## Original Article

# *Effect of Ticagrelor Loading Time on the Outcomes of Primary Percutaneous Coronary Intervention*

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## ABSTRACT

***Background:*** Patients with acute coronary syndrome experience fewer major adverse cardiovascular events when receiving ticagrelor as opposed to clopidogrel. Additionally, patients with ST-segment elevation myocardial infarction (STEMI) receiving primary percutaneous coronary intervention (PPCI) show better coronary reperfusion and prognosis. This study compared the safety and effectiveness of ticagrelor doses administered early and late in patients with STEMI undergoing PPCI.

***Methods:*** This prospective observational cohort study was conducted in a hospital with 350 patients diagnosed with recent STEMI and receiving PPCI. Patients were placed into 2 groups: prehospital (n = 179; loading dose > 60 min) and cath. lab (n = 171; loading dose < 60 min) before PPCI.

***Results:*** Following a 6-month follow-up period, the Kaplan-Meier analysis revealed that 85.2% of the cath. lab group and 88.8% of the prehospital group were still clinically free and did not have any adverse events. There was no significant difference between the 2 groups ($P$ = 0.357). The prehospital group had reduced thrombus load, greater post-PPCI ST-segment elevation resolution after 90 minutes, and considerably higher initial Thrombolysis in Myocardial Infarction (TIMI) flow grades II and III in the infarct-related artery than the cath. lab group. Both groups had comparable TIMI flow grades following PPCI.

***Conclusions:*** Prehospital administration of ticagrelor with a median time of about 2 hours before PPCI was safe and helped improve angiographic pre-PCI coronary reperfusion in STEMI patients undergoing PPCI, without increasing the risk of bleeding events, but it did not significantly affect the final angiographic results. ***(Iranian Heart Journal 2026; 27(2): 17-26)***


**KEYWORDS:** early loading; late loading; ticagrelor; ST-segment elevation myocardial infarction; primary percutaneous coronary intervention

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The majority of patients with ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation acute coronary syndrome (NSTEACS) are recommended to undergo percutaneous coronary intervention (PCI), per the most recent recommendations. For patients with STEMI, primary percutaneous coronary intervention (PPCI) is the recommended course of treatment; the earlier the better.[1]

In some patients, coronary revascularization with PPCI fails to improve the blood flow to the distal coronary vessels, as the restoration of the antegrade blood flow is not complete. These patients show no improvement in the electrocardiographic (ECG) findings associated with STEMI. This state is known as "the no-reflow phenomenon", indicating a portion of the coronary circulation with inadequate myocardial reperfusion and no angiographic indication of mechanical artery obstruction.[2]

Adequate platelet suppression via antiplatelet treatment is crucial for patients with STEMI undergoing PPCI to block P2Y12 receptors and thromboxane A2-dependent platelet aggregation.[3]

Aspirin and P2Y12 receptor inhibitors (DAPT) aim to lower the risk of developing ischemic events including (re)infarction and stent thrombosis (ST) during PCI. If we take into account that the most rapid acting oral drugs of the P2Y12 inhibitors group take at least 30 to 60 minutes to achieve their effect, then using the antiplatelet drugs P2Y12 inhibitors sooner before PCI (a method known as pretreatment) might yield superior results.[3, 4]

Pretreatment with clopidogrel may lower the incidence of ischemic episodes without causing excessive bleeding in patients with STEMI, according to a number of studies and meta-analyses.[5] The new oral P2Y12 receptor antagonists, such as ticagrelor or prasugrel, on the other hand, suppress platelet activity in less than 1 hour, which is consistent with PPCI transfer times.[6, 7]

The ACCOAST trial was carried out to assess if pretreatment with prasugrel in NSTEMI patients undergoing PCI could be safe and reduce the rate of major adverse cardiovascular events (MACEs). The results suggested that pretreatment with prasugrel increased the rate of major bleeding complications; the trial, therefore, advised against the use of prasugrel before angiography.[7]

Ticagrelor has a rapid antiplatelet action, and it performs its action by directly inhibiting the platelet P2Y12 receptors.[6] Compared with clopidogrel, ticagrelor decreases the frequency of serious cardiovascular events in STEMI patients receiving PPCI.[8] It has also been observed to improve coronary blood flow after PCI and the prognosis of these patients.[9]

This study compared the safety and effectiveness of ticagrelor doses administered to patients with STEMI via either early loading (> 60 min prior to PPCI) or late loading (< 60 min before PPCI).

## METHODS

This hospital-based, prospective, observational cohort research included 350 patients who were at least 18 years old, newly diagnosed with STEMI based on the universal definition of myocardial infarction (MI) of the European Society of Cardiology, and receiving PPCI.[4] Having obtained approval from the ethics committee of Assiut University hospitals (Assiut Medical Ethical Review Board; IRB No. 17100943), the study was carried out from June 2021 through October 2022. Every patient provided written informed consent.

The exclusion criteria of this study were patients with contraindications to ticagrelor (eg, hypersensitivity), patients who received clopidogrel as initial loading after diagnosis with STEMI or are already on treatment with clopidogrel, patients who were on chronic oral anticoagulant treatment for any indication that could not be discontinued, patients who received upstream GP IIb/IIIa inhibitors, those who were discharged from our hospital after PPCI and had their antiplatelet therapy de-escalated from ticagrelor to clopidogrel during the period of follow-up, patients with cardiogenic shock at presentation (Killip class IV) (a condition characterized by a systolic blood pressure <

90 mm Hg without the use of positive inotropes or intra-aortic balloon support, unresponsiveness to intravenous fluids and markers of hypoperfusion as cold extremities, impaired mental status, or diminished urine output because of cardiac dysfunction),[10] and patients with missed follow-up.

There were 2 groups of patients: the loading dosage was administered more than 60 minutes prior to PPCI in the prehospital group (n = 179) and less than 60 minutes prior to PPCI in the cath. lab group (n = 171).

Every patient had thorough history taking; clinical examination; laboratory testing (complete blood count, liver and renal function tests, and electrolyte and cardiac enzymes); ECG at presentation, 90 minutes after PPCI, and then every day during the hospital stay; and echocardiography for the assessment of the affected myocardial territory and left ventricular ejection fraction using the Simpson method.

All patients included in this research received a loading dose of aspirin (300 mg) and ticagrelor (180 mg). All patients received ticagrelor (90 mg twice per day) plus aspirin and the other anti-ischemic medications with strict recommendations of using ticagrelor for 1 year after PPCI upon discharge from our hospital.

**Assessment During Hospital Admission**

All patients were evaluated preprocedurally regarding chest pain onset, vital signs, Killip class, bleeding complications, and the presence of ST-segment resolution. (50% of ST-segment elevation resolution was the cutoff point.) During the procedure, all patients were evaluated concerning angiographic data as initial Thrombolysis in Myocardial Infarction (TIMI) flow grade in the infarct-related artery (IRA), thrombus burden, occurrence of the no-reflow phenomenon, the need for GP IIb/IIIa inhibitors, and the final TIMI flow grade. Postprocedural ECG was done within 90 minutes to evaluate the degree of ST-segment resolution. (50% of ST-segment elevation resolution was the cutoff point.) All patients were also monitored during their hospital stay for the occurrence of early ST, recurrence of chest pain, post-MI heart failure, arrhythmias, and bleeding complications.

The TIMI coronary grade flow was the method used to categorize the perfusion of the epicardial coronary arteries. TIMI 0 denotes complete vessel occlusion, TIMI 1 signifies faint antegrade flow with insufficient filling of the distal coronary bed, TIMI 2 implies complete but delayed filling of distal coronary bed, while TIMI 3 represents normal coronary filling.[11] The TIMI scale for thrombus burden was scored based on 5 grades.[12]

**Killip Classification of Acute MI**

The Killip classification was drawn upon to categorize each subject. The definitions of Killip classes are presented below [13]:

Killip I: Patients who are free from any clinical sign of heart failure.

Killip II: Patients with crackles in the lungs, raised jugular venous pressure, and an S3 gallop.

Killip III: Patients with acute pulmonary edema.

Killip IV: Patients with cardiogenic shock or hypotension (systolic blood pressure < 90 mm Hg) and signs of hypoperfusion (oliguria or impaired mental status).

**Bleeding Academic Research Consortium (BARC) Classification for Bleeding Complications**

BARC created a reliable and consistent classification for identifying bleeding, which was used in this research.[14]

**Follow-up After Discharge**

All patients were followed for 6 months regarding clinical outcomes as MACEs (recurrent nonfatal MI, IRA revascularization,

heart failure hospitalization, cerebrovascular stroke [CVS], and death) and bleeding manifestations according to the BARC classification.

Efficacy endpoints were TIMI flow grades in the initial and final angiography in the IRA, occurrence of the no-reflow phenomenon, pre- and post-PPCI ST-segment resolution, ST and other MACEs, while the safety endpoint was considered to be the incidence of bleeding.

**Sample Size Calculation**

Epi-info, version 7, was employed to determine the sample size. This study included 350 patients who were diagnosed with STEMI based on the fourth universal definition of MI and received PPCI.

**Statistical Analysis**

SPSS, version 26, was used for statistical analysis (IBM Inc, Chicago, IL, USA). Histograms and the Shapiro-Wilks test were utilized to assess the normality of data distribution. The mean and standard deviation (SD) of quantitative parametric variables were displayed, and the unpaired Student *t* test was used to compare the 2 groups. The Mann-Whitney test was applied to evaluate quantitative nonparametric data, which were displayed as median and interquartile range (IQR). The $\chi^2$ or Fisher exact test, as applicable, was used to examine qualitative variables, expressed as frequency and percentage (%). For the event-free survival study, the Kaplan-Meier method with the log rank test was employed. Statistical significance was defined as a 2-tailed *P* value of less than 0.05.

## RESULTS

There were no discernible differences in patients' ages, sexes, or other related comorbidities (Table 1).

Pre-PCI ST-segment resolution was recorded in 25 patients (14%) in the prehospital group, whereas the post-PCI ST resolution after 90 minutes was significantly higher among patients in the prehospital group than those in the cath. lab group. Arrhythmias, ejection fraction by the Simpson method, and MI territory were insignificantly different between the 2 groups (Table 2).

Initial TIMI flow grades II and III in the IRA were significantly higher in the prehospital group than in the cath. lab group. Median stent diameter, length and approach of PCI, final TIMI, rate of the occurrence of the no-reflow phenomenon, and the need for GP IIb/IIIa inhibitors were insignificantly different between the 2 studied groups. Thrombus burden was significantly higher in the cath. lab group than in the prehospital group. A comparison of the initial and final TIMI grades in each study group separately showed that both groups had significant improvements in TIMI flow ($P < 0.001$) (Table 3).

Development of in-hospital MACE (ST and death), Killip classification, and number of patients who developed bleeding complications according to the BARC classification were insignificantly different between the 2 studied groups (Table 4).

During 6 months of follow-up, only 2 cases died (of cardiovascular causes), 10 cases (2.9%) developed recurrent ACS, another 10 cases (2.9%) were rehospitalized due to heart failure, 1 case developed ST, and 4 cases (1.1%) needed IRA revascularization. Nonetheless, there was no discernible difference in MACE development between the 2 groups (Table 5).

According to the Kaplan-Meier analysis after 6 months of follow-up, 85.2% of the cath. lab group vs 88.8% of the prehospital group were still clinically free and did not develop adverse events, with no significant difference between the 2 groups ($P = 0.357$) (Figure 1).

**Table 1.** Baseline characteristics of the 2 studied groups

| | Cath. Lab (No.= 171) | Prehospital (No.= 179) | *P* |
|---|---|---|---|
| Age (y) | 55.02 ± 11.41 | 55.47 ± 9.83 | 0.688 |
| Male sex | 143(83.6%) | 160(89.4%) | 0.114 |
| Diabetes | 59(34.5%) | 52(29.1%) | 0.273 |
| Hypertension | 54(31.6%) | 52(29.1%) | 0.607 |
| Ischemic heart disease | 23(13.5%) | 19(10.6%) | 0.414 |
| Smoking | 111(64.9%) | 129(72.1%) | 0.150 |

Data are presented as mean ± SD or frequency (%).

**Table 2.** ECG findings and echocardiographic assessment of left ventricular ejection fraction and myocardial infarction territory in both studied groups

| | | Cath. Lab (No. = 171) | Prehospital (No. = 179) | *P* |
|---|---|---|---|---|
| ECG Finding | | | | |
| Pre-PCI ST resolution | | -- | 25(14.0%) | ---- |
| Post-PCI ST resolution after 90 min | | 135(78.9%) | 167(93.3%) | <0.001* |
| Arrhythmias | | 10(5.8%) | 12(6.7%) | 0.731 |
| VT | | 4(2.3%) | 7(3.9%) | |
| VF | | 2(1.2%) | 2(1.1%) | |
| AF | | 3(1.8%) | 2(1.1%) | |
| All of the above | | 1(0.6%) | 1(0.6%) | |
| Heart block | | 0(0.0%) | 0(0.0%) | |
| EF by the Simpson method (%) | | 50.0 (30 – 66) | 49.0 (31 - 68) | 0.948 |
| Myocardial infarction territory | Anterior | 91(53.2%) | 106(59.2%) | 0.207 |
| | Inferior | 76(44.4%) | 65(36.3%) | |
| | Lateral | 4(2.3%) | 8(4.5%) | |

Data are presented as median (IQR) or frequency (%).

* Significant *P* value < 0.05
ECG: electrocardiography; PCI: percutaneous coronary intervention; VT: ventricular tachycardia; VF: ventricular fibrillation; AF: atrial fibrillation; EF: ejection fraction

**Table 3.** Angiographic and procedural findings between the 2 studied groups

| | | Cath. Lab (No.= 171) | Prehospital (No. = 179) | *P*[1] |
|---|---|---|---|---|
| Median duration between loading and wire crossing (minutes) | | 36(11–59) | 120(60–369) | <0.001* |
| Median stent diameter | | 3.5 (2.25–4.5) | 3.5(2.5–4.5) | 0.672 |
| Median stent length | | 32.5(15–90) | 30.0(2–120) | 0.143 |
| PCI approach | Femoral | 164(95.9%) | 175(97.8%) | 0.319 |
| | Radial | 7(4.1%) | 4(2.2%) | |
| Thrombus burden at initial angiography | 3 | 10(5.8%) | 14(7.8%) | <0.001* |
| | 4 | 25(14.6%) | 56(31.3%) | |
| | 5 | 136(79.5%) | 109(60.9%) | |
| Initial TIMI grade | Grade 0 | 136(79.5%) | 109(60.9%) | <0.001* |
| | Grade 1 | 7(4.0%) | 7(3.9%) | |
| | Grade 2 | 11(6.4%) | 11(6.1%) | |
| | Grade 3 | 17(9.9%) | 52(29.0%) | |
| Final TIMI grade | Grade 1 | 1(0.6%) | 2(1.1%) | 0.142 |
| | Grade 2 | 12(7.0%) | 5(2.8%) | |
| | Grade 3 | 158(92.4%) | 172(96.1%) | |
| No reflow | | 7(4.1%) | 6(3.4%) | 0.714 |
| Use of GP IIb/IIIa inhibitors | | 62(36.3%) | 71(39.7%) | 0.511 |
| *P* value[2] | | <0.001* | <0.001* | |

Data are presented as median (IQR) or frequency (%).

* Significant *P* value < 0.05; *P* value[1]: for comparing both studied groups, *P* value[2]: for comparing TIMI flow grade in the same group overtime

PCI: percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction

**Table 4.** In-hospital events and bleeding complications between the 2 studied groups

| | | Cath. Lab (No. = 171) | Prehospital (No. = 179) | *P* |
|---|---|---|---|---|
| Hospital Events | | | | |
| Killip class | 1 | 162(94.7%) | 164(91.6%) | 0.547 |
| | 2 | 8(4.7%) | 14(7.8%) | |
| | 3 | 1(0.6%) | 1(0.6%) | |
| In-hospital MACE | In-hospital mortality | 1(0.6%) | 0(0.0%) | 0.489 |
| | Acute ST (0-24 h) | 1(0.6%) | 0(0.0%) | |
| Bleeding Events | | | | |
| In-hospital bleeding complications according to the BARC classification | Non (Type 0) | 154(90.1%) | 160(89.4%) | 0.862 |
| | BARC (1-5) | 17(9.9%) | 19(10.6%) | |
| | Type 1 | 4(2.3%) | 8(4.5%) | |
| | Type 2 | 13(7.6%) | 11(6.1%) | |
| | Type 3 | 0(0.0%) | 0(0.0%) | |
| | Type 4 | 0(0.0%) | 0(0.0%) | |
| | Type 5 | 0(0.0%) | 0(0.0%) | |
| Follow-up period bleeding events according to the BARC classification | | 14(8.2%)<br>14(8.2%)<br>0(0.0%)<br>0(0.0%)<br>0(0.0%)<br>0(0.0%) | 13(7.3%)<br>12(6.7%)<br>1(0.6%)<br>0(0.0%)<br>0(0.0%)<br>0(0.0%) | 0.734 |
| | Type 1 | | | |
| | Type 2 | | | |
| | Type 3 | | | |
| | Type 4 | | | |
| | Type 5 | | | |

Data are presented as frequency (%).

MACE: major adverse cardiovascular events; BARC: Bleeding Academic Research Consortium; ST: stent thrombosis

**Table 5.** Six-month events between the 2 studied groups

| | Cath. Lab (No. = 171) | Prehospital (No. = 179) | *P* |
|---|---|---|---|
| All-cause mortality | 2(1.2%) | 0(0.0%) | 0.238 |
| Cardiovascular mortality | 2(1.2%) | 0(0.0%) | 0.238 |
| Recurrent ACS | 6(3.5%) | 4(2.2%) | 0.534 |
| Heart failure hospitalization | 6(3.5%) | 4(2.2%) | 0.534 |
| Stent thrombosis | 1(0.6%) | 0(0.0%) | 0.489 |
| IRA revascularization | 3(1.8%) | 1(0.6%) | 0.360 |
| CVS | 0(0.0%) | 0(0.0%) | ---- |
| Total MACE | 18(10.5%) | 9(5.0%) | 0.054 |

Data are presented as frequency (%).

ACS: acute coronary syndrome; CVS: cerebrovascular stroke; MACE: major adverse cardiovascular events; IRA: infarct-related artery

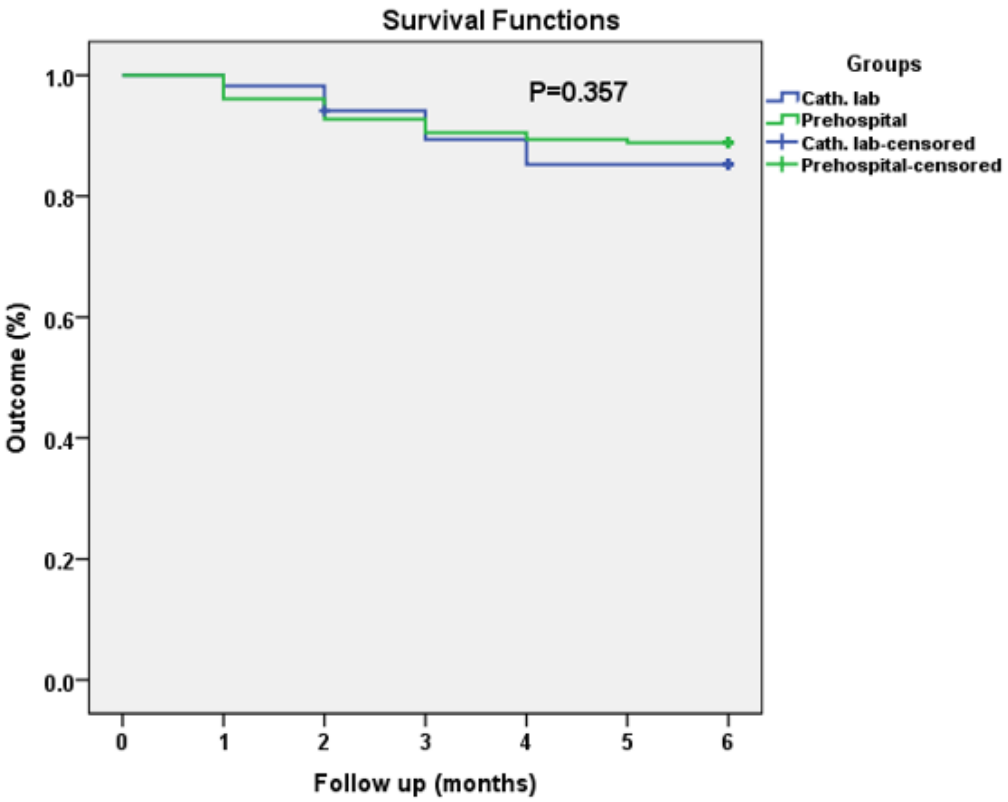


**Figure 1.** The Kaplan-Meier curve for the comparison of time to outcome (death, recurrent acute coronary syndrome, admission with heart failure, infarct-related artery revascularization, cerebrovascular stroke, or bleeding) between the 2 studied groups

## DISCUSSION

In order to limit myocardial ischemia, reduce the size of infarction, and lower the risk of heart failure caused by left ventricular dysfunction following MI, it is crucial to diagnose and treat STEMI as soon as possible. STEMI is a life-threatening acute manifestation of coronary artery disease that manifests if complete obstruction of the coronary vessels happens and is accompanied with a high morbidity and mortality rate.[15]

Regarding thrombus burden, in the present study, the prehospital group showed a statistically significant decrease in the patient population with a totally occluded IRA (grade 5) compared with the cath. lab group with greater number of patients having grades 3 and 4 thrombus size.

With respect to the TIMI grade flow in the IRA, the prehospital group showed a statistically significant improvement of flow (TIMI grade 3) in the initial angiography. Similar results were documented by Zhang et al.[16] Likewise, Lupi et al[17] retrospectively compared 143 patients with STEMI loaded with ticagrelor at the site of first STEMI diagnosis or in the ambulance with a median transfer time of at least 1.5 hours with 143 patients with STEMI loaded in the lab before PPCI. Similar findings were reported in the large RENOVAMI registry for patients with STEMI.[18]

Our findings vis-à-vis the initial TIMI flow grade were different from those in the ATLANTIC trial.[19] The prehospital ticagrelor administration was proved to be secure in the ATLANTIC trial,[19] but it had little effect on the pre-PCI TIMI grade flow. This could be explained by the short period between

loading and angiography; our study showed a median time gap of 120 minutes compared with 48 minutes in the ATLANTIC trial due to a delayed referral system. Nevertheless, if we compare the final TIMI flow grade after PCI on the IRA, there will be no significant difference between both study groups with a predominant TIMI 3 flow grade in the final angiography in both groups. Similar outcomes were obtained by the ATLANTIC trial,[19] Zhang et al,[16] and D'Entremont et al.[20] Similar outcomes as regard ECG findings were documented by Zhang et al.[16] In the ATLANTIC trial,[19] there was a difference between both groups regarding more than 70% ST-segment resolution after PCI in favor of the prehospital group, although the difference was not statistically significant. In the study by D'Entremont et al,[20] there was also a nonsignificant difference between both groups in favor of the non–PCI-capable hospital transfer group.

In terms of ECG results, the 2 groups were similar regarding the measurements of left ventricular systolic function measured by the Simpson method, chiming with the results reported by Zhang et al.[16]

The Killip classification of patients with STEMI revealed no discernible difference between the 2 study groups, with more than 90% of patients presenting with Killip I in both groups. Similar results were obtained in the ATLANTIC trial.[19] Zhang et al[16] reported that the number of patients with new-onset heart failure was higher in the cath. lab group. A similar result was found by D'Entremont et al.[20]

In the current study, the 2 groups had comparable rates of arrhythmic complications. In-hospital mortality due to reinfarction, heart failure, stroke, or definite ST did not significantly differ between the 2 studied groups. Only 1 case died during the hospital admission period. These results are concordant with findings reported by the ATLANTIC trial,[19] Zhang et al,[16] Lupi et al,[17] and D'Entremont et al.[20]

Follow-up of the study population for 6 months was done searching for MACEs (all-cause mortality, reinfarction, ST, IRA revascularization, heart failure hospitalization, and CVS) and bleeding complications. The results revealed no statistical difference between the 2 studied groups. These findings are in line with the data from the ATLANTIC trial[19] and Zhang et al,[16] considering the fact that they had a shorter follow-up period (only 1 month).

With regard to bleeding complications, all bleeding events were minor events among types 1 and 2 according to the BARC classification, with the results showing no difference between both groups. Finally, no cases of CVS were reported during the follow-up period. These follow-up results were in line with the results of the ATLANTIC trial,[19] which indicated no difference between both groups regarding bleeding events. Zhang et al[16] reported similar findings, noting that the preprocedural group had fewer patients with definite ST and reinfarction within 28 days following PCI than those in the in-lab group. They were, however, unable to achieve statistically significant results.

Our results were more aligned with the study of Zhang et al,[16] which concluded that the median duration from ticagrelor loading to angiography in the preprocedural group was 59 minutes, and associated with significantly higher population with patent IRA, early ST-segment elevation resolution, significant reduction of new-onset heart failure, and reduced risk of ST compared with the in-lab group.

## CONCLUSIONS

Positive results of early ST-segment elevation resolution and early IRA reperfusion indicated that prehospital loading with ticagrelor, with a median time

of roughly 2 hours prior to PPCI, was safe and improved angiographic pre-PCI coronary reperfusion in STEMI patients undergoing PPCI. It did not significantly alter the final angiographic results, nor did it increase the risk of bleeding events. However, important outcomes, including ST, heart failure, arrhythmias and overall mortality, did not differ between the 2 studied groups of patients.

**Study Limitations**

One of the study limitations was the comparatively small sample size. The statistical power of the results was constrained by the study's single-center design. The cornerstone of the trial design was the accurate timing of obtaining the loading dosage of ticagrelor; consequently, we overlooked some patients who arrived with STEMI and had PPCI who we could not know the exact moment of loading. The angiographic findings with reference to the final TIMI flow grade might have been impacted by the usage of GP IIb/IIIa inhibitors. It is impossible to fully rule out observational bias because the patient groups were not randomly assigned.

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**Conflict of Interest:** Not applicable.

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