

## ORIGINAL STUDIES

# Effect of prehospital treatment in STEMI patients undergoing primary PCI

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## Abstract

**Background:** The appropriate timing to administer antithrombotic therapies in ST-elevation myocardial infarction (STEMI) remains uncertain. This study aims to evaluate the role of antithrombotic therapy administration at first medical contact (FMC) compared with the administration in the Cathlab.

**Methods:** We conducted a “before-after” observational study enrolling STEMI undergoing primary percutaneous coronary intervention (PCI). Outcomes were evaluated during two successive periods, before (control group: aspirin only at FMC) and after (pretreated intervention group: heparin, aspirin plus ticagrelor at FMC) the introduction of a new regional pretreatment protocol.

**Results:** A total of 537 consecutive patients (300 in control vs. 237 in intervention group) were enrolled. The pretreated compared with no pretreated population showed better basal reperfusion, expressed as basal Thrombolysis in Myocardial Infarction (TIMI)-flow ( $p$  for trend  $p < 0.001$ ). Pretreated population showed lower frequency of TIMI 0 (56.5% vs. 73.7%, odds ratio [OR]: 0.46, 95% confidence interval [CI]: 0.32–0.67,  $p < 0.001$ ) and higher frequency of TIMI 2–3 (33.3% vs. 19.3% OR: 2.0, 95% CI: 1.38–2.00,  $p < 0.001$ ) and TIMI 3 (14.3% vs. 9.7%, OR: 1.56, 95% CI: (0.92–2.65),  $p = 0.094$ ). Pretreated compared with no pretreated population showed reduced infarct size expressed as Troponin Peak (20,286 (8726–75,027) versus 48,676 (17,229–113,900),  $p = 0.001$ ), and higher left ventricular ejection fraction at discharge (53% (44–59) vs. 50% (44–56),  $p = 0.027$ ). In-hospital BARC  $\geq 2$  bleeding were similar (2.1% vs. 2.0%,  $p = 0.929$ , in pretreated versus no pretreated population, respectively).

**Conclusion:** This study provides support for an early pretreatment strategy in STEMI patients and confirmed the importance of an efficient organization of STEMI networks which allow initiation of antithrombotic treatment at FMC.

## KEYWORDS

anticoagulation, DAPT, myocardial reperfusion, prehospital, primary PCI, STEMI, ticagrelor

## 1 | INTRODUCTION

Achievement of early restoration of myocardial blood flow is one of the main goals in ST-elevation myocardial infarction (STEMI) to optimize myocardial salvage and to reduce mortality.<sup>1</sup>

Current practice guidelines emphasize the organization of STEMI networks since they decrease transfer time to primary percutaneous coronary intervention (PCI) centers and may allow the initiation of early treatment at first medical contact (FMC) by trained and equipped medical or paramedical staff.

STEMI is a dynamic event in which platelet activation is a key step in the process leading up to thrombus formation. Instituting early antithrombotic therapy when the platelet content of the fresh coronary thrombus is maximal and thus more susceptible to powerful antithrombotic agents may be an opportunity for improving the outcome of STEMI. Whereas it has been recognized that therapies as parenteral anticoagulation and dual antiplatelet therapy (DAPT, a combination of aspirin and a P2Y12 inhibitor) in patients treated with primary PCI are the cornerstone of treatment,<sup>1</sup> there is limited evidence with respect to when pharmacotherapy should be initiated in STEMI patients. Indeed only aspirin is recommended as soon as possible, anticoagulation is still recommended in addition to antiplatelet therapy during primary PCI<sup>1</sup> and the only randomized study testing the safety and efficacy of different timings of P2Y12 inhibitor initiation in STEMI is the ATLANTIC (Administration of Ticagrelor in the Cath lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) trial; prehospital (pre-H) administration of ticagrelor appeared to be safe but did not improve basal (pre-PCI) reperfusion compared with administration in the catheterization laboratory (Cath lab).<sup>2</sup> However, it is possible that in the setting of a randomized trial, the brief interval time from study drug administration in the ambulance to Cath lab may have limited the potential benefit of early pretreatment.

The aim of this study was to evaluate in a real-world STEMI network the potential role of early administration of antithrombotic therapy (pretreatment at FMC: in the ambulance or at the emergency department) compared with administration of treatment in the Cath lab.

## 2 | METHODS

### 2.1 | Study design and population

We conducted a “before-after” observational study enrolling patients with STEMI undergoing primary PCI at the Cardiology Department of the University hospital of Trieste, Italy, between January 2018 and September 2020. Outcomes of patients were evaluated during two successive periods, before (control group) and after (intervention

group) the introduction of a new regional treatment protocol, which started on June 18, 2019.

All STEMI patients were consecutively enrolled in a primary PCI-Registry where clinical history, main demographic, clinical, laboratory, electrocardiographic, procedural data, and reperfusion times were included in a central database. The study received institutional review board approval.

The diagnosis of STEMI was determined according to European Society of Cardiology (ESC) guidelines.<sup>1</sup>

“Patient’s delay” was defined as the time of patient’s response to initial symptoms (i.e., the time from symptom onset to the emergency system [EMS] call or to arrival to the emergency department). “ECG to balloon” was defined as the time from ECG to wire crossing. “Ischemia time” was defined as the time from the onset of chest pain to the wire crossing.

### 2.2 | Study treatment

From June 18, 2019, following a new regional treatment protocol, all the STEMI patients started to be pretreated with heparin and DAPT at FMC. Conversely, before June 18, 2019, all patients were treated with heparin and DAPT in the Cath lab. According to different protocol treatments, the whole population was therefore divided into two groups:

*No pretreated population (control group)* included all the patients before the introduction of the new regional treatment protocol. These patients received only aspirin (lysine salicylate 250 mg IV) at FMC. Only upon the arrival in the Cath lab, patients received heparin (70 UI/kg or max 5000 UI) and loading dose of clopidogrel or prasugrel or ticagrelor. The use of clopidogrel was relegated to patients who had contraindications to prasugrel and ticagrelor, and patients receiving oral anticoagulants. The choice of prasugrel or ticagrelor administration was left to the discretion of the operator. The recommended loading dose of clopidogrel was 300–600 mg orally followed by a maintenance dose of 75 mg, for ticagrelor the loading dose was 180 mg orally followed by 90 mg b.i.d and for prasugrel the loading dose was 60 mg orally, followed by 10 mg/day.

*Pretreated population (intervention group)* included all the patients enrolled after the introduction of the new regional treatment protocol. The protocol consisted of receiving pretreatment administration at the FMC with heparin (70 UI/kg or max 5000 UI), dual antiplatelet therapy consisting of aspirin (lysine salicylate 250 mg IV) plus ticagrelor loading dose (180 mg). All patients enrolled after the introduction of the new regional treatment protocol were considered as “intention to treat” (ITT) pretreated population and analyzed accordingly. Conversely, a “per protocol” (PP) population included only patients who complied with the treatment protocol (i.e., received heparin and aspirin plus ticagrelor loading dose at FMC).

In both the populations, control and intervention groups, the choice of the vascular access route (i.e., radial vs. femoral) was left to the discretion of the operator, although radial approach was strongly recommended. Thrombus aspiration, lesion predilatation, and the use of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors were left to the discretion of the operator. Furthermore, according to the institutional protocol, a complete echocardiographic evaluation was performed before discharge and echocardiographic data were also included in the central database.

## 2.3 | Study end points

The primary endpoint of the study was basal Thrombolysis in Myocardial Infarction (TIMI) flow defined according to TIMI study group.<sup>3</sup> The secondary endpoints were troponin peak, left ventricular ejection fraction (LVEF) at discharge (calculated with Simpson biplane methods according to guidelines<sup>4</sup>) and the use of GPIIb/IIIa inhibitors during PCI.

Safety endpoint was in-hospital bleeding defined as BARC (Bleeding Academic Research Consortium Definition for Bleeding<sup>5</sup>)  $\geq 2$  bleeding.

Subgroup analyses to evaluate variations in treatment effect on the main outcomes was performed in the PP population. Subgroups analysis was performed according to Patient delay, ECG to balloon time and ischemia time.

## 2.4 | Statistical analysis

All statistical analyses were performed using IBM SPSS Statistical Package 25. Clinical, instrumental, and laboratory variables were expressed as median and interquartile range (IQR) for non-normally distributed continuous variables; as average and standard deviation (SD) for normally distributed continuous variables or as percentage (%) for nominal variables. Comparisons between groups have been made by the  $\chi^2$  test for the discrete variables; by the analysis of variance (ANOVA) test on continuous variables or by the non-parametric Mann-Whitney test when necessary. The strength of the association between the outcomes was quantified calculating the odds ratio (OR) with logistic regression. *p* value for interaction refers to Breslow Day Test for categorical variables.

## 3 | RESULTS

### 3.1 | Patients characteristics

A total of 537 consecutive STEMI patients who underwent primary PCI were enrolled in the study. The mean age was  $67 \pm 12.8$  years and most of them were males (74.9%). More than half of the patients suffered from hypertension (56.2%) and were smokers (53.4%). Dyslipidaemia (45.4%), family history of cardiovascular

disease (26.5%), and diabetes mellitus (20.1%) were other well-represented risk factors.

The no pretreated population consisted of 300 STEMI patients and the pretreated ITT population of 237 STEMI patients. The differences between the administration of treatment at FMC and administration in the cath lab was 78 min (IQR: 61–101).

The no pretreated population did not differ consistently regarding to baseline characteristics, compared with the pretreated one, as shown in Table 1. The only exceptions was the lower percentage of history of arterial hypertension (49.4% vs. 61.7%,  $p = 0.004$ ) in pretreated ITT population compared with no pretreated population.

### 3.2 | PP population

The pretreated PP population consisted of 182 patients, indeed a total of 55 patients were excluded because they did not receive ticagrelor as pretreatment strategy but received P2Y12 inhibitors (clopidogrel or prasugrel) in the Cath lab. The baseline characteristics of the excluded population compared with the PP pretreated population are shown in Table S1. The PP population and the no pretreated population did not differ consistently regarding to baseline characteristics as shown in Table S2. Similarly to ITT pretreated population, PP population had lower percentage of arterial hypertension compared with the no pretreated group (50.0% vs. 61.7%,  $p = 0.012$ ). The renal function (glomerular filtration rate [eGFR]) was higher in PP population compared with the no pretreated population (98.6 (79.6–117.1) vs. 89.4 (74.8–109.3),  $p = 0.035$ ).

### 3.3 | Main outcomes

#### 3.3.1 | Intention to treat (ITT) analysis

The pretreated ITT population showed a better basal reperfusion, expressed as basal TIMI flow, compared with no pretreated population ( $p$  for trend  $p < 0.001$ ) (Table 2 and Figure 1A). The proportion of patients who presented a total artery occlusion upon arrival in Cath lab (basal TIMI flow = 0), was lower in the ITT pretreated population compared with no pretreated population (56.5% vs. 73.7%, OR: 0.46, 95% CI: 0.32–0.67,  $p < 0.001$ ); conversely, basal TIMI flow 2–3 was more frequent compared with the no pretreated group (33.3% vs. 19.3% OR: 2.0, 95% CI: 1.38–2.00,  $p < 0.001$ ). Basal TIMI III flow was numerically higher in the pretreated ITT population compared with no pretreated population (14.3% vs. 9.7%, OR: 1.56, 95% CI: 0.92–2.65,  $p = 0.094$ ).

Regarding the secondary endpoints, troponin peak was lower in the pretreated ITT population compared with no pretreated population (20,286 (8726–75,027) vs. 48676 (17,229–113,900),  $p = 0.001$ ) (Figure 1B). Consistently, left ventricular ejection fraction (LVEF%) at discharge was higher in the pretreated ITT population compared with

**TABLE 1** Descriptive analysis between no pretreated population and intention to treat (ITT) pretreated population

Variable	No pretreated population (n = 300)	ITT pretreated population (n = 237)	p value
Age (year) ± SD	67 ± 12.9	66 ± 12.5	0.139
Age > 75, n(%)	103 (34.3%)	69 (29.1%)	0.198
Male gender, n(%)	226 (75.3%)	176 (74.3%)	0.776
<b>Medical history</b>			
Previous MI, n (%)	25 (8.3%)	25 (10.5%)	0.380
Previous PCI, n (%)	24 (8.0%)	25 (10.5%)	0.309
Arterial hypertension, n (%)	185 (61.7%)	117 (49.4%)	<b>0.004</b>
Family history of CVD, n (%)	84 (28.1%)	58 (24.5%)	0.345
Diabetes mellitus, n (%)	65 (21.7%)	43 (18.1%)	0.312
Smoke, n (%)	156 (52.0%)	131 (55.3%)	0.450
Dyslipidaemia, n (%)	135 (45.0%)	109 (46.0%)	0.862
<b>Clinical features</b>			
Heart rate (bpm) ± SD	77 ± 18.8	76 ± 17.3	0.369
SBP (mmHg) ± SD	132 ± 29.9	130 ± 25.9	0.583
DBP (mmHg) ± SD	75 ± 16.5	75 ± 13.8	0.769
BSA (m <sup>2</sup> ) ± SD	1.9 ± 0.01	1.9 ± 0.3	0.326
Glycemia (mg/dl), (IQR)	154(125.0–183.0)	140 (121.0–175.0)	0.147
Baseline hemoglobin concentration (g/dl), (IQR)	13.9 (12.5–15.1)	14.1 (13.1–15.0)	0.383
Anemia, n(%)	130 (43.3%)	88 (37.1%)	0.146
Renal failure, n (%)	48 (16.0%)	30 (12.7%)	0.275
Creatinine concentration (mg/dl), (IQR)	0.89 (0.8–1.0)	0.86 (0.7–1.0)	0.273
eGFR (ml/min), (IQR)	89.4 (74.8–109.3)	97.2 (78.0–115.4)	0.280
Killip Class 3-4, n (%)	46 (15.3%)	29 (12.2%)	0.304
<b>Coronary angiography data</b>			
Culprit proximal LAD, n (%)	73 (24.3%)	46 (19.4%)	0.172
Culprit mid distal LAD, n (%)	69 (23.0%)	67 (28.3%)	0.163
Culprit RCA, n (%)	102 (34.0%)	85 (35.9%)	0.652
Culprit LCX, n (%)	43 (14.3%)	24 (10.1%)	0.143
Culprit LAD diagonal branch, n (%)	6 (2.0%)	9 (3.8%)	0.209
Culprit left main, n (%)	4 (1.3%)	3 (1.3%)	0.945
Culprit ramus intermedius, n (%)	3 (1.0%)	1 (0.4%)	0.439
Graft, n (%)	0 (0.0%)	1 (0.4%)	0.260
Internal mammary artery, n (%)	0 (0.0%)	1 (0.4%)	0.260
<b>Procedural data</b>			
1 stent implanted	68%	73%	0.58
>1 stent implanted	24%	20%	
No stent implanted	8%	7%	
Thrombus aspiration, n (%)	41 (13.8%)	20 (8.4%)	0.054
Intraortic balloon pump, n (%)	15 (5.0%)	13 (5.5%)	0.816

(Continues)

TABLE 1 (Continued)

Variable	No pretreated population (n = 300)	ITT pretreated population (n = 237)	p value
Ischemia times			
Patient delay (min), (IQR)	75 (30–165)	76 (29–192)	0.958
ECG to balloon time (min), (IQR)	74 (60–96)	77 (61–98)	0.481
Total ischemia time (min), (IQR)	185 (128–291)	190 (129–292)	0.720

Note: Bold values indicate statistically significant p values.

Abbreviations: ASA, acetylsalicylic acid; BSA, body surface area; DBP, diastolic blood pressure; eGFR, glomerular filtration rate; IQR, interquartile range, LAD, left anterior descending; LCX, left circumflex artery; MI, myocardial infarction; PCI, percutaneous coronary angioplasty, RCA, right coronary artery; SD, standard deviation; SBP, systolic blood pressure.

TABLE 2 Outcomes in no pretreated population vs. ITT pretreated population

Outcomes	No pretreated population (n = 300)	ITT pretreated population (n = 237)	OR (95% CI)	p value
Basal Timi Flow, n(%)	TF0 221 (73.7%) TF1 21 (7.0%) TF2 29 (9.7%) TF3 29 (9.7%)	TF0 134 (56.5%) TF1 24 (10.1%) TF2 45 (19%) TF3 34 (14.3%)		<b>&lt;0.001</b>
Basal Timi Flow=0, n(%)	221 (73.7%)	134 (56.5%)	0.46 (0.32–0.67)	<b>&lt;0.001</b>
Basal Timi Flow= 2-3, n(%)	58 (19.3%)	79 (33.3%)	2.00 (1.38–2.00)	<b>&lt;0.001</b>
Basal Timi Flow=3, n(%)	29 (9.7%)	34 (14.3%)	1.56 (0.92–2.65)	0.094
Troponin I (ng/ml), (IQR)	48676 (17,229–113,900)	20286 (8726–75,027)		<b>0.001</b>
Basal LVEF, (IQR)	48 (40–55)	51 (45–59)		<b>0.028</b>
Basal LVEF < 50%, n(%)	88 (32.2%)	52 (24.2%)	0.67 (0.45–1.00)	<b>0.051</b>
LVEF at discharge, (IQR)	50 (44–56)	53 (44–59)		<b>0.027</b>
LVEF < 50% at discharge, n(%)	66 (24.4%)	52 (24.4%)	0.99 (0.65–1.50)	0.966
GPIIb/IIIa inhibitors n(%)	73 (24.5%)	29 (12.2%)	0.43 (0.27–0.69)	<b>&lt;0.001</b>
Bleeding BARC ≥ 2, n(%)	6 (2.0%)	5 (2.1%)	1.00 (0.32–3.50)	0.929
In-Hospital all cause of death, n(%)	15 (5.0%)	17 (7.2%)	1.47 (0.71–3.00)	0.291
30-days all cause of death, n(%)	17 (5.7%)	17 (7.2%)	1.29 (0.64–2.58)	0.477
30-day stent thrombosis, n(%)	5 (1.7%)	3 (1.3%)	0.76 (0.18–3.19)	0.704
30-day acute MI, n(%)	6 (2.0%)	3 (1.3%)	0.63 (0.16–2.54)	0.510

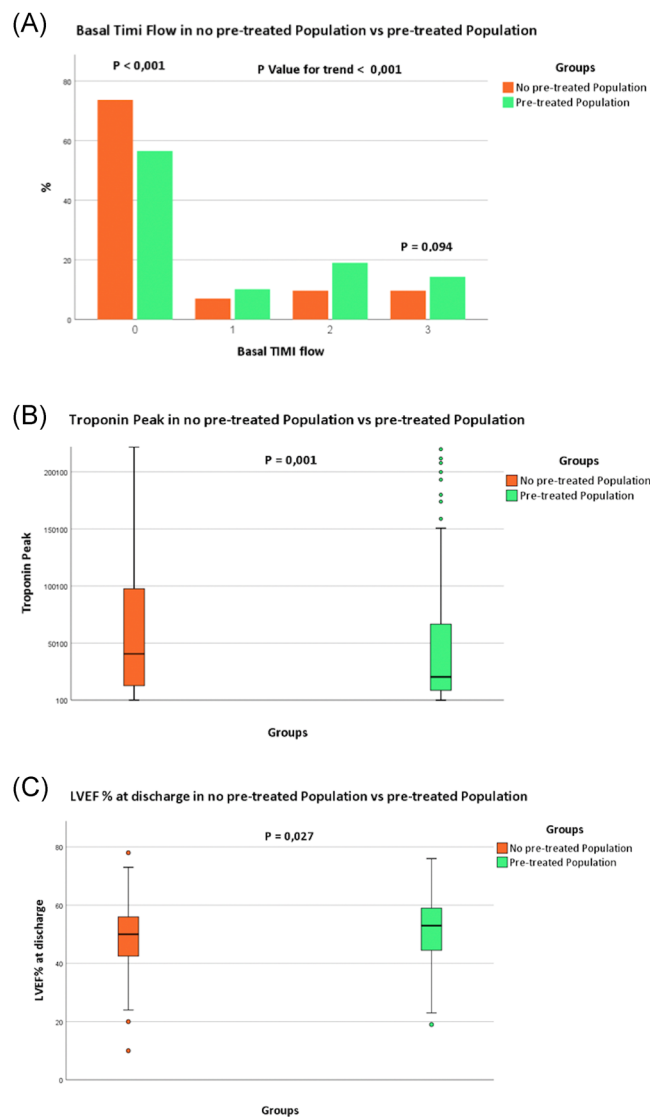
Note: Bold values indicate statistically significant p values.

Abbreviations: BARC, Bleeding Academic Research Consortium; IQR, interquartile range; ITT, intention to treat; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

no pretreated population (53% (44–59) vs. 50% (44–56),  $p = 0.027$ ) (Figure 1C). The use of GPIIb/IIIa inhibitors was significantly less frequent in the pretreated ITT population compared with no pretreated population (12.2% vs. 24.5%, OR: 0.43, 95% CI: 0.27–0.69,  $p < 0.001$ ).

Regarding the in-hospital bleeding safety endpoint, no differences were noticed between the two groups (In hospital BARC ≥ 2

bleeding, 2.1% vs. 2.0%,  $p = 0.929$ , in pretreated ITT population and no pretreated population, respectively). Femoral approach was performed only in 16.1%, and in hospital BARC ≥ 2 bleeding were similar also in patients treated with femoral approach (0% vs. 4.5%,  $p = 0.929$ , in pretreated vs. no pretreated patients, respectively) or with radial approach (2.5% vs. 1.6%  $p = 0.492$  in pretreated vs. no pretreated patients, respectively).



**FIGURE 1** (A) Basal TIMI flow in no pretreated versus pretreated population. Troponin peak (B) and left ventricular ejection fraction at discharge (C) in no pretreated versus pretreated population. TIMI, Thrombolysis in Myocardial Infarction [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Thirty-day all-cause mortality was similar in pretreated ITT population and no pretreated population (7.2% vs. 5.7%, OR: 1.29, 95% CI: 0.64–2.58,  $p = 0.477$ ) as well as 30-day stent thrombosis (1.3% vs. 1.7%, OR: 0.76, 95% CI: 0.18–3.19,  $p = 0.704$ ).

### 3.3.2 | PP analysis

The main results of the pretreated ITT population were confirmed in PP population. The PP population showed a better basal reperfusion, expressed as basal TIMI flow, compared with the no pretreated population ( $p$  for trend < 0.001) (Table S3 and Figure S1).

Regarding the secondary endpoints, troponin Peak was lower in the PP population (21,138 (8779–76,622) vs. 48,676 (17,229–113,900),

$p = 0.006$ ) compared with no pretreated population (Figure S2). LVEF at discharge was higher in the PP population compared with no pretreated population (53% (46–59) vs. 50% (44–56),  $p = 0.004$ ) (Figure S3).

The use of GPIIb/IIIa inhibitors was less frequent in the PP population compared with no pretreated population (12.1% vs. 24.5%, OR: 0.42, 95% CI: 0.25–0.71,  $p = 0.001$ ).

Regarding the bleeding safety endpoint, no differences were noticed between the two groups (BARC  $\geq 2$  bleeding); (2.7% vs. 2.0%,  $p = 0.594$ ) in pretreated PP population and no pretreated population, respectively.

Thirty-day all-cause mortality was similar in pretreated PP population and no pretreated population (8.8% vs. 5.7%, OR: 1.60, 95% CI: 0.79–3.26,  $p = 0.188$ ) as well as 30-day stent thrombosis (1.6% vs. 1.7%, OR: 0.99, 95% CI: 0.23–4.19,  $p = 0.988$ ).

### 3.3.3 | Subgroup analysis

Interestingly, significant interaction was present between PP pretreatment versus no pretreatment and “ischemia time” for the basal TIMI III and LVEF < 50% at discharge. Pretreated patients with an ischemia time  $\leq$  median had a significant higher probability to obtain basal TIMI III flow (OR: 3.85; 95% CI: 1.69–8.33) compared with patients with an ischemia time > median (OR: 0.71; 95% CI: 0.29–1.69); ( $p$  for interaction = 0.005) (Figure 2).

Moreover in PP population pretreatment was associated with significant higher probability to obtain basal TIMI flow > 0, irrespectively from ischemia time. Indeed pretreated patients with ischemia time  $\leq$  median had similar probability to obtain basal TIMI > 0 (OR: 2.58; 95% CI: 1.47–4.56) compared with patients with ischemia time above the median (OR: 2.11, 95% CI: 1.21–3.79); ( $p$  for interaction 0.61).

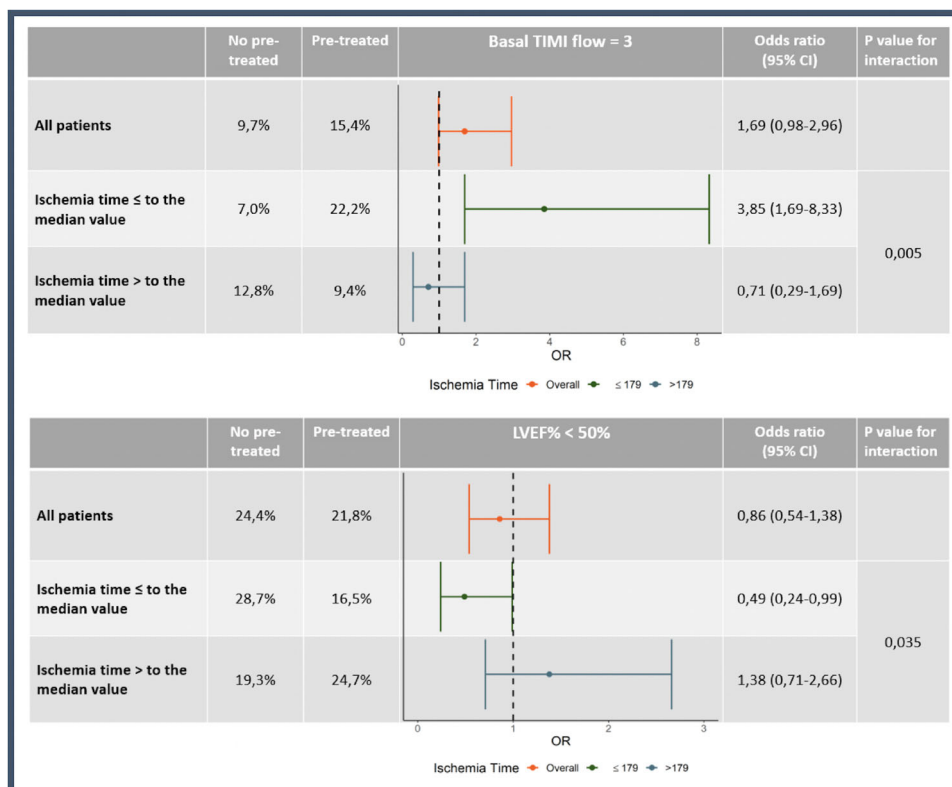
Furthermore, pretreated patients with an ischemia time  $\leq$  median had a significant lower probability to have LV dysfunction (LVEF < 50%); (OR: 0.49, 95% CI: 0.24–0.99) compared with patients with an ischemia time > median (OR: 1.38, 95% CI: 0.71–2.66); ( $p$  for interaction 0.035) (Figure 2).

Pretreated patients with an anterior MI had similar probability to obtain basal TIMI III flow (OR: 0.55; 95% CI: 0.24–1.25) compared with patients with no anterior MI (OR: 0.63; 95% CI: 0.29–1.35); ( $p$  for interaction 0.802). Pretreated patients with Killip III-IV had similar probability to obtain basal TIMI III flow (OR: 0.45; 95% CI: 0.05–4.01) compared with patients with Killip I-II (OR: 0.66; 95% CI: 0.34–1.10); ( $p$  for interaction 0.782).

## 4 | DISCUSSION

In this “before-after” observational study we evaluated the potential effect of an early pretreatment strategy in STEMI patients to achieve better patency of the infarct-related vessel before PCI.

The main findings of our study are (1) the administration of heparin and DAPT at FMC compared with the administration upon



**FIGURE 2** Effect modification for basal TIMI flow 3 and left ventricular ejection fraction at discharge of per-protocol treatment in subgroups according to ischemia time. TIMI, Thrombolysis in Myocardial Infarction [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

the arrival in Cath lab resulted in a better basal TIMI flow, significantly reducing the number of patients who presented with total occlusion (TIMI = 0) of the culprit artery. (2) Pretreatment administered at FMC reduced infarct size expressed as troponin peak and improved LVEF% at discharge. (3) The need of GPIIb/IIIa inhibitors during the procedure was significantly lower in patients who received pretreatment at FMC. (4) Importantly, in the current era of STEMI treatment where radial approach is frequently used, as in our population, pretreatment strategy resulted to be safe and was not associated to higher prevalence of bleedings compared with no pretreatment population. These results have been consistently observed both in "intention to treat" and in "per protocol population."

Interestingly, while the basal TIMI 3 flow showed a trend to be significantly more frequent in the pretreated group compared with the no pretreated patients, PP subgroup analysis showed that pretreatment seems to be more effective in patients with shorter ischemia time ( $\leq$ median). Indeed, pretreated patients with an ischemia time  $\leq$  median had higher probability to obtain basal TIMI III flow ( $p$  for interaction = 0.005) and less ventricular dysfunction at discharge (LVEF < 50%) ( $p$  for interaction = 0.035). This may suggest that the therapeutic effect of pre-H treatment is likely to be modulated by the duration of coronary occlusion and may support the rationale of early administration of anticoagulant and DAPT when coronary thrombus is more susceptible to antithrombotic therapy. This may also highlights the importance of reducing patients delay,<sup>6</sup> one of the main component of total ischemia time, and the

importance of an efficient organization of STEMI networks which may allow the initiation of STEMI treatment at FMC.

In the ATLANTIC trial, there were no significant differences between the pre- and in-hospital treatment groups in terms of pre-PCI coronary reperfusion,<sup>2</sup> however the brief time interval between the study drug administration in the ambulance to catheterization laboratory (33 min) may have limited the potential benefit of prehospital ticagrelor administration. Whereas the short time to PCI achieved in the ATLANTIC study represents excellent practice, it may not reflect routine practice which includes unselected population with also longer pre-H times. Therefore, testing early antithrombotic therapy in the real-world setting, as in our study where differences between administration of treatment at FMC and administration in the cath lab was 78 min, is relevant to better understand the potential role of early pharmacotherapy in improving pre-PCI myocardial reperfusion. Moreover it should be considered that in the ATLANTIC trial, early pretreatment, helped to achieve reperfusion before PCI in patients with longer transfer allowing the drug to become biologically active.<sup>7</sup> Interestingly, in the ATLANTIC trial, the use of glycoprotein IIb/IIIa inhibitors was numerically lower in prehospital versus in-hospital administration of ticagrelor, an endpoint that was confirmed in our study.

Early pretreatment with ticagrelor has been evaluated in a randomized study only in the ATLANTIC trial; in a nationwide cohort of STEMI patient, pre-H administration of DAPT was associated with improved survival, compared with administration once the patients

were admitted to the hospital.<sup>8</sup> Contrastingly, pretreatment with P2Y12 receptor antagonists in Sweden was safe but not associated with improved infarct-related artery patency or better clinical outcome than with in-hospital administration.<sup>9</sup> However a recent meta-analysis of early versus delayed P2Y12 inhibition in STEMI patients undergoing PCI showed a reduction of risk of major adverse cardiac events with no significant difference in terms of bleeding.<sup>10</sup>

The importance of treatment at FMC is also suggested by the fact that early use of heparin was an independent predictor of reperfusion in the ATLANTIC trial<sup>7</sup> and TASTE trial.<sup>11</sup> Despite the paucity of evidence,<sup>12,13</sup> early administration of anticoagulant at the time of diagnosis, as it was in the intervention group of our study, is common in many European STEMI networks and supported also by European Position Paper.<sup>14</sup> While further randomized trial, investigating the pre-Hospital effect of heparin administration, should be performed, we showed that a full prehospital treatment with heparin and DAPT was safe and effective in patients with STEMI.

Conversely, administering antithrombotic drugs when the likelihood of STEMI diagnosis is low could lead to an overtreatment of patients who will not ultimately undergo PCI, potentially exposing them to an increased bleeding risk with no potential benefit, or even more deleterious consequence if, for example, urgent surgery is needed for aortic dissection. The risk of overtreatment is one of the main reasons why pretreatment is not recommended (Class III) in non-ST-elevation myocardial Infarction patients.<sup>15</sup> However, nowadays prehospital STEMI diagnosis accuracy is high, during our enrollment period we had false-positive diagnoses less than 8% and therefore the likelihood of PCI in STEMI patients is now very high. As a result, the net potential benefit of pretreatment in STEMI should not be denied. However, in cases in which the STEMI diagnosis is not clear, delaying at least P2Y12 inhibitor loading until the anatomy is known should be considered.<sup>1</sup>

Potential methods to accelerate the onset of the antiplatelet effects of oral P2Y12 inhibitors include crushing or chewing the tablets<sup>16,17,18</sup> However, the increase in bioavailability of oral P2Y12 inhibitors with these strategies appears limited. The use of a fast-acting antiplatelet agent, such as cangrelor,<sup>19</sup> may be a further strategy to achieve immediate inhibition of platelet aggregation, however in the recent FABOLUS-FASTER trial, tirofiban demonstrated superior efficacy than cangrelor on inhibition of platelet aggregation in patients undergoing primary PCI.<sup>20</sup> Moreover, novel subcutaneous therapeutic strategies (as subcutaneous P2Y12 Inhibitors: Selatogrel and RUC-4) can achieve rapid, high-grade and rapidly reversible platelet inhibition. These features have the potential to enable new prehospital strategies<sup>21</sup> but further studies powered for clinical endpoints are needed.

#### 4.1 | Limitations

This study has limitations. This study is a “before” and “after” intervention observational study which relies on the assumption that the characteristics of the populations remain unchanged throughout the study period. This was the case with the only exception of a small baseline difference in the percentage of history of arterial hypertension.

Nevertheless, the slightly lower percentage of hypertension in the pretreated population is unlikely to have influenced the main outcomes of the study also considering that blood pressure values at presentation were similar in the two groups.

The results of our study support the administration of antithrombotic therapy (i.e., concomitant administration of anticoagulation plus DAPT) at FMC with respect to the administration of this therapy upon the arrival in the Cath lab, however we cannot distinguish if the effect on outcomes was driven by ticagrelor, heparin, or the synergistic effect of both agents.

We did not collect data of pre-PCI ST-segment resolution (STR), as well as of myocardial blush grade. Finally, we did not collect information regarding the administration of ticagrelor as crushed or as whole tablet and we did not collect information regarding the use of morphine during the acute phase of STEMI treatment.

## 5 | CONCLUSIONS

This study provides support for an early pretreatment strategy in STEMI patients. Patients who received antithrombotic therapy at FMC have better basal TIMI flow, lower Troponin Peak, and better LVEF at discharge. Early pretreatment resulted also to be safe, showing no increase of bleeding events. We then confirmed the importance of an efficient organization of STEMI networks which may allow the initiation of antithrombotic treatment at FMC.

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### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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