AUCTORES
Globalize your Research

Journal of Clinical Cardiology and Cardiovascular Interventions
Mehdi Sheibani *

Open Access

Research Article

No-Reflow Phenomenon after Primay Percutaneous Coronary Intervention in patients with ST segment elevation myocardial infarction treated with ticagrelor versus clopidogrel plus eptifibatide: A Randomized Clinical Trial

Mohammad Sadeghian [1], Maryam Ahmadi [2], Hossein Toreyhi [3], Najmeh Ahmadpour [3], Mahshid Nazarieh [4], Mehdi Sheibani [5]*

[1]Assistant professor of interventional cardiology, Department of cardiology, Tehran Heart Center, Tehran university of Medical Sciences, Tehran, Iran

[2]Shahroud University of medical sciences, Imam Hossein Hospital

[3]Student research committee, Faculty of medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4]Department of Sports and Exercise Medicine,Imam Khomeini Hospital (Tums), Tehran, Iran

[5]Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Corresponding Author:** Mehdi Sheibani, Department of Cardiology, Shahid Beheshti University of Medical Sciences, Loghman-hakim Hospital, kamali Avenue, South Kargar Street, Tehran, Iran.

Received date: September 16,2024; **Accepted date:** September 30, 2024; **Published date:** October 21, 2024

Citation: Mohammad Sadeghian, Maryam Ahmadi, Hossein Toreyhi, Najmeh Ahmadpour, Mahshid Nazarieh, et al, (2024), No-Reflow Phenomenon after Primay Percutaneous Coronary Intervention in patients with ST segment elevation myocardial infarction treated with ticagrelor versus clopidogrel plus eptifibatide: A Randomized Clinical Trial, *J Clinical Cardiology and Cardiovascular Interventions*, 7(12); **DOI: 10.31579/2641-0419/416**

Abstract

Background and Aims

No reflow phenomenon (NRP) is one of the essential complications of primary percutaneous intervention (PPCI). Anti-platelets have essential role in prevention of NRP. The aim of this study is comparison the NRP between ticagrelor and clopidogrel+glycoprotein IIb/IIIa Inhibitor in ST elevation myocardial infarction (STEMI) patients candidate for PPCI.

Methods

From January 2022 to January 2023 in a randomized clinical trial we compare ticagrelor and clopidogrel plus eptifibatide (a glycoprotein IIb/IIIa inhibitor) in terms of NRP and secondary outcome include mortality, stent thrombosis, vascular complications, bleeding complications and major cardiovascular adverse events (MACE). NRP was defined as TIMI flow grade less than 3.

Results:

140 patients were randomly assigned to two study groups. Mean age of patients was 59 years and 82% were male. Baseline characteristics and culprit vessels was not significantly different between study groups.NRP at the end of procedure was occurred in 47.5% in ticagrelor group and 53.7% in clopidogrel + eptifibatide group without statistical significant difference (Pvalue: 0.48). Two major and two minor bleeding occurred in in the clopidogrel+eptifibatide group and no bleeding was reported in ticagrelor group. Bleeding complications was not significantly different between study groups. In hospital mortality, vascular complications and MACE were also not significantly different between study groups.

Conclusion:

Clopidogrel plus eptifibatide in PPCI has similar outcome with ticagrelor and could be administered if ticagrelor is unavailable or prohibited.

Keywords: no reflow phenomenon; primary percutaneous intervention; Tcagrelor; eptifibatide

Introduction

Abbreviations:

PPCI: Primary percutaneous intervention

STEMI: ST-segment elevation myocardial infarction

NRP: No-reflow phenomenon

GFR: glomerular filtration rate
CABG: coronary artery bypass graft surgery
ACT: activated clotting time

Introduction

Primary percutaneous intervention (PPCI) is the treatment of choice recommended by the European Society of Cardiology's international guidelines to restore epicardial coronary supply in ST-segment elevation myocardial infarction (STEMI). (1) Despite significant reductions in STEMI mortality achieved through PPCI, STEMI still results in 7% death and 22% heart failure annually. (2) No-reflow phenomenon (NRP) is defined as the absence or slowness of blood flow toward the subtle capillaries of epicardium and is characterized by a TIMI flow grade of <3 in the absence of significant stenosis in the epicardial vessels. NRP is one of the critical complications of PPCI that limits the procedure's efficacy. (3)

NRP management includes pharmacological and non-pharmacological strategies for prophylaxis and treatment. (4) Among the pharmacological treatments, antiplatelets are crucial in the prevention and treatment of NRP. According to clinical practice guidelines, a dual antiplatelet therapy regimen that includes aspirin and a p2y12 inhibitor is recommended in all STEMI patients. (5) Among the two most commonly used p2y12 inhibitors (clopidogrel and ticagrelor), ticagrelor has a faster, more potent, and predictable antiplatelet activity than clopidogrel. Glico-Protein (GP) IIb / IIIa inhibitors are kept on hand as intravenous antiplatelet drugs in STEMI patients who have a large thrombus, no reflow, or other thrombotic complications. (6)

However, no comprehensive study has compared the therapeutic effects and also the potential side effects of combined administration of these antiplatelet agents. Because of the significance of this issue and the potential benefits of combined therapy (such as in No-reflow prevention), this study is conducted to compare the therapeutic effect and safety of clopidogrel plus eptifibatide (a GP IIb / IIIa inhibitor) versus routine ticagrelor treatment in patients with STEMI who are candidates for Primary PCI. The effect of the aforementioned drugs on the prevention of No-reflow phenomenon as well as the rate of complications were investigated in this study.

Methods

Study population

This is a prospective, randomized clinical trial of patients with STEMI at Imam Khomeini Hospital in Tehran from January 2022 to January 2023. This study was approved by Medical Ethics Committee of Tehran University of Medical Sciences and registered in Iranian Registery of Clinical Trial (code: IRCT2020318046810N1). Patients with the diagnosis of STEMI whom candidate for primary PCI entered the study. Informed consent was obtained from all patients. Moreover, patients with the following conditions were excluded: patients on ticagrelor or clopidogrel, patients with cardiogenic shock, patients with CHF decompensation (NYHA class III & IV), patients with severe valvular heart disease, patients whom referred after 12 hours of MI event based on history, patients older than 85 years old, low serum platelet count (<100,000/μL) severe renal dysfunction (glomerular filtration rate (GFR) <30 ml/24h), severe hepatic failure (cirrhosis CHILD class B or more) and left main lesions. Patients who were candidates for coronary artery bypass graft surgery (CABG) and did not undergo stent implantation were also excluded from the study.

A case report sheet includes demographic data, past medical history, cardiovascular risk factors and laboratory tests was filled for each patient. Basic ECG and ECG of 90 minutes after PCI were evaluated by a cardiologist to determine ST resolution. ST resolution was defined as at least 50% decrease in ST elevation after PCI in the lead with highest ST elevation. The culprit vessel (coronary artery responsible for acute myocardial infarction) including the LAD, LCX, and RCA was determined and documented in all patients during angiography.

Endpoints

The primary endpoint was no reflow phenomena after stenting. No reflow phenomena was defined as TIMI flow grade less than 3 after stenting. **Supplementary table 1** showed TIMI flow grade method definition in detail. The no reflow phenomenon occurs when a TIMI Flow of less than 3 is achieved during Primary PCI. TIMI flow grade was evaluated two times for each patient. First after wire crossing (mid procedure) and second, after stent deployment and post dilation if required (end procedure). Secondary endpoints were ejection fraction (EF), in-hospital mortalitystent thrombosis, vascular complications (including hematoma, pseudo aneurysm, and arteriovenous (AV) fistula), major cardiovascular adverse events (MACE) and bleeding complications. MACE was defined as the composite of mortality, cerebrovascular accident (CVA) and recurrent myocardial infarction. CVA was defined as presence of signs or symptoms of CVA that confirmed in brain MRI in neurology service consultation. **Supplementary table 2** showed definition of bleeding complications.

• **TIMI flow 0:** The lack of forward flow beyond the coronary stenosis area
• **TIMI flow 1** (penetration without perfusion)**:** There is weak anterior flow beyond the stenosis or occlusion, but the end bed of the above vessel is not completely filled.
• **TIMI flow 2** (partial reperfusion)**:** Beyond the coronary stenosis, there is a delayed and slow forward flow, and the coronary artery is completely filled.
• **TIMI flow 3** (Complete perfusion)**:** A normal and complete flow exists beyond the coronary stenosis to the vessel's end.

Supplementary table 1. TIMI flow classification

• **Major bleeding:** Any intracranial hemorrhage (with the exception of bleeding less than 10 mm based on MRI findings), clear evidence of hemorrhage greater than or equal to 5 g/dl hemoglobin (Hb), and lethal hemorrhage
• **Minor bleeding:** clinically obvious bleeding (as determined by imaging) results in the decrease in hemoglobin from 3 to less than 5 g/dL
• **Bleeding necessitates medical attention:** clear evidence of bleeding that does not meet major and minor criteria and necessitates intervention, both medical and surgical, as well as an increase in hospital stay and costs
• **Minimal bleeding:** Any obvious bleeding that does not meet the criteria listed above is considered

Supplementary table 2. Bleeding classification

Study treatment

Patients were randomly (by randomization table and random numbers) assigned to one of two study groups based on antiplatelet regimen: first group treated with clopidogrel plus eptifibatide and second group treated with ticagrelor. In the first group, clopidogrel 600 mg was loaded before angiography, and eptifibatide 180 mcg / kg was injected into the coronary artery twice at ten-minute intervals after crossing the wire and before stenting. Patients in the second group were given 180 mg ticagrelor before angiography. Administration of clopidogrel and ticagrelor was done as soon as possible just after randomization. All patients underwent PPCI through femoral approach and administrated 100 units/kg unfractionated heparin during procedure. Adjusted doses of unfractionated heparin was administered to achieve activated clotting time(ACT) of 250-300 during procedure in ticagrelor group and 200-250 in clopidogrel + eptifibatide group. If no reflow phenomenon occurred management with eptifibatide and adenosine was done at the discretion of the interventional cardiologist and due to large thrombus bulk some patients underwent thrombo-aspiration. Pre-treatment with adenosine was not done for none of the patients. Due to administration of eptifibatide in some patients of ticagrelor group with NRF, secondary endpoints compared in three groups; ticagrelor group, ticagrelor plus eptifibatide and clopidogrel plus eptifibatide. This cross-over between groups was occurred after evaluation of NRF and had no impact on primary outcome of the study. All of the patients receive aspirin and other guideline directed medications for ST elevation myocardial infarction. Target lesion only strategy was done in PPCI of all the patients.

Statistics

SPSS ver. 26 software was used to perform the statistical analysis of the data. The qualitative variables in the statistical study were described as percentages and ratios using descriptive indicators. A proportional statistical test with Chi-Square was also used to investigate the relationship between qualitative and qualitative variables, or if Chi-Square conditions were not met and the two-state qualitative variable was compared, the Fisher-Exact test was used. A significant level was defined as a P-value less than 0.05. Linear regression analysis was performed to examine the independent relationship of various variables with the endpoints under consideration Furthermore, as sensitivity analysis, we compare groups after excluding participants undergone thrombo-aspiration.

Results

After considering the inclusion and exclusion criteria and receiving informed consent, 140 people were enrolled in the study, with 14 of them being excluded after randomization. Five patients excluded due to cardiogenic shock during PCI and 9 patients candidates for urgent CABG and stent implantation was not done for them **(Figure 1)** .Therefore, a total of 67 patients were treated with clopidogrel plus eptifibatide, and 59 patients were treated with ticagrelor.

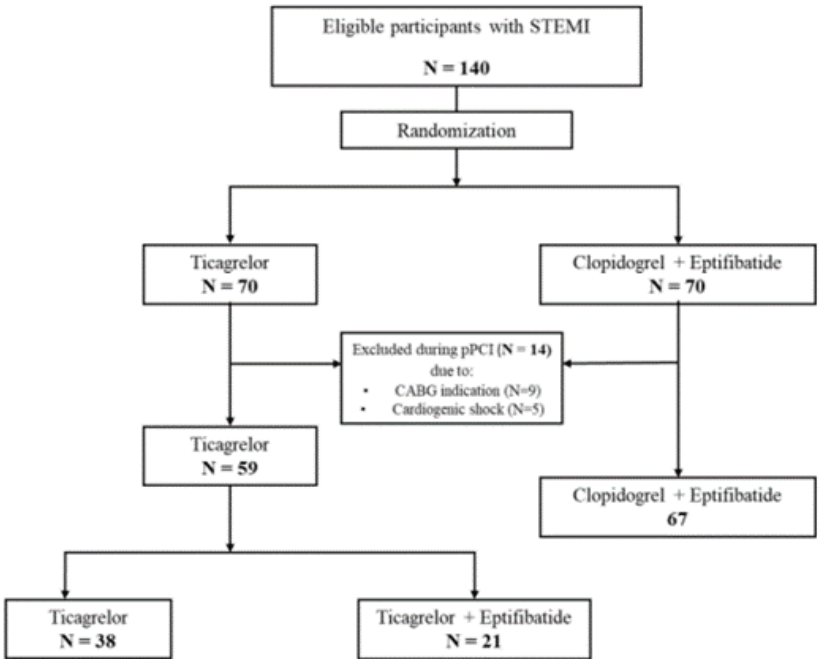

Figure 1: *Algorithm of patient selection and randomization. STEMI: ST segment Elevation Myocardial Intervention, CABG: Coronary Arteries Bypass Graft Surgery, PPCI: primary percutaneous intervention*

Table 1 shows the participants' baseline characteristics. One hundred and four (82.5 %) of the participants were men. The mean [standard deviation (SD)] age of the participants was 59.13 (12.20), with no significant differences between study groups. Furthermore, the study groups had no differences in terms of basic characteristics and risk factors except mean plasma creatinine level and prevalence of type 2 diabetes mellitus (T2DM).

Demographic information	Total (n=126)	Clopidogrel + Eptifibatide(n=67)	Ticagrelor(n=59)	P value
Male	104 (82.5)	55 (82.1%)	49 (83.1)	0.88**
Female	22 (17.5)	12 (17.95)	10 (16.9)	
Age (years)	59.13 (12.20)	58.91 (11.78)	59.38 (12.76)	0.77
– Weight (kilogram)	77.70 (11.67)	76.19 (12.45)	77.81 (10.77)	0.50
– Height (centimeter)	174.35 (55.43)	168.87 (22.44)	180.57 (77.30)	0.67
– BMI, (kg/m^2)	26.22 (3.52)	25.83 (3.75)	26.66 (3.22)	0.45
Plasma creatinine, mg/dl	1.1 (0.26)	1.16 (0.24)	1.04 (0.26)	**0.017**
Comorbidities				
– Smoker, n (%)	58 (46)	29 (43.3)	29 (49.2)	0.51
– Hypertension, n (%)	45 (35.7)	25 (37.3)	20 (33.9)	0.69
– T2DM, n (%)	30 (23.8)	10 (14.9)	20 (33.9)	**0.013**
– Opium addiction, n (%)	29 (23)	19 (28.4)	10 (16.9)	0.12
– Hyperlipidemia, n (%)	23 (18.3)	15 (22.4)	8 (13.6)	0.20
– IHD, n (%)	11 (8.7)	5 (7.5)	6 (10.2)	0.59
– Family history of premature CVD, n (%)	11 (8.7)	7 (10.4)	4 (6.8)	0.46
– History of CVA, n (%)	2 (1.6)	1 (1.5)	1 (1.7)	1

BMI; body mass index, T2DM; type2 diabetes mellitus, IHD; ischemic heart disease, CVD; cardiovascular disease, CVA; cerebrovascular accident

*Values are shown as Mean (SD) and number (%), for continuous and categorical variables, respectively.

** Unlike other p-values, the suggested one is related to the difference between men and women.

Table 1. Baseline characteristic of the participants *.

Twenty (34%) patients in the ticagrelor group and 25(37%) patients in the clopidogrel + eptifibatide group receive morphine sulfate in the emergency room and there was no significant difference between study groups (p value: 0.69).

Table 2 illustrates the MI characteristics of the participants, including STE type based on electrocardiogram (ECG), stenotic vessels, and culprit vessels. With a prevalence of 52 (41.3%) and 32 (25.4%), respectively, the most common types of STEMI among study participants were inferior and anterior MI. Notably, no significant differences in STEMI type were found between the study groups. The LAD was the most commonly culprit vessel, accounting for 67 (53.2 percent) of total participants. In this study, a total of 226 arteries had significant obstruction with had no significant difference between two study groups. Twenty-six (20.7%) patients were single vessel disease, 72 (57.1%) were two vessel disease and 28 (22.2%) were three vessel disease. It should be noted that due to high thrombotic bulk, 13 (10.3%) patients underwent thrombo-aspiration (9 patients in clopidogrel + eptifibatide group and 4 patients in ticagrelor group) and 77 (61.1%) patients underwent pre-dilatation (46 patients in clopidogrel + eptifibatide group and 31 patients in ticagrelor group (at the discretion of the operator. Forty one patients (32.5%) was post-dilated with non-compliant balloons at the session of primary PCI due to stent under-expansion (25 patients in the Plavix + eptifibatide and 16 in the ticagrelor group). There was no difference in the number of patients who underwent this procedures between study groups (p values: 0.22, 0.06 and 0.43 for thrombo-aspiration, pre-dilation and post-dilation respectively).

Type of STEMI	Total	Clopidogrel + Eptifibatide	Ticagrelor	P value
Anterior (V2-V4)	32 (25.4%)	20 (29.9%)	12(20.3%)	
Extensive anterior (V1-V6)	21 (16.7%)	8 (11.9%)	13 (22.0%)	
Anterolateral (V2-V4, I, aVL)	6 (4.8%)	5 (7.5%)	1 (1.7%)	
Extensive anterolateral (V1-V6, I, aVL)	6 (4.8%)	4 (6%)	2 (3.4%)	
Inferior (II, III, aVF)	52 (41.3%)	28 (41.8%)	24 (40.7%)	0.22
Inferolateral (I, II, III, aVF, aVL)	2 (1.6%)	0 (0%)	2 (3.4%)	
Inferior+ RV (II, III, aVF, V4R-V6R)	4 (3.2%)	1 (1.5%)	3 (5.1%)	
Lateral (I, aVL, V5, V6)	2 (1.6%)	1 (1.5%)	1 (1.7%)	
Inferoposterior (II, III, aVF, V7-V9)	1 (0.8%)	0 (0%)	1 (7%)	
Culprit vessels				
LAD	67 (53.2%)	38 (56.7%)	29 (49.2%)	
RCA	48 (38.1%)	26 (38.8%)	22 (37.3%)	0.19
LCX	11 (8.7%)	3 (4.5%)	8 (13.6%)	
Stenotic vessels *				
LAD	33 (26.2%)	17 (25.4%)	16 (27.1%)	
LCX	5 (4.0%)	1 (1.5%)	4 (6.8%)	
RCA	16 (12.7%)	8 (11.9%)	8 (13.6%)	0.30
LAD-LCX	20 (15.9%)	13 (19.4%)	7 (11.9%)	
LAD-RCA	18 (14.3%)	13 (19.4%)	5 (8.5%)	
LCX-RCA	6 (4.8%)	3 (4.5%)	3 (5.1%)	
LAD-LCX-RCA	28 (22.2%)	12 (17.9%)	16 (27.1%)	

STEMI: ST-elevation myocardial infarction, LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery
Values are shown as number (%) variables.
*stenotic vessel was defined as vessels with more than 50% luminal stenosis

Table 2. Details of STEMI among study participant.

	Total	Clopidogrel + Eptifibatide	Ticagrelor	P value
Type of STEMI				
– Anterior (V2-V4)	32 (25.4%)	20 (29.9%)	12(20.3%)	
– Extensive anterior (V1-V6)	21 (16.7%)	8 (11.9%)	13 (22.0%)	

– Anterolateral (V2-V4, I, aVL)	6 (4.8%)	5 (7.5%)	1 (1.7%)	
– Extensive anterolateral (V1-V6, I, aVL)	6 (4.8%)	4 (6%)	2 (3.4%)	
– Inferior (II, III, aVF)	52 (41.3%)	28 (41.8%)	24 (40.7%)	0.22
– Inferolateral (I, II, III, aVF, aVL)	2 (1.6%)	0 (0%)	2 (3.4%)	
– Inferior+ RV (II, III, aVF, V4R-V6R)	4 (3.2%)	1 (1.5%)	3 (5.1%)	
– Lateral (I, aVL, V5, V6)	2 (1.6%)	1 (1.5%)	1 (1.7%)	
– Inferoposterior (II, III, aVF, V7-V9)	1 (0.8%)	0 (0%)	1 (7%)	
Culprit vessels				
– LAD	67 (53.2%)	38 (56.7%)	29 (49.2%)	
– RCA	48 (38.1%)	26 (38.8%)	22 (37.3%)	0.19
– LCX	11 (8.7%)	3 (4.5%)	8 (13.6%)	
Stenotic vessels *				
– LAD	33 (26.2%)	17 (25.4%)	16 (27.1%)	
– LCX	5 (4.0%)	1 (1.5%)	4 (6.8%)	
– RCA	16 (12.7%)	8 (11.9%)	8 (13.6%)	0.30
– LAD-LCX	20 (15.9%)	13 (19.4%)	7 (11.9%)	
– LAD-RCA	18 (14.3%)	13 (19.4%)	5 (8.5%)	
– LCX-RCA	6 (4.8%)	3 (4.5%)	3 (5.1%)	
– LAD-LCX-RCA	28 (22.2%)	12 (17.9%)	16 (27.1%)	

STEMI: ST-elevation myocardial infarction, LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery
Values are shown as number (%) variables.
*stenotic vessel was defined as vessels with more than 50% luminal stenosis.

Table 2. Details of STEMI among study participant.

Table 3 shows continuous and categorical analysis of TIMI flow results. The mean (SD) mid-procedure TIMI flow score (after crossing the wire) for the clopidogrel + eptifibatide and ticagrelor groups was 1.88 (0.47) and 1.96 (0.41), respectively. The mean TIMI flow score in these groups at the end of the procedure (after stent implantation and post dilation if required) was 2.41 (0.60) and 2.94 (0.56), respectively. There was no significant difference between the two groups in terms of mid-TIMI flow (p-value: 0.276) or end-TIMI flow (p-value: 0.515). After crossing the wire and at the end of the procedure, 63 (94%) and 36 (53.7%) of the clopidogrel + eptifibatide group had TIMI flow scores of less than 3. Similarly, in the ticagrelor group, 55 (93.2 percent) and 28 (47.5 percent) of patients experienced mid-procedure and end-procedure no reflow phenomenon (TIMI flow < 3). The incidence of no reflow at the middle and end of the procedure did not differ significantly between the clopidogrel + eptifibatide and ticagrelor groups (p-value: 1 and 0.482, respectively). We repeated the tests after excluding patientwho had undergone thrombo-aspiration as a sensitivity analysis, and the results remained essentially unchanged **(Supplementary Table3).**

Table 3. Continues and categorical analysis of TIMI flow

	Total	Clopidogrel + Eptifibatide	Ticagrelor	P value
Continues				
Mid-procedure	1.92±0.44	1.88±0.47	1.96±0.41	0.27
End-procedure	2.45±0.58	2.41±0.60	2.94±0.56	0.51
Categorical				
Mid-procedure				
– 3	8(6.3%)	4(6.0%)	4(6.8%)	1
– < 3	118(93.7%)	63(94.0%)	55(93.2%)	
End-procedure				
– 3	62(49.2%)	31(46.3%)	31(52.5%)	0.48
– < 3	64(50.8%)	36(53.7%)	28(47.5%)	

Values are shown as Mean (SD) and number (%), for continuous and categorical variables, respectively.
Mid-procedure: after crossing the wire, end-procedure: after stent implantation

Supplementary Table3. Continues and categorical analysis of TIMI flow after excluding patients who had undergone thrombo-aspiration				
	Total	Clopidogrel + Eptifibatide	Ticagrelor	P value
Mid-procedure				
– 3	7(6.2%)	3(5.2%)	4(7.3%)	0.71
– < 3	106(93.8%)	55(94.8%)	51(92.7%)	
End-procedure				
– 3	57(50.4%)	27(46.6%)	30(54.5%)	0.39
– < 3	56(49.6%)	31(53.4%)	25(45.5%)	
Values are shown as Mean (SD) and number (%), for continuous and categorical variables, respectively. Mid-procedure: after crossing the wire, end-procedure: after stent implantation				

Supplementary Table 3: Mid-procedure: after crossing the wire, end-procedure: after stent implantation

Given that 21 patients of the ticagrelor group whom had NRP, were treated with eptifibatide on the recommendation of the operator, secondary outcomes were compared in the three clopidogrel + eptifibatide, ticagrelor, and ticagrelor + eptifibatide groups. TIMI flow was evaluated before Eptifibatide in all patients in the ticagrelor group. The mean EF of the patients in each group after the procedure was 35.59% (10.71) in the clopidogrel + eptifibatide group, 36.57% (9.01) in the ticagrelor group, and 33.80% (12.93) in the ticagrelor + eptifibatide group. The EF differences between groups were not statistically significant (p-value: 0.79). Furthermore, the mean duration of hospitalization in the three groups was 5.83 (2.67), 5.73 (2.23), and 5.33 (2.0), with no difference between the three groups (p-value: 0.77).

Patients' post-procedure complications are illustrated in **Table 4**. Vascular complications occurred in two patients, one in the clopidogrel + eptifibatide group and the other in the ticagrelor group, with no statistically significant difference (p-value = 0.95). Only two people in the clopidogrel + eptifibatide group experienced major bleeding. Similarly, only two patients in the same group experienced minor bleeding. Furthermore, only one patient in the ticagrelor group experienced minimal bleeding. Bleeding requiring medical attention occurred in 2, 1, and 1 patient in the clopidogrel + eptifibatide, ticagrelor, and ticagrelor + eptifibatide groups, respectively. However, there was no significant difference in the incidence of bleeding (of any kind) between the three groups (p-value = 0.70). In the clopidogrel + eptifibatide, ticagrelor, and ticagrelor + eptifibatide groups, the incidence of MACE was 3%, 2.6%, and 9.5 %, respectively. The difference in MACE between the three groups was not statistically significant (p-value: 0.35). Stent thrombosis occurred in one patient of the ticagrelor group and no stent thrombosis occurred in other two groups.

	Total	Clopidogrel + Eptifibatide	Ticagrelor	Ticagrelor + Eptifibatide	p-value
Vascular	2 (1.6%)	1(1.5%)	1(2.6%)	-	0.73
Bleeding					0.63
Major	2 (1.6%)	2 (3%)	-	-	
Minor	2 (1.6%)	2 (3%)	-	-	
Minimal	1 (0.8%)	-	1 (2.6%)	-	
Require medical attention	4 (3.2%)	2 (3%)	1 (2.6%)	1 (4.8%)	
Total	9 (7.1%)	6 (9.0%)	2 (5.3%)	1 (4.8%)	0.70
Contrast nephropathy	10 (7.9%)	5 (7.5%)	3 (7.9%)	2 (9.5%)	0.95
MACE	5 (4%)	2 (3%)	1 (2.6%)	2 (9.5%)	0.35
MACE: major adverse cardiac and cerebrovascular events					

Table 4: The complications of participants after procedures during hospitalization.

Discussion

The current study included 126 STEMI patients who were candidates for primary PCI and we compared them in the two groups of clopidogrel + eptifibatide and ticagrelor in terms of safety and efficacy of anti-platelet therapy. The initial characteristics of the two groups were nearly identical. The TIMI Flow findings indicate that No-reflow phenomenon does not differ significantly between these groups. Moreover, we didn't find any difference in adverse events between study groups.

High platelet activity was seen to has association with NRP in STEMI patients.(7) Ticagrelor, as a reversible direct-acting oral antagonist of P2Y12- receptor antagonist with no catabolite activation, could have a significant impact on platelet inhibition faster and more consistently than clopidogrel. (8) The efficacy and safety of ticagrelor and clopidogrel were compared in previous studies with acceptable heterogenicity (I2 = 64%) in a meta-analysis conducted by Wang et al. (9) They found no differences in efficacy or risk of bleeding, MI, or stroke between the two groups. Another meta-analysis by Dai etal reported that loading dose of ticagrelor compare with clopidogrel effectively reduces NRP during PPCI. (10) In PLEIO study the superiority of ticagrelor to clopidogrel in recovery of endothelial function is shown .(11)In contrast to this findings a recent clinical trial showed that the incidence of NRP is not affected by the type of P2Y12Inhibitor.(12) Eptifibatide is a short-acting, small-molecule competitive inhibitor of the GP IIb/IIIa receptor. (13) The role of GP II/III inhibitors, particularly tirofiban, has always been taken into account. According to a meta-analysis of prior trials on the effect of tirofiban on TIMI flow result, it reduces the risk of thrombosis by approximately 75% and the risk of MACE by 90%. (14) A recent meta-analysis reported the effectiveness of tirofinal and eptifibatide in preventing NRP in primary PCI. (15) Given that this drug's bleeding trend did not reach a significant level, it would be a promising choice for combination therapy for ACS patients. Another meta-analysis on two common glycoprotein inhibitors, tirofiban and eptifibatide, found that treatment with tirofiban or eptifibatide had no effect on favorable outcome, functional outcome, or last available National Institutes of Health Stroke Scale (NIHSS), but may increase mortality. (16) However, considering tirofiban increased the risk of fatal ICH while decreasing the risk of ICH, maybe eptifibatide could be a better option to adjunctive therapy.

However, the efficacy of the addition of eptifibatide to clopidogrel has been examined by Moazez et al in a randomized clinical trial. (17) They suggested that platelet reactivity could be further reduced by using glycoprotein IIb/IIIa inhibitors in addition to P2Y12 inhibitors. It is worth noting that the endpoint of this study was based on laboratory

measurements of platelet aggregation (PA) and activated clotting time (ACT). Because of the therapeutic dose of heparin used in this study, laboratory measurements could be easily influenced by confounding factors. The major adverse effects of combination therapy were not compared in this study, and the safety of eptifibatide should be investigated in future studies (18) To the best of our knowledge, this is the first study to compare the efficacy and safety of the eptifibatide plus clopidogrel versus ticagrelor in the total ACS population with any troponin level status.

Shimada et al evaluated whether the use of a glycoprotein IIb/IIIa inhibitor improves the relative efficacy and safety of ticagrelor when compared to clopidogrel in the Platelet Inhibition and Patient Outcomes (PLATO) Trial. (19) However, no interaction was found between treatment and tirofiban use for the primary efficacy and safety end points of P2Y12 inhibitors. Moreover, stent thrombosis was found with a prevalence of about 1% in the ticagrelor group with GP IIb/IIIa inhibitor.

In our study, stent thrombosis was observed in only one case of the ticagrelor group, while the other two groups did not report any cases of MI or stent thrombosis. Due to the small number of patients, we did not have enough power to evaluate and compare stent thrombosis in different groups.

Limitation:

Some limitations could be considered for this study. This study was conducted in one center with 140 patients. We recommend to design a multicenter study with more cases to confirm our findings.

Conclusion

Clopidogrel plus eptifibatide in PPCI procedure for STEMI has similar outcomes with ticagrelor and could be administered if ticagrelor is unavailable or prohibited.

Funding

“This research received no specific grant from any funding agency in the public or commercial.

Disclosure of interest

The authors declare that they have no competing interest.

All authors have read and approved the final version of the manuscript and had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Mehdi Sheibani affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Konijnenberg LS, Damman P, Duncker DJ, Kloner RA, Nijveldt R, Van Geuns R-JM, et al. (2020). Pathophysiology and diagnosis of coronary microvascular dysfunction in ST-elevation myocardial infarction. Cardiovascular Research.;116(4):787-805.
2. Bulluck H, Chan MH, Bryant JA, Chai P, Chawla A, Chua TS, et al. (2019).Platelet inhibition to target reperfusion injury trial: Rationale and study design. Clinical cardiology. 42(1):5-12.
3. Annibali G, Scrocca I, Aranzulla TC, Meliga E, Maiellaro F, Musumeci G.9 (2022).“No-Reflow” Phenomenon: A Contemporary Review. Journal of Clinical Medicine.;11(8):2233.
4. Rezkalla SH, Stankowski RV, Hanna J, Kloner RA.(2017).Management of No-Reflow Phenomenon in the Catheterization Laboratory. JACC: Cardiovascular Interventions.;10(3):215-223.
5. Ha ACT, Bhatt DL, Rutka JT, Johnston SC, Mazer CD,(2021).Verma S. Intracranial Hemorrhage During Dual Antiplatelet Therapy. Journal of the American College of Cardiology.;78(13):1372-1384.
6. Jourdi G, Godier A, Lordkipanidzé M, Marquis-Gravel G, Gaussem P. (2022.).Antiplatelet therapy for atherothrombotic disease in 2022: from population to patient-centered approaches. Frontiers in cardiovascular medicine.
7. Aitmokhtar O, Paganelli F, Benamara S, Azaza A, Bonello L, Hamza O, et al. (2017).Impact of platelet inhibition level on subsequent no-reflow in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Archives of cardiovascular diseases.;110(11):626-633.
8. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. (2006).Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. European heart journal.;27(9):1038-1047.
9. Wang D, Yang XH, Zhang JD, Li RB, Jia M, Cui XR. Compared efficacy of clopidogrel and ticagrelor in treating acute coronary syndrome: a meta-analysis. BMC cardiovascular disorders. 2018;18(1):217.
10. Dai W, Ye Z, Li L, Su Q. (2018).Effect of preoperative loading dose ticagrelor and clopidogrel on no-reflow phenomenon during intervention in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis. Drug design, development and therapy.:2039-2049.
11. Park K, Cho Y-R, Park J-S, Park T-H, Kim M-H, Kim Y-D. (2019).Comparison of the effects of ticagrelor and clopidogrel on microvascular dysfunction in patients with acute coronary syndrome using invasive physiologic indices. Circulation: Cardiovascular Interventions.;12(10):e008105.
12. Elewa MG, Eletriby SA, Elserafy AS. (2021).Comparison Between the Incidence of Coronary No-Reflow in Patients with Acute ST-Elevation Myocardial Infarction receiving ticagrelor versus clopidogrel loading doses. QJM: An International Journal of Medicine.;114(Supplement_1):hcab090. 17a.
13. Batchelor WB, Tolleson TR, Huang Y, Larsen RL, Mantell RM, Dillard P, et al. (2002).Randomized comparison of platelet inhibition with abciximab, tirofiban and eptifibatide during percutaneous coronary intervention in acute coronary syndromes: the COMPARE trial. Circulation.;106(12):1470-1476.
14. Qin T, Xie L, Chen M-H. (2013).Meta-analysis of randomized controlled trials on the efficacy and safety of intracoronary administration of tirofiban for no-reflow phenomenon. BMC cardiovascular disorders.;13(1):68.
15. Hofbauer F, Stibleichinger M, Wendt J, Klappacher G. (2022).Comparative efficacy of fibrinolytics and glycoprotein IIb/IIIa inhibitors in preventing coronary no-reflow: a network meta-analysis. European heart journal. 1;42(Supplement_1):ehab724. 1433.
16. Liu J, Yang Y, Liu H.(2021). Efficacy outcomes and safety measures of intravenous tirofiban or eptifibatide for patients with acute ischemic stroke: a systematic review and meta-

analysis of prospective studies. Journal of thrombosis and thrombolysis..

17. Marian MJ, Abu Daya H, Chatterjee A, Al Solaiman F, Sasse MF, Fonbah WS, et al. (2019).Effects of Crushed Ticagrelor Versus Eptifibatide Bolus Plus Clopidogrel in Troponin-Negative Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention: A Randomized Clinical Trial. Journal of the American Heart Association. x;8(23):e012844.
18. Henry TD, Tomey MI, Tamis-Holland JE, Thiele H, Rao SV, Menon V, et al.(2021). Invasive Management of Acute Myocardial Infarction Complicated by Cardiogenic Shock: A Scientific Statement From the American Heart Association. Circulation.;143(15):e815-e29.
19. Shimada YJ, Bansilal S, Wiviott SD, Becker RC, Harrington RA, Himmelmann A, et al. (2016).Impact of glycoprotein IIb/IIIa inhibitors on the efficacy and safety of ticagrelor compared with clopidogrel in patients with acute coronary syndromes: Analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. American heart journal.;177:1-8.

DOI:10.31579/2641-0419/416