Original Article

# Comparison between Intracoronary Abciximab and Intravenous Eptifibatide Administration during Primary Percutaneous Coronary Intervention of Acute ST-Segment Elevation Myocardial Infarction

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## Abstract

***Background:*** *Administration of glycoprotein IIb/IIIa inhibitors is an effective adjunctive treatment strategy during primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction (STEMI). Recent data suggest that an intracoronary administration of these drugs can increase the efficacy of PPCI. This study was done to find any potential difference in terms of efficacy of administering intracoronary Abciximab vs. intravenous Eptifibatide in primary PPCI.*

***Methods:*** *A total of 40 STEMI patients who underwent PPCI within 12 hours of symptom onset were randomized to either an intracoronary Abciximab (0.25 µg/kg) bolus or two boluses of intravenous Eptifibatide (0.180 µg/kg) each 10 minutes. The primary end points were enzymatic infarct size, myocardial reperfusion measured as ST-segment resolution (STR), and post-procedural thrombolysis in myocardial infarction (TIMI) grade flow of the infarct-related artery. The secondary end points were intra-procedural adverse effect (arrhythmia) and no-reflow phenomenon, in-hospital mortality, reinfarction, hemorrhage, and post-procedural global systolic function.*

***Results:*** *Post-procedural TIMI grade 3 flow was achieved in 95% and 90% of the intracoronary Abciximab and intravenous Eptifibatide groups, respectively (p value = 0.61). The infarct size, as assessed by the area under the curve of creatine phosphokinase-MB in the first 48 hours after PPCI (µmol/L/hr ), was similar between the intracoronary Abciximab and intravenous Eptifibatide groups: 6591 (interquartile range [IQR], 3006.0 to 11112.0) versus 7,294 (IQR, 3795.5 to 11803.5); p value = 0.59. Complete STR was achieved in 55% and 45% of the intracoronary Abciximab and intravenous Eptifibatide groups, respectively (p value = 0.87). No deaths, urgent revascularizations, reinfarctions, or TIMI major bleeding events were observed in either group.*

***Conclusion:*** *The intracoronary administration of Abciximab was not superior to the intravenous administration of Eptifibatide in the STEMI patients who underwent primary PCI.*

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***Keywords:*** *Angioplasty • Myocardial infarction • Eptifibatide • Abciximab*

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## Introduction

Primary percutaneous coronary intervention (PPCI) is the treatment of choice in the management of acute ST-segment elevation myocardial infarction (STEMI). It has been constantly observed that, despite restoring a good epicardial flow with PCI, myocardial perfusion at the cellular level remains impaired in nearly 50% of STEMI patients.[1] This is attributable to the embolization of the coronary thrombus into the distal vasculature, producing microvascular plugging, vasospasm, interstitial edema, and cellular injury. Via Doppler guide-wire technology, it has been estimated that an average of 25 embolic events occur during PPCI for STEMI.[2-4] There is consequently less salvage of the infarct size, as well as reduced left ventricular function and poor clinical outcomes.

There have been efforts to identify mechanical and pharmacological strategies to improve myocardial perfusion after PPCI. Compared with the systemic administration of intravenous (IV) pharmacotherapies, a highly localized administration of intracoronary (IC) pharmacotherapy may be associated with a several-hundred-fold increase in the local concentration of an agent in the epicardial artery and microcirculation. A number of pharmacotherapies, including Adenosine,[5, 6] calcium channel blockers,[7] vasodilators,[8, 9] antithrombotics,[10, 11] and antiplatelet agents[12-14] have been used to treat microvascular dysfunction.

Platelet receptor occupancy studies have demonstrated that if there are fewer glycoprotein (GP) IIb/IIIa receptors free and available for cross-linking with fibrinogen, myocardial perfusion is improved.[15] In recent years, randomized trials have demonstrated that glycoprotein inhibitors administered via the IC route are safe and effective in reducing the infarct size and providing better clinical outcomes than when given intravenously, without a significant increase in major bleeding.[14, 16] Furthermore, no adverse events were reported during the IC administration of glycoprotein inhibitors, and nor was the IC strategy, compared with the IV route, associated with any significant delay in revascularization.[14]

The absolute number of GP IIb/IIIa receptors available for cross-linking is reduced among patients with successful restoration of myocardial perfusion and ST-segment resolution (STR) in an STEMI population.[17] Thus, the hypothesized mechanistic basis for the IC administration of GP IIb/IIIa inhibitors is that high local concentrations of the drug would lead to fewer GP IIb/IIIa receptors being available for cross-linking with fibrinogen in the coronary microcirculation and, therefore, promote clot disaggregation with minimal systemic drug concentrations. This greater blockade of GP IIb/IIIa receptors would in turn reduce the incidence of microcirculatory thrombosis, enhance myocardial perfusion, and ultimately augment clinicaloutcomes.[14, 15]

We hypothesized that the IC administration of Abciximab, rather than IV Eptifibatide, during PPCI for STEMI would be safe and associated with higher rates of myocardial reperfusion and smaller myocardial infarct size.

## Methods

In the present study, the investigators randomized 40 STEMI patients, presenting within 12 hours of symptom onset to either a single IC bolus of Abciximab or two boluses of IV Eptifibatide. For randomization, a random number table was applied as the odd numbers (1, 3, 5, 7, 9) and even numbers (0, 2, 4, 6, 8) were used for a single IC bolus of Abciximab and two boluses of IV Eptifibatide, respectively.

STEMI was defined as chest pain suggestive of myocardial ischemia for at least 30 minutes before hospital admission and the electrocardiogram (ECG) with new ST-segment elevation in 2 or more contiguous leads of 0.2 mV or more in leads V2 to V3 and/or 0.1 mV or more in other leads.

The exclusion criteria were as follows: 1- Patients presenting with STEMI after 12 hours from symptom onset; 2- Patients presenting with vasospastic angina (as determined by the resolution of ST-segment elevation and relief of symptoms after an IV administration of nitroglycerin); 3- Patients presenting with non-STEMI; 4- Contraindications for antiplatelets such as bleeding disorders including gastrointestinal bleeding, hematuria, or any known bleeding tendency either inherited or acquired; 5- Thrombocytopenia (platelet count $< 100.000/\mu l$); 6- Recent (< 6 months) stroke; 7- Intracranial hemorrhage at any time in the patient's life or any known intracranial malformation; 8- Cardiogenic shock; and 9- Left bundle branch block (LBBB) change in the ECG. The patients' baseline characteristics are listed in Table 1.

All the patients received 325 mg of Acetylsalicylic acid sublingually and a 600 mg loading dose of Clopidogrel at the emergency department. Maintenance doses of Clopidogrel at 150 mg/day for one week and then according to the patient's condition 75 mg/day for at least one month to maximum one year was continued after PPCI. A bolus dose of unfractionated heparin was administered and titrated to achieve an activated clotting time of 200-250 seconds.

An IC bolus dose of Abciximab (0.25 μg/kg) was administered in the IC group. Microcatheter through coronary guiding catheters was used to administer the IC Abciximab. When the wire had crossed the occlusion, the drug was administered. In the IV group, two boluses (each 180 μg/kg) of Eptifibatide were administered every 10 minutes. Thrombus aspiration was performed using the Export catheter, if it was necessary. Stenting was performed for all the patients. The intra-aortic balloon pump (IABP) was not used for any patient.

The primary end points of the trial were enzymatic infarct size, myocardial reperfusion measured as STR, and post-procedural TIMI grade flow of the infarct-related artery. The secondary end points were intra-procedural

Table 1. Baseline characteristics of the 40 patients randomized to intracoronary Abciximab or intravenous administration of Eptifibatide*

| | Intracoronary Abciximab Group (n=20) | Intravenous Eptifibatide Group (n=20) | P value |
|---|---|---|---|
| Age (y) | 53.8±7.8 | 58.60±7.0 | 0.45 |
| Male gender | 18 (90) | 17 (85) | 0.07 |
| Cardiovascular risk factors | | | |
| Hypertension | 9 (45) | 5 (25) | 0.23 |
| Hypercholesterolemia | 5 (25) | 6 (30) | 0.09 |
| Diabetes mellitus | 4 (20) | 6 (30) | 0.08 |
| Family history | 4 (20) | 2 (10) | 0.12 |
| Smoking | 14 (70) | 11 (55) | 0.23 |
| Ischemic time (min) | | | 0.63 |
| Mean | 158.3±88.0 | 142.3±101.7 | |
| Median | 120 | 120 | |
| Number of diseased vessels | | | |
| 1 | 4 (20) | 8 (40) | 0.36 |
| 2 | 7 (35) | 5 (25) | 0.63 |
| 3 | 9 (45) | 7 (35) | 0.37 |
| Infarct-related artery | | | |
| LAD | 10 (50) | 11 (55) | 0.21 |
| LCX | 3 (15) | 0 | 0.87 |
| RCA | 7 (35) | 9 (45) | 0.24 |
| TIMI flow grade | | | 0.36 |
| 0 | 17 (85) | 17 (85) | |
| 1 | 3 (15) | 2 (10) | |
| 2 | 0 | 1 (5) | |
| 3 | 0 | 0 | |
| Thrombus | 18 (90) | 19 (95) | 0.18 |
| Thrombus aspiration | 15 (75) | 13 (65) | 0.36 |
| Balloon predilatation | 10 (50) | 9 (45) | 0.15 |
| Postdilatation | 13 (65) | 12 (60) | 0.27 |
| DES | 12 (60) | 14 (70) | 0.38 |

*Data are presented as n (%)
LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; TIMI, Thrombolysis in myocardial infarction; DES, Drug-eluting stent

adverse effect (arrhythmia) and no-reflow phenomenon, in-hospital mortality, reinfarction, and hemorrhage (major or minor) using TIMI criteria, and post-procedural global left ventricular systolic function, using global ejection fraction.

For the evaluation of the ECG end points, a 12-lead ECG was acquired at the time of presentation and at 90 minutes after PPCI. STR was assessed by comparing the ST-segment elevation in the infarct-related area on the ECG after PPCI with the ECG at presentation. STR indirectly indicated the myocardial reperfusion. In our study, STR was categorized as complete (≥ 70%), partial (30% to < 70%), or absent (< 30%).[18]

The infarct size was measured indirectly by the area under the curve (AUC) of the cardiac creatine kinase-MB (CPK-MB) release, derived from measurements 0, 6, 24, and 48 hours after PPCI.

"TIMI Grade Flow" is a scoring system from 0-3, referring to the levels of the coronary blood flow as assessed during percutaneous coronary angioplasty:

• TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.

• TIMI 1 flow (penetration without perfusion) is a faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.

• TIMI 2 flow (partial reperfusion) is a delayed or sluggish antegrade flow with complete filling of the distal territory.

• TIMI 3 flow (complete perfusion) is a normal flow which fills the distal coronary bed completely.[19]

A single observer reviewed all the angiographic and ECG data.

In-hospital clinical course was obtained from the central personal records database, hospital records, and interviews

with the patients and/or their general practitioners. Mortality was considered cardiac unless an unequivocal non-cardiac cause of death was established. Reinfarction was defined as recurrent symptoms suggestive of ischemia with new ST-segment elevation and/or elevation of the levels of cardiac markers.[20]

Major or minor hemorrhage was determined using the TIMI criteria, including:

A) Major criteria: intracranial hemorrhage or clinical bleeding associated with loss of greater than 5 mg/dl of hemoglobin (or hematocrit decrease by > 15 points or by 10-15 points with clinical bleeding) and

B) Minor criteria: loss of greater than 3 gm/dl of hemoglobin (or hematocrit decrease by < 10 points) with clinical bleeding or loss of greater than 4 mg/dl of hemoglobin (or hematocrit decrease by 10-15 points) with no clinical bleeding. Clinical bleeding was comprised of large hematoma, gastrointestinal blood loss, and retroperitoneal bleeding.

All the patients prior to discharge underwent a conventional transthoracic echocardiographic examination (TTE) to assess the global left ventricular systolic function (LVEF) via the two-dimensional eyeballing approach.

Due to the absence of normal distribution of the data and the small sample size in each group, the quantitative data are described by median and inter-quartile range and compared by the Mann-Whitney U test. The categorical data are described by frequencies and percentages and analyzed by the chi square test and the Fisher exact test. The AUC was calculated by the trapezoidal rule. Significance level was determined at a p value < 0.05. For the statistical analyses, the statistical software SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL) was used.

The study protocol was approved by the Cardiovascular Research Center of Shahid Beheshti University of Medical Sciences.

## *Results*

Angiographically apparent thrombus was noted in 90 (IC group) and 95% (IV group) of the cases. More than 95% of the arteries had a closed artery (TIMI grade 0/1 flow) before PPCI, as is noted in Table 1. No deaths, urgent revascularizations, or reinfarctions were observed among the 40 patients of both groups. There were no TIMI major bleeding events. One TIMI minor bleeding event was noted; it was treated with IC Abciximab. No adverse events, including arrhythmias, were detected during the IC Abciximab administration.

Post-procedural TIMI grade 3 flow was achieved in 95% and 90% of the IC and IV groups, respectively (p value = 0.61) (Table 2).

The enzymatic infarct size, as assessed by the AUC of CPK-MB in the first 48 hours after PPCI (µmol/L/hr), was similar between the IC and IV groups: 6.591, interquartile range [IQR], 3.006.0 to 11.112.0) vs. 7.294 (IQR, 3.795.5 to 11.803.5); p value = 0.59. Also, the other enzymatic criteria were similar between the IC and IV groups. Peak CPK-MB (U/L) was 268.0 (IQR, 123 to 360) versus 257.5 (IQR, 115 to 420); p value = 0.57; and time-to-peak CPK-MB (hour) was 6.4 in intracoronary Abciximab and 6.1 in intravenous Eptifibatide; p value = 0.25 (Table 3; Figures 1-3).

The median STR was 63% (IQR, 55% to 79%) in the IC group versus 63.5% (IQR, 50 to 75%) in the IV group (p value = 0.64). The primary end point of complete STR was achieved in 55% of the IC group and 45% of the IV group (p value = 0.64). Therefore, myocardial reperfusion was similar between the two groups. STR data as well as categorization (absent, partial, or complete) are presented in Table 4.

The global left ventricle (LV) systolic function, as assessed by the ejection fraction (two-dimensional eyeballing approach) on TTE before discharge, was 46.5% (IQR, 35.0% to 53.7%) in the IC group vs. 40% (IQR, 38.5 to 45%) in the IV group (p value = 0.22) (Table 5).

Table 2. Post-procedural TIMI flow grade of the infarct-related artery*

| Post-procedural TIMI flow grade | Intracoronary Abciximab Group (n = 20) | Intravenous Eptifibatide Group (n = 20) | P value |
|---|---|---|---|
| 3 | 19 (95) | 18 (90) | 0.61 |
| 2 | 1 (5) | 2 (10) | 0.85 |

*Data are presented as n (%)
TIMI, Thrombolysis in myocardial infarction

Table 3. Enzymatic infarct size in both groups

| | Intracoronary Abciximab Group (n = 20) | Intravenous Eptifibatide Group (n = 20) | P value |
|---|---|---|---|
| Median time to peak CPK-MB (hr) | 6.4 | 6.1 | 0.25 |
| Time to peak CPK-MB (hr)* | 13.5±9.2 | 9.7±7.7 | 0.25 |
| Peak CPK-MB, (U/L)** | 268.0 (123-360) | 257.5 (115-420) | 0.57 |
| AUC 48 CPK-MB (µmol/L/hr)** | 6591 (3006.0-11112.0) | 7294 (3795.5-11803.5) | 0.59 |

*Data are presented as mean±SD
**Data are presented as median (IQR)
AUC, Area under the curve; CPK-MB, Creatine phosphokinase-MB; IQR, Interquartile range

Table 4. Distribution of myocardial reperfusion as assessed by ST-segment resolution (STR)

| Post-PCI STR | Intracoronary Abciximab Group (n=20) | Intravenous Eptifibatide Group (n=20) | P value |
|---|---|---|---|
| Median (IQR) (%) | 63 (55-79) | 63.5 (50-75) | 0.64 |
| Mean±SD (%) | 64.20±20.75 | 61.35±15.25 | 0.63 |
| Absent (<30%)* | 1 (5) | 1 (5) | 1.00 |
| Partial (≥30 - <70%)* | 9 (45) | 10 (50) | 0.75 |
| Complete (≥70%)* | 11 (55) | 9 (45) | 0.87 |

*Data are presented as n (%)
IQR, Interquartile range

Table 5. Ejection fraction (EF) in both groups before discharge

| | Intracoronary Abciximab Group (n=20) | Intravenous Eptifibatide Group (n=20) | P value |
|---|---|---|---|
| Median (IQR) (%) | 46.5 (35.0-53.7) | 40 (38.5-45) | 0.22 |
| Mean±SD (%) | 45.1±9.3 | 42.0±5.9 | 0.21 |

EF, Ejection fraction; IQR, Interquartile range

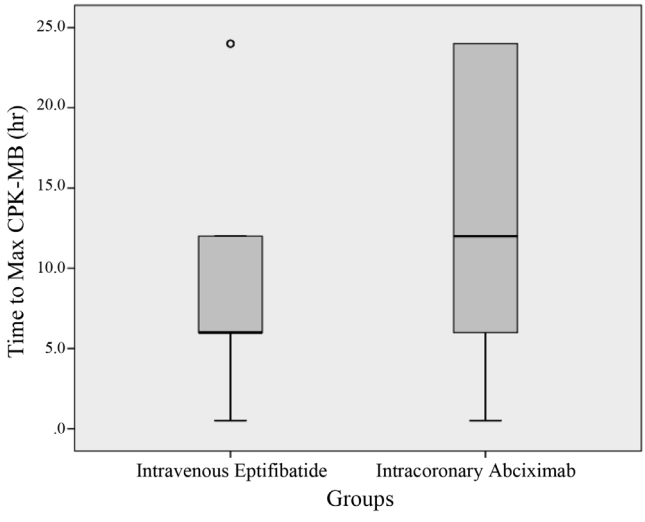


Figure 1. Time-to-peak CPK-MB enzyme level (hr)
CPK-MB, Creatine phosphokinase-MB

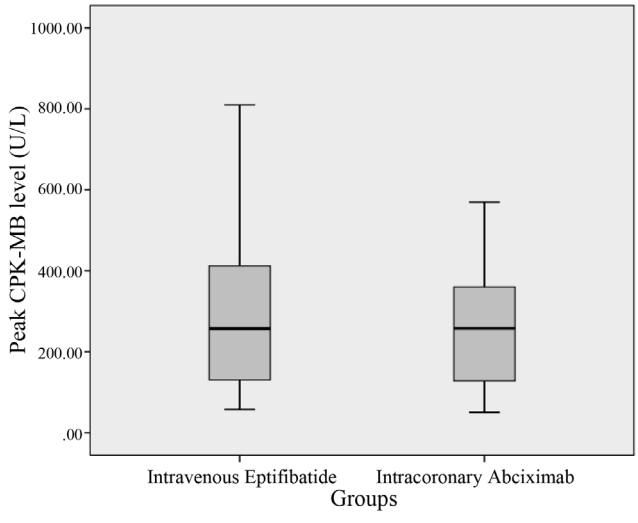


Figure 2. Peak of CPK-MB enzyme level during the first 48 hours after primary percutaneous coronary intervention
CPK, Creatine phosphokinase

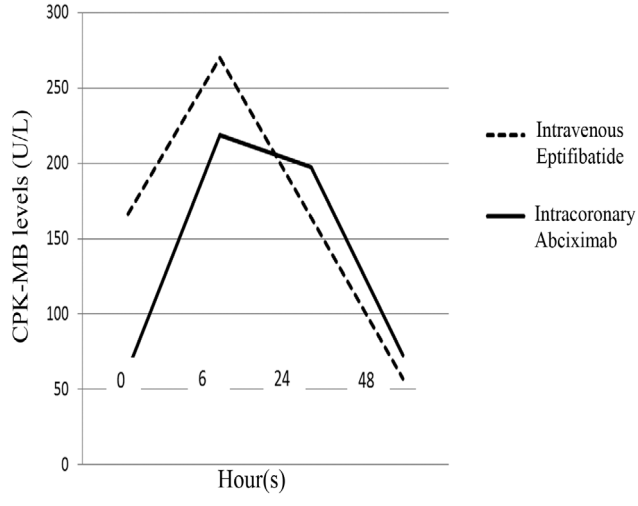


Figure 3. Serum CPK-MB level changes during the first 48 hours after primary percutaneous coronary intervention
CPK-MB, Creatine phosphokinase-MB

## *Discussion*

Mechanisms underlying impaired myocardial perfusion after the restoration of the epicardial blood flow are likely to be multifactorial such as oxygen free radicals, cellular and interstitial edema, endothelial dysfunction, vasoconstriction, and thromboembolism.[21, 22] The application of Gp IIb/IIIa inhibitors like Abciximab, Eptifibatide, and Tirofiban is shown to improve the outcomes of PPCI safely and efficaciously in terms of reduction in the infarct size and periprocedural MI as well as improvement in the TIMI flow.[16]

Depending on the relation of the inflow and outflow and the size of the ischemic area, the local Abciximab concentration can vary substantially. However, even in situations with restitution of the normal flow and perfusion in the infarct-related artery, an IC drug bolus administration will result in

very high local concentrations; this might be much higher than that in the usual IV application, which might reduce platelet aggregation further.[23] Another potential mechanism of high local concentration benefits might be related to the anti-inflammatory properties of GP IIb/IIIa inhibitors.[24] These considerations are supported by experimental data showing a dose-dependent platelet disaggregation. Concentrations that produce complete platelet disaggregation also induce the partial displacement of platelet-bound fibrinogen, which might play a role in the clinical setting.[25]

The angiographic and electrocardiographic end points are well established for the assessment of perfusion at the epicardial and microvascular levels. The sensitive ECG assessment at a later measurement was reported to have reflected an improvement in tissue perfusion.[26]

In our study, the IC administration of Abciximab was not superior to the IV administration of Eptifibatide with respect to the primary end points, which were improving myocardial reperfusion as assessed by STR, the enzymatic infarct size as measured by the AUC of CPK-MB in the first 48 hours after PPCI, and post-procedural TIMI grade flow of the infarct-related artery.

The other findings of the present investigation were the absence of significant differences in moderate and/or severe bleeding complications, deaths, urgent revascularizations or reinfarctions, and adverse events (during IC Abciximab administration), including arrhythmias, between the two groups. Moreover, we discovered that if balloon post dilation was necessary, it could be performed safely, with minimal risk of the no-reflow phenomenon.

Recently, the IC and IV approaches were compared in some trials and studies, which reported different results. For example, in the CICERO (The Comparison of Intracoronary Versus Intravenous Abciximab Administration during Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction) Trial,[18] 534 patients with STEMI undergoing PPCI with thrombus aspiration within 12 hours of symptom onset were randomized to either IC or IV bolus of Abciximab (0.25 mg/kg). No difference was noted in STR between the IC and IV groups. However, the IC administration was associated with improved myocardial perfusion as assessed by the myocardial blush grade and a smaller enzymatic infarct size.

Similarly, in the Intracoronary Eptifibatide (ICE) Trial,[27] the IC bolus administration of Eptifibatide during PCI in patients with acute coronary syndromes resulted in higher local platelet glycoprotein IIb/IIIa receptor occupancy, which was associated with improved micro-vascular perfusion as demonstrated by an improved corrected TIMI Frame Count.

The Randomized Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV vs. IC in ST-Elevation Myocardial Infarction Trial[28] showed that the IC bolus administration of Abciximab in PPCI was superior to the standard IV treatment with respect to infarct perfusion (according to STR at 90 minutes). In that study, each group contained 77 patients.

In the RELAX-AMI Trial,[29] the angiographic perfusion grade after PCI was similar between the IV Abciximab group and previously published results, whereas the IC Abciximab group had no statistically significant higher perfusion grades.

A retrospective analysis of angiographic and clinical outcomes among 59 patients who received IC Eptifibatide as part of clinical management of PPCI for STEMI between January 2001 and March 2005 showed that IC Eptifibatide could be administered safely during PPCI and that it was associated with few adverse events.[14]

In one study in patients with STEMI who underwent PPCI, the IC bolus application of Tirofiban was not associated with a reduction in the MACE rates and the enzymatic infarct size compared to the IV administration. At six months, the incidence of MACE was 6.25% in the IV group and 11.1% in the IC group (p value = 0.45). Peak creatine phosphokinase (CPK) levels between the IV and IC groups were also statistically non-significant (2657 ± 2181 U/L in the IV group and 2529 ± 1929 U/L in the IC group) (p value = 0.92).[30]

For the AIDA STEMI Trial,[31] 2,065 STEMI patients undergoing PCI between July 2008 and April 2011, were randomized to receive Abciximab by an IV infusion or directly into the blocked coronary artery for 12 hours. The IC bolus administration of Abciximab did not add a benefit in comparison to the standard IV bolus, with respect to the combined primary study end points, consisting of death, reinfarction, and new congestive heart failure within 90 days. Although the previous research suggested that an IC dose during PCI could boost the concentration of Abciximab at the treatment site, limit heart tissue destruction, and improve the blood flow, the AIDA STEMI researchers did not find a difference in the blood flow or infarct size (assessed by AUC CK-Release; p value = 0.74) and early STR (p value = 0.37) between the two routes. The IC route might be related only to reduced rates of new congestive heart failure.

As can be seen, the results of the comparison between IC and IV GP IIa/IIIb inhibitor administration during PPCI in STEMI patients are diffusely varied in many studies and trials. This might be the reason why the American Heart Association (AHA) and the American College of Cardiology (ACC), in the updated 2011 guidelines for PPCI, noted that in patients undergoing PPCI with Abciximab, it may be reasonable to administer IC Abciximab (class IIb). This, however, is not emphasized for the other GP inhibitor drugs.[32]

On the other hand, many trials, studies, and meta-analyses among STEMI patients undergoing PPCI have shown similar results between Abciximab and Eptifibatide (albeit via the IV route) in terms of angiographic (post-procedural TIMI flow grade 3 of the infarct-related artery and post-PCI myocardial blush grade), electrocardiographic (complete STR after PCI), and clinical outcome (in-hospital bleeding, in-hospital and 30-days' mortality, reinfarction, stroke/transient ischemic attack, target vessel revascularization, and

death or MI during one year).[33-37] Therefore, the AHA and the ACC, in the updated 2011 revascularization guidelines, recommended that in STEMI patients undergoing PPCI treated with unfractionated heparin, it is reasonable (class IIa) to administer an IV GP IIb/IIIa inhibitor (Abciximab, double-bolus Eptifibatide, or high-bolus dose Tirofiban), whether or not patients are pretreated with Clopidogrel (for GP IIb/IIIa inhibitor administration in patients not pretreated with Clopidogrel, level of evidence: A; for GP IIb/IIIa inhibitor administration in patients pretreated with Clopidogrel, level of evidence: C).[32]

Although in our study, all the angiographic and ECG measurements were blinded, the interventionalists were aware of the group assignment. Thus, a potential investigator bias cannot be ruled out entirely. Another important problem was the inadequate number of patients in each group, which was due to the wide range of the exclusion criteria.

Confirmation of the results with respect to the clarification of the long-term effects on the infarct size, myocardial reperfusion, ventricular size and function, and, more importantly, clinical outcome requires a larger trial.

## Conclusion

The results of this study show that the intracoronary administration of Abciximab is not superior to the intravenous administration of Eptifibatide in STEMI patients who underwent primary PCI.

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