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Research Article

# Impact of P2Y12 Inhibitors on Thrombus Burden in Patients with ST-Segment Elevation Myocardial Infarction

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**Introduction and Aim:** In this study, we aimed to investigate the effects of P2Y12 inhibitors administered at the time of admission to the emergency department in patients presenting with ST-segment elevation myocardial infarction (STEMI) and undergoing primary percutaneous coronary intervention on the thrombus score in the culprit lesion.

**Materials and Methods:** This retrospective study planned to compare the pre-procedural thrombus scores of 225 patients who presented with STEMI underwent primary percutaneous coronary intervention, and received different P2Y12 inhibitors within 2 hours after the onset of chest pain.

**Results:** A total of 225 patients were included in our study. Among them, 72 patients received clopidogrel, 85 received ticagrelor, and 68 received prasugrel as the P2Y12 inhibitor. The pre-procedural Grade 5 thrombus was significantly lower in the ticagrelor group compared to the other groups (Clopidogrel 77.78%, Ticagrelor 61.18%, Prasugrel 77.94%; p=0.017).

**Conclusions:** In our study, ticagrelor among the pre-procedurally loaded P2Y12 inhibitors was found to be superior in terms of early thrombus intensity, and these results are thought to be associated with the early onset antiplatelet effect of ticagrelor.

**Keywords:** ST segment elevation myocardial infarction, Clopidogrel, Prasugrel, Ticagrelor, Thrombus score

## 1. INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a common condition caused by intracoronary thrombosis following plaque rupture.[1] In patients with STEMI who undergo primary percutaneous coronary intervention (PCI), intracoronary thrombosis has been observed in up to 91.6% of cases during angiography.[2] A study comparing 900 STEMI patients investigated the relationship between thrombus score and cardiac events (death, myocardial infarction, and recurrent revascularization). The study found that the TIMI thrombus score was associated with 2-year mortality in patients with grade 0-3 thrombus compared to grade 4-5 thrombus (p<0.001).[2] Thus, a large thrombus was identified as an independent predictor of mortality and major cardiac events. In guidelines, PCI is considered the best and most current treatment option for STEMI.[3] Intracoronary thrombus in STEMI patients is regarded as a negative prognostic factor for in-hospital and long-term adverse cardiac events.[4] Early reperfusion in the culprit lesion before intervention has been shown to create significant changes in ejection fraction (EF), microvascular obstruction, and infarct area.[5]

For patients presenting with STEMI, dual antiplatelet therapy (aspirin and an ADP antagonist) is recommended, with prasugrel

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or ticagrelor primarily suggested. Clopidogrel is recommended if prasugrel and ticagrelor are unavailable, contraindicated, or cannot be tolerated.[3] In this study, we aimed to investigate the effect of the P2Y12 inhibitor given at the time of admission to the emergency department on the thrombus score in the culprit lesion.

## 2. MATERIALS AND METHODS

Our study was conducted by retrospectively examining the files and coronary angiography images of patients with a diagnosis of STEMI followed in the Coronary Intensive Care Unit of Sakarya University Training and Research Hospital Cardiology Department between 01/01/2018 and 30/08/2019

Patients aged between 30 and 75 years, who presented with chest pain within the first 3 hours and underwent primary PCI, and who received dual antiplatelet therapy at the time of diagnosis in the emergency department were included in the study. Patients with a history of previous coronary revascularization, stent thrombosis, thrombophilia, active treatment for oncologic disease, a history of chemotherapy, rheumatic disease, end-stage renal failure, hemodialysis, those who had used oral antiaggregants in the last week, those with a history of hematologic disorders affecting platelet function, and those with a history of cerebrovascular disease were excluded from the study.

Two hundred twenty five patients (189 male, 36 female) were included in our study. The included patients' demographic characteristics were obtained from the hospital database records. All patients received 300 mg of aspirin and, 60 mg of prasugrel/180 mg of ticagrelor/600 mg of clopidogrel in the emergency department according to the guidelines at the time of diagnosis. All patients received UFH i.v. bolus during PCI of 70-100 IU/kg. The patients were divided into three groups according to prasugrel, ticagrelor, or clopidogrel administration. The ECGs of the patients were evaluated, and the localization of myocardial infarction was classified.

Blood samples taken from the patients during admission and in the coronary intensive care unit, as well as other laboratory values such as urea, creatinine, estimated glomerular filtration rate (GFR), LDL, HDL, triglyceride, total cholesterol, and HbA1c levels, were recorded.

Coronary angiographies were performed by experienced cardiologists. Nonionic low-osmolality contrast medium (Omnipaque 350 MG/ml; GE Healthcare, Cork, Ieland) was used in coronary interventions. Coronary angiography images were reviewed by two different interventional cardiologists, and the culprit lesion, TIMI thrombus score, initial TIMI flow grade, and post-procedure TIMI flow grade were evaluated.

The door-to-cross-wire time was calculated based on the admission and cross-wire times. Angiographic classification of thrombus density was performed using the TIMI thrombus classification[6] , which includes Grade 0 to Grade 5 thrombus.

According to this classification:

Grade 0: Thrombus is not visible angiographically.

Grade 1: Suspected thrombus, irregularity at the lesion borders, decreased contrast density.

Grade 2: Definite thrombus present, size ≤1/2 of the luminal diameter.

Grade 3: Definite thrombus present, size <1/2-<2 of the luminal diameter.

Grade 4: Definite thrombus present, size >2 times the luminal diameter.

Grade 5: Total occlusion is present. Thrombus burden cannot be evaluated due to this.

### 2.1 Statistical Analysis

Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL) software. The normal distribution of variables was examined using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Continuous variables were expressed as mean (±standard deviation) or median (interquartile range) depending on their normality distribution. Non-normally distributed variables were compared using the Kruskal-Wallis test. Pairwise comparisons were made using the Mann-Whitney U test and evaluated with Bonferroni correction. Normally distributed variables were compared using a one-way ANOVA test. The homogeneity of variances was assessed using the Levene test. The chi-square test was used to determine whether there was a difference in categorical variables between the groups. Post-hoc analysis results were considered. A type-1 error level of 5% was used for statistical significance.

## 3. RESULTS

Two hundred twenty five atients (189 male, 36 female) were included in our study. The mean age of the patients was 55.5±8.3 years, and there was no significant difference between the groups (56.2±7.1 in the clopidogrel group, 55.9±9.4 in the ticagrelor group, 54.1±9 in the prasugrel group; p=0.245). Among these patients, 114 had inferior MI, 79 had anterior MI, 11 had extensive anterior MI, 9 had inferoposterior, 6 had inferolateral, 3 had high lateral, 2 had posterior, and 1 had posterolateral MI diagnosis.

Seventy two patients received clopidogrel, 85 received ticagrelor, and 68 received prasugrel loading in appropriate doses. There was no statistically significant difference between the study groups regarding age, gender, hypertension, diabetes mellitus, smoking status, hyperlipidemia, presence of coronary artery disease (Table 1)

The creatinine levels in the emergency department were higher in the clopidogrel group compared to the other groups (Clopidogrel 0.95 (0.82-1.1), Ticagrelor 0.84 (0.74-0.99), Prasugrel 0.85 (0.71-0.96); p=0.002), and the GFR was lower in the clopidogrel group (Clopidogrel 88.0 (66.0-98.0), Ticagrelor 98.8 (83.2-104.0), Prasugrel 101.5 (88.3-107.0); p<0.001) (Table 2)

**Table 1.**

*Comparison of Baseline Characteristics Among the Study Groups*

| Parameter | Clopidogrel | Ticagrelor | Prasugrel | p-value |
|---|---|---|---|---|
| **Age (years)** | 56.2±7.1 | 55.9±9.4 | 54.1±9.9 | 0.245 |
| **Gender (Female/Male) %** | 15.3/84.7 | 16.5/83.5 | 16.2/83.8 | 0.978 |
| **Hypertension (%)** | 45.8 | 36.5 | 29.4 | 0.130 |
| **Diabetes Mellitus (%)** | 29.2 | 22.4 | 29.4 | 0.522 |
| **Smoking (%)** | 63.9 | 77.6 | 77.9 | 0.089 |
| **Hyperlipidemia (%)** | 22.2 | 25.9 | 38.2 | 0.089 |
| **Coronary Artery Disease (%)** | 5.6 | 7.1 | 4.4 | 0.780 |
| **Family History (%)** | 4.2 | 5.9 | 5.9 | 0.867 |

**Table 2.**

*Comparison of Laboratory Values Among the Study Groups*

| Parameter | Clopidogrel | Ticagrelor | Prasugrel | p-value |
|---|---|---|---|---|
| **Creatinine (mg/dL)** | 0.95 (0.82-1.1) | 0.84 (0.74-0.99) | 0.85 (0.71-0.96) | **0.002*** |
| **GFR (mL/min/1.73 $m^2$)** | 88.0 (66.0-98.0) | 98.8 (83.2-104.0) | 101.5 (88.3-107.0) | **<0.001**** |
| **WBC ($10^3/mm^3$)** | 11.0 (9.2-13.6) | 11.1 (9.6-14.1) | 12.2 (9.6-15.6) | 0.446 |
| **LDL (mg/dL)** | 137.1±32.6 | 142.8±30.8 | 147.0±36.5 | 0.150 |
| **TG (mg/dL)** | 95.0 (59.0-187.5) | 87.0 (56.5-166.5) | 113.0 (65.3-196.5) | 0.254 |
| **HDL (mg/dL)** | 42.0 (36.5-48.0) | 43.0 (36.5-49.0) | 40.0 (36.0-46.0) | 0.125 |
| **HbA1C (%)** | 5.8 (5.5-6.2) | 5.7 (5.4-6.3) | 5.7 (5.5-7.5) | 0.109 |
| **Initial Troponin (ng/L)** | 49.2 (11.7-186.0) | 34.0 (8.8-154.0) | 37.5 (12.3-140.5) | 0.286 |

**GFR=** Glomerular Filtration Rate , **WBC=** White Blood Count, **LDL=**Low-Density Lipoprotein, **TG=**Triglyserides, **HDL=** High-Density Lipoprotein, HbA1C: Haemoglobin A1C

*: Creatinine is higher in the Clopidogrel group.

**: GFR is lower in the Clopidogrel group compared to other groups.

The culprit lesion in the patients was located in the LAD in 89, RCA in 89, CX in 33, RCA's posterolateral branch in 5, major OM in 4, D1 in 2, IM in 2, and PDA in 1 patient. The door-to-cross time, pain-to-cross time, tirofiban infusion rate, and no-reflow rate were similar among the groups (Table 3).

When initial TIMI flow rates were divided into 0/1 and 2/3 and compared, no significant difference was observed among the groups (Figure 1).

The initial Grade 5 thrombus was significantly lower in the ticagrelor group compared to the other groups (Clopidogrel 77.78%, Ticagrelor 61.18%, Prasugrel 77.94%; p=0.017). (Figure 2).

**Table 3.**

*Angiographic Findings Among the Study Groups*

| Parameter | Clopidogrel | Ticagrelor | Prasugrel | p-value |
|---|---|---|---|---|
| **Door-to-Cross Time (minutes)** | 39.0 (27.5-51.0) | 38.0 (31.0-48.0) | 33.5 (26.5-43.5) | 0.057 |
| **Pain-to-Cross Time (minutes)** | 151 (96.25-196.0) | 138 (95-208.5) | 122 (86.5-171) | 0.156 |
| **Tirofiban Infusion (%)** | 2.8 | 1.2 | 5.9 | 0.245 |
| **No-Reflow (%)** | 4.2 | 4.7 | 1.5 | 0.530 |

**Figure 1.**

*İnitial TIMI Flow in the Study Groups*

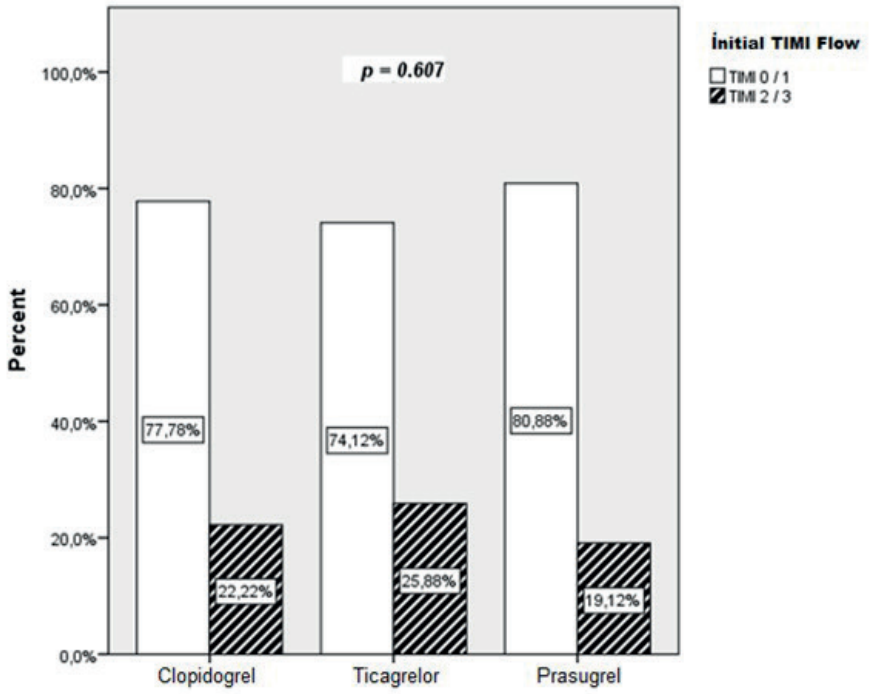
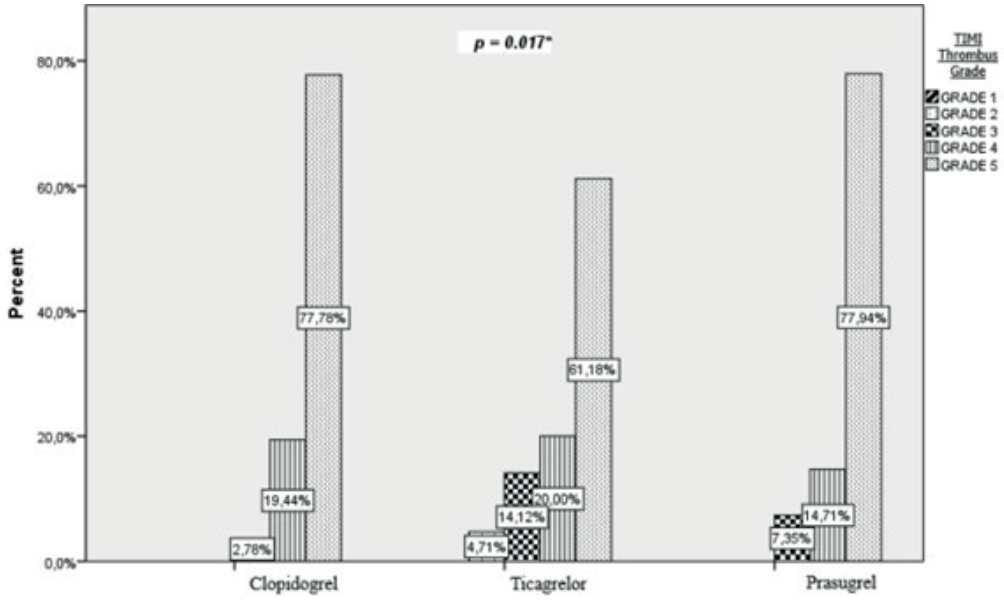



**Figure 2.**

*Thrombus Scores and Grades in the Study Groups*




*Grade 5: Lower in the ticagrelor group compared to the other groups
*Grade 3 : Clopidogrel group has a lower incidence of Grade 3 thrombus compared to the ticagrelor group and is similar to the prasugrel group.

## 4. DISCUSSION

In our study, the pre-procedural thrombus burden in the ticagrelor group was significantly lower than in the other groups. This finding is believed to be related to the early onset of antiplatelet efficacy of ticagrelor. In our study, an evaluation has been made in terms of preoperative thrombus burden, and this is the first study conducted on this subject. Since our study was conducted in 2018, emergency department administered P2Y12 inhibitors according to the 2017 ESC STEMI guidelines.[7] However, the 2023 ESC Acute Coronary Syndrome guidelines have reclassified P2Y12 inhibitor loading as Class 2b.[3]

Ticagrelor inhibits adenosine uptake from red blood cells and increases extracellular adenosine, leading to platelet aggregation inhibition and vasodilation.[8] In healthy volunteers, ticagrelor reached maximum plasma concentration within approximately 1.5 hours after the loading dose.[9] In stable coronary artery patients, after 180 mg of ticagrelor loading, significant antiplatelet effects were achieved within the first 30 minutes, and a nearly complete antiplatelet effect (>80%) was observed within 1 hour.[10] In our study, the door-to-cross time was 38.0 (31.0-48.0) minutes in the ticagrelor group, similar to the other groups, indicating that ticagrelor's early-onset antiplatelet effect reduced thrombus burden more compared to other preparations.

The PLATO study demonstrated the superiority of ticagrelor over clopidogrel in platelet inhibition.[11] Another study comparing ticagrelor and prasugrel in STEMI patients found that ticagrelor had superior platelet inhibition after 5 days.[12] As an active drug, Ticagrelor provides early platelet inhibition compared to prasugrel because of its mechanism.[13] Significant platelet inhibition was reported in the PLATO PLATELET sub-study in 4/5 of STEMI patients and 7/7 of NSTEMI patients within 1 hour after 180 mg of ticagrelor loading.[14] Moreover, in a meta-analysis of 14 studies involving 1822 patients evaluating platelet inhibition, ticagrelor had higher platelet inhibition than prasugrel (High on-treatment platelet reactivity (HTPR) rates were 1.5% for ticagrelor and 9.8% for prasugrel ($p<0.001$)).[15] This earlier onset of platelet inhibition with ticagrelor, compared to clopidogrel and prasugrel, is consistent with the results of our study favoring ticagrelor in terms of thrombus score.

The ATLANTIC study, published in 2014, is the only randomized controlled trial conducted regarding the timing of P2Y12 inhibitors.[16] In this study, ticagrelor was compared in STEMI patients by administering it pre-hospital and in the catheter laboratory. No significant differences were found in pre-procedural TIMI 3 flow presence, ST-segment resolution, or composite endpoints. Major and minor bleedings were similar in both arms. However, when other endpoints of the study were examined, stent thrombosis was significantly less in the pre-hospital group ($p=0.008$). Furthermore, limitations of the study mentioned delayed absorption due to morphine intake, and a significant difference in EKG-based primary endpoint was observed in patients not taking morphine. The study did not include an angiographic evaluation of thrombus burden. In our study, although there was no significant difference among the groups in terms of TIMI flow rates, the favorable difference in thrombus score in favor of ticagrelor may be associated with its early onset effects.

The ISAR-REACT 5 study is the trial comparing ticagrelor and prasugrel in patients with acute coronary syndrome.[17] In this study, the composite of death from cardiovascular causes, myocardial infarction, or stroke occurred in 161 out of 2012 patients (8.1%) in the ticagrelor group and 124 out of 2006 patients (6.3%) in the prasugrel

group (hazard ratio, 1.32; 95% CI, 1.04 to 1.66). Angiographic data were not examined in the study, and one-year clinical outcomes were evaluated. According to the results of this study, despite the early onset of antiplatelet effect with ticagrelor, prasugrel is more effective in the long term.

## LIMITATIONS

Our study was limited by its single-center design and a relatively small number of patients, which may have impacted the evaluation of clinical outcomes. Additionally, the study was retrospective and non-randomized and the results of TIMI grade flow and TIMI thrombus assessment conducted by operators could differ from evaluations done by a core lab, which could introduce bias.

## CONCLUSION

In our study, the thrombus burden before the procedure was significantly lower in the ticagrelor group compared to the other groups, while no significant difference was observed between the prasugrel and clopidogrel groups. This finding suggests that the early onset of ticagrelor's antiplatelet effect may contribute to its effectiveness in reducing thrombus burden. However, further randomized and prospective studies are needed to confirm these findings.

## Financial Support

No financial support was received from any institution for the study.

## Conflict of Interest

There is no conflict of interest between the authors.

## Author contribution

All authors contributed to substantial contributions to conception and design (EE,MBV ), or acquisition of data (DY,EE), or analysis and interpretation of data (MBV-DY), drafting the article or revising it critically for important intellectual content (EE-MBV) and final approval of the version to be published.

## Ethical Statement

The study was performed in accordance with the ethical considerations of the Helsinki Declarations. The study was approved by the ethics committee of Sakarya University, with decision number 71522473/050.01.04/77, dated September 18, 2019.

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