IIIa (+) vs. (–)	8.44 (3.54-20.18)	<0.001
Age (per year)	1.02 (0.99-1.06)	0.185
Female vs. male	1.02 (0.35-2.72)	0.963
Shock (absent vs. present)	0.76 (0.30-2.02)	0.578
Chronic kidney disease	0.82 (0.26-2.27)	0.708
Femoral access	1.05 (0.37-3.33)	0.926

CI: Confidence interval, OR: Odds ratio, GP IIb/III: Glycoprotein IIb/IIIa. Firth penalized logistic regression with profile likelihood CIs

guidelines, the femoral approach remains commonly used in Türkiye, particularly in patients with cardiogenic shock, due to easier vascular access and potential time savings.[30]

Given the relatively small number of bleeding events (n=26), Firth's penalized logistic regression was Firth penalized logistic regression was employed to reduce small-sample bias (events-per-variable ratio=4.3). Six predictors were included in the model: age, sex, cardiogenic shock, chronic kidney disease, femoral vascular access, and GP IIb/IIIa inhibitor use. Despite the inclusion of chronic kidney disease and femoral access-both of which were more prevalent in the GP IIb/IIIa group-GP IIb/IIIa inhibitor use remained the only independent predictor of bleeding, with an approximately 8.44-fold increase in risk. The robustness of this finding was further supported by IPTW analysis, which yielded a consistent estimate (OR: 7.97; 95% CI: 3.24–19.62; p<0.001) after balancing all measured confounders between groups. The agreement between these two distinct analytical approaches-multivariable regression and propensity score weighting-strengthens the conclusion that the observed bleeding risk is attributable to GP IIb/IIIa inhibitor use rather than baseline imbalances. Importantly, the absence of a significant difference in 12-month mortality between the GP IIb/IIIa and non-GP IIb/IIIa groups should be interpreted with caution. Given the relatively small number of patients in the GP IIb/IIIa group (n=44), the study was likely underpowered to detect clinically meaningful differences in long-term outcomes; therefore, a true effect on mortality cannot be excluded. In the CHAMPION trials, GP IIb/IIIa inhibitor use was associated with an approximately 3.5-fold increase in bleeding risk, with most events being mild to moderate in severity, findings that are consistent with those of our study. We speculate that the higher incidence of gastrointestinal bleeding as a major bleeding event may be related to the pharmacologic profile of GP IIb/IIIa inhibitors. Although both agents achieve potent platelet inhibition, GP IIb/IIIa inhibitors are associated with a more pronounced bleeding risk, likely due to their distinct targets, lack of reversibility, and sustained antiplatelet effects after infusion discontinuation. In addition, the higher prevalence of chronic kidney disease in the GP IIb/IIIa group may have further contributed to the increased bleeding risk.

The present study demonstrated that 74% of patients receiving GP IIb/IIIa inhibitors presented with STEMI, and the frequency of arrhythmia was significantly higher in this group, suggesting that these agents are more often used in clinically unstable scenarios. However, the absence of a statistically significant difference between the groups in terms of cardiogenic shock or Killip class indicates that GP IIb/IIIa inhibitors are not exclusively administered in the most severe clinical presentations but may also be used in response to acute procedural complications during PCI.

Table 4. Hemodynamic and interventional decision determinants directly related to GP IIb/IIIa use

Characteristic	Overall n=411	GP IIb/IIIa (-) n=367	GP IIb/IIIa (+) n=44	p value[1]
Inotropic support, n (%)	163 (40)	144 (39)	19 (43)	0.63
Mechanical circulatory support, n (%)	2 (0.5)	2 (0.6)	0 (0)	>0.99
Cardiopulmonary arrest, n (%)	102 (25)	88 (24)	14 (32)	0.26
Arrhythmia, n (%)	90 (22)	74 (20)	16 (36)	0.015
Systolic blood pressure (mmHg), median (Q1, Q3)	100 (80, 125)	100 (80, 125)	100 (82, 115)	0.90
Diastolic blood pressure (mmHg), median (Q1, Q3)	60 (45, 74)	60 (45, 74)	60 (50, 70)	0.82
Admission heart rate (bpm), median (Q1, Q3)	86 (70, 105)	86 (70, 106)	87 (69, 100)	0.47
LVEF (%), median (Q1, Q3)	40 (30, 53)	40 (30, 55)	37 (30, 50)	0.090
Culprit lesion, n (%)				0.22
0	29 (7.1)	29 (7.9)	0 (0)	
1	216 (53)	192 (52)	24 (55)	
2	66 (16)	55 (15)	11 (25)	
3	94 (23)	85 (23)	9 (20)	
4	3 (0.7)	3 (0.8)	0 (0)	
5	3 (0.7)	3 (0.8)	0 (0)	
Bifurcation, n (%)				0.31
Yes	71 (17)	61 (17)	10 (23)	
No	340 (83)	306 (83)	34 (77)	
Number of diseased vessels, n (%)				0.23
0	3 (0.7)	3 (0.8)	0 (0)	
1	169 (41)	152 (41)	17 (39)	
2	139 (34)	125 (34)	14 (32)	
3	95 (23)	84 (23)	11 (25)	
4	4 (1.0)	3 (0.8)	1 (2.3)	
5	1 (0.2)	0 (0)	1 (2.3)	
PCI duration (min), median (Q1, Q3)	39 (25, 55)	39 (25, 55)	35 (30, 55)	0.72
Contrast volume (mL), median (Q1, Q3)	150 (110, 220)	150 (105, 220)	190 (120, 250)	0.20
Number of stents, n (%)				0.71
0	11 (2.7)	10 (2.7)	1 (2.4)	
1	250 (62)	227 (62)	23 (55)	
2	113 (28)	99 (27)	14 (33)	
3	25 (6.2)	22 (6.0)	3 (7.1)	
4	6 (1.5)	5 (1.4)	1 (2.4)	
5	1 (0.2)	1 (0.3)	0 (0)	
Total stent length (mm), median (Q1, Q3)	29 (20, 44)	29 (20, 44)	36 (20, 56)	0.29
DES/BMS, n (%)				0.22
0	4 (1.0)	2 (0.6)	2 (4.5)	
1	377 (94)	336 (95)	41 (93)	
2	11 (2.8)	10 (2.8)	1 (2.3)	
3	6 (1.5)	6 (1.7)	0 (0)	
4	1 (0.3)	1 (0.3)	0 (0)	

[1]Pearson's chi-squared test; Fisher's exact test; Wilcoxon rank sum test
LVEF: Left ventricular ejection fraction, GP IIb/III: Glycoprotein IIb/IIIa, PCI: Percutaneous coronary intervention, DES: Drug-eluting stent, BMS: Bare-metal stent

Table 5. Bleeding risk and contraindication indicators influencing GP IIb/IIIa use decision

Characteristic	Overall n=411	GP IIb/IIIa (-) n=367	GP IIb/IIIa (+) n=44	p value[1]
Hemoglobin (g/dL), median (Q1, Q3)	13.00 (11.60, 14.60)	13.00 (11.60, 14.70)	12.60 (11.50, 14.60)	0.62
Chronic kidney disease, n (%)	76 (19)	63 (17)	13 (30)	0.047
Dialysis, n (%)	11 (2.7)	9 (2.5)	2 (4.5)	0.34
48-hour bleeding (BARC), n (%)				<0.001
0	383 (94)	351 (96)	32 (73)	
1	16 (3.9)	7 (1.9)	9 (20)	
2	3 (0.7)	3 (0.8)	0 (0)	
3a	5 (1.2)	3 (0.8)	2 (4.5)	
3A	1 (0.2)	0 (0)	1 (2.3)	
5a	1 (0.2)	1 (0.3)	0 (0)	
48-hour bleeding (GUSTO), n (%)				<0.001
0	386 (94)	353 (96)	33 (75)	
1	15 (3.6)	8 (2.2)	7 (16)	
2	7 (1.7)	4 (1.1)	3 (6.8)	
3	3 (0.7)	2 (0.5)	1 (2.3)	
Bleeding site, n (%)				<0.001
Other	25 (6.1)	14 (3.8)	11 (25)	
None	386 (94)	353 (96)	33 (75)	
Transfusion requirement, n (%)	15 (3.7)	10 (2.7)	5 (11)	0.015
Surgery requirement, n (%)	1 (0.2)	1 (0.3)	0 (0)	>0.99
Vascular complication, n (%)	2 (0.5)	1 (0.3)	1 (2.3)	0.20

[1]Wilcoxon rank sum test; Pearson's chi-squared test; Fisher's exact test
BARC: Bleeding Academic Research Consortium, GUSTO: Global Utilization of Strategies to Open Occluded Coronary Arteries, GP IIb/III: Glycoprotein IIb/IIIa

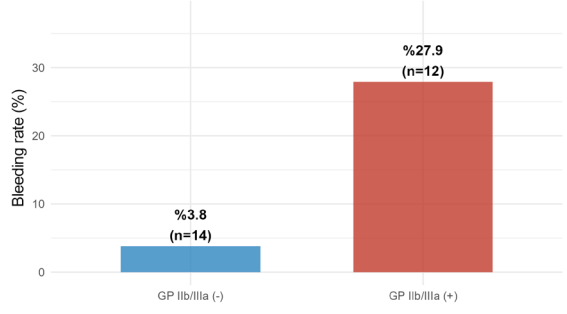

Figure 1. The impact of adding glycoprotein IIb/IIIa inhibitors on bleeding risk in patients treated with cangrelor (rates of any bleeding at 48 hours)

When procedural characteristics were examined, the higher prevalence of chronic kidney disease in the GP IIb/IIIa inhibitor group further supports the notion that this population represents a particularly vulnerable subgroup, predisposed to both thrombotic and hemorrhagic complications. One of the most notable findings of this study was the association between GP IIb/IIIa inhibitor use and bleeding complications. The incidence of any bleeding event was 27.9% in the GP IIb/IIIa inhibitor group compared with 3.8% in the control group. Notably, the significantly higher need for blood transfusion in the GP IIb/IIIa inhibitor group (12% vs. 2.7%) suggests that clinically relevant bleeding events are strongly associated with GP IIb/IIIa inhibitor use.

Study Limitations

The multicenter design and the use of real-world clinical data represent important strengths of this study. The consistency of the primary finding across both Firth's penalized logistic regression and IPTW propensity score analyses further supports the robustness of the results. However, several limitations should be acknowledged.

First, the retrospective design may introduce inherent selection and information biases. Second, due to reimbursement policies in Türkiye, cangrelor use is largely restricted to high-risk patient populations, which may limit the generalizability of the findings to the broader spectrum of coronary artery disease. Third, certain procedural variables that may influence bleeding risk, such as sheath size, were not collected and therefore could not be included in the analysis. Fourth, the relatively small number of patients receiving GP IIb/IIIa inhibitors (n=44) limits the statistical power to detect differences in long-term clinical outcomes, such as 12-month mortality, and the lack of a survival difference should not be interpreted as definitive evidence of no effect. Fifth, despite adjustment for multiple clinical covariates using both multivariable regression and propensity score weighting,

residual confounding from unmeasured variables-such as procedural complexity, thrombus burden severity, and anticoagulation dosing protocols-cannot be excluded and may have influenced the observed associations. Therefore, larger prospective studies encompassing the full spectrum of coronary artery disease presentations are warranted to validate and extend the findings of this analysis.

CONCLUSION

This study represents the first large-scale, multicenter retrospective analysis in Türkiye focusing on the concomitant use of GP IIb/IIIa inhibitors with cangrelor in a high-risk population of patients with ACS and CCS. The findings indicate that, in patients unable to receive oral P2Y12 inhibitors and therefore treated with cangrelor, the addition of bailout or rescue GP IIb/IIIa inhibitors was not associated with improved clinical outcomes, while being associated with an approximately eightfold increase in non-severe bleeding events.

Although chronic kidney disease and femoral vascular access were more prevalent in the GP IIb/IIIa group, neither was independently associated with bleeding after multivariable adjustment, suggesting that the increased bleeding risk is primarily driven by the pharmacological intensity of the combined antiplatelet regimen. In routine clinical practice, when considering the use of this potent antiplatelet combination (cangrelor plus GP IIb/IIIa inhibitors) during primary or non-pPCI, clinicians should carefully balance potential ischemic benefits against the increased bleeding risk. Whenever feasible, radial access should be preferred to minimize bleeding complications, and individualized risk-benefit assessment should guide therapeutic decision-making.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Trakya University School of Medicine (aproval number: TUTF-GOBAEK-2024/560, date: 20.01.2025).

Informed Consent: Patient consent was waived due to the retrospective nature of the study.

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