

Glycoprotein Iib/Iiia Inhibitors in Acute ST-Segment Elevation Myocardial Infarction: Evaluation of Clinical Practice and Cost/Efficacy Analysis

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Abstract

Associated to primary percutaneous coronary intervention (pPCI), pharmacotherapy in acute ST-Segment elevation myocardial infarction (STEMI) patients have transformed the management of the acute phase. Use of glycoprotein Iib/IIIa inhibitors (GPI) remains debatable, level of guidelines has been modified in the successive editions of guidelines. In the latest European Society of Cardiology guidelines, GPI have a Iib B level in upstream use and Iia C in bail out during pPCI procedure. In front of the varying recommendations, we analysed clinical characteristics of patients with ST-Segment elevation myocardial infarction according to the use of GPI. We evaluate complications during hospitalization, particularly bleeding events. The cost of patients' management was also analysed.

We conducted a retrospective, descriptive and monocentric study from January 2010 to December 2012 including all consecutive STEMI patients with symptoms evolving for less than 12 hours treated by pPCI.

GPI were administered as recommended in patients with high thrombotic risk, low bleeding risk, with early presentation and more likely anterior location. Despite an initial more severe clinical presentation, no statistical difference among each group on in-hospital complications and duration of hospital stay was observed. Nevertheless patients treated with abciximab have a significant higher cost of overall management compared to HNF only (+30%) or other GPI (+37%). In selected clinical indications, in line with the European guidelines, GPI use appears safe, efficient and cost effective with regards to eptifibatide/tirofiban.

Keywords: Antiplatelet therapy; Glycoprotein Iib-IIIa inhibitors; ST-Segment elevation myocardial infarction; Primary percutaneous coronary intervention; Cost effectiveness

Abbreviations: ACS: Acute Coronary Syndrome; GPI: Glycoprotein Iib-IIIa Inhibitors; ICCU: Intensive Cardiac Care Unit; LVEF: Left Ventricular Ejection Fraction; PPCI: Primary Percutaneous Coronary Intervention; STEMI: ST-Segment Elevation Myocardial Infarction.

Introduction

In-hospital mortality related to ST-Segment elevation myocardial infarction (STEMI) patients depends of many settings: age, Killip classification, comorbid condition (diabetes, kidney failure) but also management delay and treatment delivered. Recent studies [1,2], have highlighted the relationship between decrease in acute and long term mortality and guidelines guided therapy regarding myocardial reperfusion. While HORIZON MI study [3-5], has compared bivalirudin *versus* heparin plus a glycoprotein Iib/IIIa inhibitor (GPI) in patients with STEMI undergoing primary percutaneous coronary intervention (pPCI), and showed a decreased 1-year cardiac mortality (2.1% *versus* 3.8%, $p=0.005$) and all-cause mortality (3.5% *versus* 4.8%, $p=0.037$) in the bivalirudin group. Some recent studies, NAPLES 3 study [6], and HEAT-PPCI study, have reported conflicting results with reduced incidence of major adverse ischemic events, with no increase in bleeding complications in the heparin group [7]. In the EUROMAX study, upstream use of bivalirudin, for pPCI, reduces major bleeding compared with both patients treated with heparin added to routine or even bailout GPI [8], reviving the debates. As well European and American guidelines have, regularly, modified the level and class of recommendation of GPI [9-14]. In 2012, the European guidelines [12] limit the routine use of GPI with a class Iib level B recommendation, proposed that GPI should be considered in bailout therapy in case of thrombotic

complication (class Iia, level C) and expressed that in high risk patient GPI may be used in upstream (class Iib, level A for abciximab, B for Eptofibatide and Tirofiban).

Even with various clinical studies and pharmacological rational, in front of the varying recommendations and contradictory results of randomized trials, we decided to evaluate in a single tertiary center the real life indications of GPI. Among STEMI patients we analyzed clinical characteristics, complications during hospitalization, particularly bleeding events as well as cost issues related to the drug used.

Methods

Method

This study was retrospective, descriptive and monocentric from January 2010 to December 2012. Inclusion criteria were adult patients with STEMI admitted to the coronary care unit (CCU) at Lariboisière university hospital (Paris, France) and treated by pPCI. Patients were eligible if admitted for *de novo* STEMI within 12 h from symptoms

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Received February 08, 2018; **Accepted** March 06, 2018; **Published** March 13, 2018

Citation: Cuny P, Benmiloud S, Oliary J, Dillinger JG, Sideris G, et al. (2018) Glycoprotein Iib/Iiia Inhibitors in Acute ST-Segment Elevation Myocardial Infarction: Evaluation of Clinical Practice and Cost/Efficacy Analysis. Cardiovasc Pharm Open Access 6: 236. doi: [10.4172/2329-6607.1000236](https://doi.org/10.4172/2329-6607.1000236)

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onset to pPCI. Exclusion criteria were patients with medical history: prior myocardial infarction, prior PCI or prior coronary artery bypass graft, cardiogenic shock at admission, cardiac arrest. The aim of our study was to define the clinical characteristics of patients with STEMI according to the use of GPI, to compare in hospital major ischaemic and bleeding events as well as global in hospital cost.

According to the treatment administered, we analysed cardiovascular risk factors, the management delay between the onset of chest pain and arrival in coronary angiography, the culprit artery, MI location, vascular access, transfusion, heart failure during hospitalization, duration of hospital stay, LVEF by transthoracic Doppler ultrasound (ETT) at hospital discharge and hospital management cost.

Data collection

To compare patients with or without administration of GPI, we used angiography database and medical files. Data of consecutive patients admitted from 2010 to 2012 were retrospectively collected and recorded. We reported also bleeding events and costs. The duration of hospitalization in ICCU and in the general cardiology ward were also recorded.

Cost analyses

Costs evaluation of patient's management was performed using data analytical accounting of Assistance Publique des Hôpitaux de Paris (data from the Public Health Department). All expenses of the year are listed by hospital department and unit. Direct costs included: human resources (medical, nursing, other), drugs, labile blood products, implantable medical devices. Indirect costs were: loads induced laboratory, functional tests, imaging, for example. It was obtained an average cost per day and patient of a unit or service.

Statistical analyses

Three independent groups (abciximab, eptifibatide / tirofiban or without GPI) were compared. Discrete variables were presented as percentages and counts. For quantitative variables, mean +/- standard deviation were calculated. Discrete variables were analyzed by a group Chi-square test (χ^2). Continuous variables groups were compared by analysis of variance. For all analyses, a p value <0.05 was considered to be statistically significant.

Results

From January 2010 to December 2012, 534 STEMI patients were admitted in our department, among them 294 patients fulfilled the inclusion criteria and were analyzed. We distinguished three groups:

- The "abciximab" group (187 patients) included all patients treated with this drug during the acute phase of ACS.
- The tirofiban / eptifibatide" group comprised 39 patients who received one of the two molecules (tirofiban: 15 patients and eptifibatide: 24 patients).
- 68 patients did not receive any GPI during the acute phase of STEMI: no-GPI group. Note that these patients may have received bivalirudin (27 patients) during the pPCI.

Clinical characteristics

Clinical characteristics at admission are presented in Table 1. According to the use and the type of GPI, we reported only sex and age difference between groups. Male received more GPI than women (p=0.01). The average age of all patients was 60 years (+/-14 years), patients without GPI were older, particularly men. Other cardiovascular risk factors did not differ between the three groups.

Medical management delay

The average time between chest pain and coronary angiography (Table 2) was 3.9 hours (+/-2.5 hours). It was significantly lower in the abciximab group 3.5 hours (+/-2.3) (p=0.01), and much longer among patient who received no GPI (4.1+/-2.6 hours). Among women (not shown), there was no significant difference between groups. On the opposite among men under 60 years, the delay was increased in the eptifibatide/tirofiban group compared to the other two groups (p=0.03).

Angioplasty

The anatomical location of STEMI was obtained from electrocardiographic patterns. Acute myocardial infarction affected inferior wall in 45.9% of patients and anterior wall in 41.8%. There was no significant difference among groups. Culprit coronary artery was reported for each patient (Table 2) and was predominantly the left anterior descending artery (46.3%). Thus, among patients treated with tirofiban or eptifibatide, left anterior descending artery was less

	Total (n=294)	Abciximab (n=187)	Tirofiban Eptifibatide (n=39)	No-GPI (n=68)	p value
Age (y) mean (SD)	60 (14.0)	58 (12.4)	61 (15.7)	65 (15.7)	0.02
Men (y) mean (SD)	57(12)	57 (10.8)	60 (15.8)	59 (13)	0.01
Women (y) mean (SD)	70 (16.3)	66 (16.6)	67 (14.6)	75 (15.3)	0.86
<60 years n (%)	157 (53.4%)	106 (67.5%)	23 (14.6%)	28 (17.9%)	0.01
60-74 years n (%)	83 (28.2%)	57 (68.7%)	7 (8.4%)	19 (22.9%)	
≥ 75 years n (%)	54 (18.4%)	24 (44.4%)	9 (16.7%)	21 (38.9%)	
Men n (%)	232 (78.9%)	157 (83.9%)	30 (76.9%)	45 (66.2%)	0.01
BMI (kg.m-2) mean (SD)	26 (3.6)	26,3 (3.6)	25.3 (4.0)	25.5 (3.5)	0.63
Diabetes mellitus n (%)	44 (15%)	27 (14.5%)	6 (15.4%)	11 (16.2%)	0.94
High Blood Pressure n (%)	112 (38.1%)	73 (39%)	13 (33.3%)	26 (38.2%)	0.80
Dyslipidemia n (%)	122 (41.5%)	80 (42.8%)	16 (41%)	26 (38.2%)	0.81
Active smoking n (%)	150 (51.0%)	99 (52.9%)	23 (58.8%)	28 (41.2%)	0.19
Obesity n (%)	44 (15.0%)	31 (16.6%)	5 (12.8%)	8 (11.8%)	0.60
Cardiovascular heredity n (%)	80 (27.2%)	53 (28.3%)	11 (28.2%)	16 (23.5%)	0.74

Table 1: Baseline clinical characteristics.

	Total (n=294)	Abciximab (n=187)	Tirofiban Eptifibatide (n=39)	No-GPI (n=68)	p value
Medical management delay					
Hours mean (SD)	3.9 (2.5)	3.5 (2.3)	4.9 (3.1)	4.1 (2.6)	0.01
Medical management delay among men <60 years					
hours mean (SD)	3.6 (2.5)	3.4 (2.3)	4.7 (3.4)	3.7 (2.4)	0.03
Time of Administration GP Iib-IIIa Inhibitors					
Upstream n (%)	16 (7.1%)	14 (7.5%)	2 (5.1%)	x	*
During/After PCI n (%)	190 (84.1%)	155 (82.9%)	35 (89.7%)	x	0.28
Not specified n (%)	20 (8.8%)	18 (9.6%)	2 (5.2%)	x	*
MI Location					
Anterior/apical n (%)	123 (41.8%)	87 (46.5%)	9 (23.1%)	27 (39.7%)	0.02
Circumferential n (%)	3 (1.1%)	3 (1.6%)	0 (0%)	0 (0%)	*
Lateral n (%)	28 (9.5%)	9 (4.8%)	12 (30.8%)	7 (10.3%)	0.01
Inferior n (%)	135 (45.9%)	86 (46%)	17 (43.6%)	32 (47.1%)	0.94
Undetermined n (%)	5 (1.7%)	2 (1.1%)	1 (2.5%)	2 (2.9%)	*
Culprit Coronary Artery					
Left Anterior descending artery n (%)	136 (46.2%)	95 (50.8%)	10 (25.6%)	31 (45.6%)	0.02
Left Circumflex n (%)	55 (18.8%)	26 (13.9%)	14 (35.9%)	15 (22.1%)	0.03
Right coronary artery n (%)	103 (35%)	66 (35.3%)	15 (38.5%)	22 (32.3%)	0.81
Adjonctive Antiplatelet Therapy					
Clopidogrel n (%)	199 (67.7%)	136 (72.7%)	25 (64.1%)	38 (55.9%)	0.03
Prasugrel n (%)	66 (22.5%)	40 (21.4%)	8 (20.5%)	18 (26.5%)	0.66
Ticagrelor n (%)	16 (5.4%)	4 (2.1%)	3 (7.7%)	9 (13.2%)	0.01
Not specified n (%)	13 (4.4%)	7 (3.8%)	3 (7.7%)	3 (4.4%)	*

*Not evaluated

Table 2: Primary PCI characteristics.

often involved (25.6%, $p=0.02$) than in abciximab group. For them, the Circumflex was predominantly the culprit coronary artery. Radial access was mainly used in 91.2% of the procedures without any difference between groups on access site.

Time of GPI administration, upstream or during/after PCI, showed no difference between the groups ($p=0.28$). Thromboaspiration during angioplasty was performed in the majority of the patients in abciximab group (62%), in 41% of the patients in the tirofiban/eptifibatide group and in 39.7% in the no-GPI group. There is a significant difference between the groups ($p=0.01$).

In combination with aspirin, the most frequent oral antiplatelet therapy loaded at the initial acute phase of ACS was clopidogrel (67.7%), a fortiori for patients treated with GPI (80.9%). In contrast, ticagrelor was administered more frequently in the no-GPI group. Prasugrel was administered in 22.5% of patients, without difference among groups. All the culprit lesions were successfully treated, with final TIMI grade flow >2 .

Left ventricular ejection fraction

The left ventricular ejection fraction (LVEF) was analysed at hospital discharge in all patients. In 79.6% of cases, LVEF was greater than or equal to 45%. There was no significant difference among groups.

In-hospital complications and duration of hospital stay

No difference was found in in-hospital events between the three groups (Table 3). During the study period, the STEMI in-hospital mortality was 2.7%. The mortality rate did not differ between the groups despite a trend of higher rate in the no-GPI group: 2.7% vs. 0% vs. 4.4%, $p=0.76$. Transfusions were required in 4.4% of patients, with a higher trend in the group treated with small molecules (tirofiban

and eptifibatide): 3.7% vs. 7.7% vs. 4.4%, $p=0.55$. Global duration of hospital stay was 5.6 days, without difference among groups.

Cost analysis

Cost analysis was presented in Table 4. The cost of hospital stay per patient treated for STEMI was 5426 euros. No significant difference was found among groups on this endpoint. The overall cost was calculated by adding the cost of hospital stay (average of 5426 euros) and cost of medications (GPI). Overall cost was 6074 euros, and per day 1140 euros. Patients treated with abciximab had a higher overall cost, compared to other two groups ($p=0.01$) +37% compared to the tirofiban / eptifibatide" group and +30% compared to the no-GPI group.

Discussion

In our French retrospective analysis, we found a large prescription of GPI: nearly 77% of patients treated within the first 12 hours of *de novo* STEMI. This percentage is higher than that of the FAST-MI registry 42.7% in 2010 [15]. This could be explained by the geographical characteristics with short transportation delays due to high PPCI centers density and the absence of fibrinolysis required in this network and a short median symptom to balloon delay. Pre-hospital and cath lab physicians' choice of therapeutic strategies were in line with the then prevailing European guidelines [10].

Patients' characteristics

The average age was 60 years (+/-14); in women 69 years (+/-16.3) and men 57 years (+/-12). 21.1% of patients were women. The population of the study is comparable to population described in the FAST-MI 2010 registry and European registries [16-19].

	Total (n=294)	Abciximab (n=187)	Tirofiban Eptifibatide (n=39)	No-GPI (n=68)	p value
Death n (%)	8 (2.7%)	5 (2.7%)	0 (0%)	3 (4.4%)	0.76
Acute renal failure n (%)	11 (3.7%)	6 (3.2%)	0 (0%)	5 (7.3%)	0.27
Left heart failure n (%)	6 (2.0%)	3 (1.6%)	0 (0%)	3 (4.4%)	0.45
Ventricular fibrillation n (%)	13 (4.4%)	10 (5.3%)	1 (2.6%)	2 (2.9%)	0.63
Recurrent MI n (%)	2 (<0.1%)	2 (<0.1%)	0 (0%)	0 (0%)	
Transfusion n (%)	13 (4.4%)	7 (3.7%)	3 (7.7%)	3 (4.4%)	0.55
Duration of hospital stay (days) mean (SD)	5.61 (4.87)	5.73 (5.18)	4.87 (3.24)	5.70 (4.80)	0.56
Duration of stay in ICCU (days) mean (SD)	4.08 (1.95)	4.16 (1.99)	4.10 (2.19)	3.85 (1.66)	0.53

ICCU: Intensive Cardiac Care Unit; AMI: Acute myocardial infarction.

Table 3: In-hospital events and duration of hospital stay.

	Total (n=294)	Abciximab (n=187)	Tirofiban Eptifibatide (n=39)	no-GPI (n=68)	p value
Cost of Hospital Stay (Euros)					
Cost of hospital stay mean (SD)	5426 (5167)	5761 (6058)	4644 (2884)	4947 (2995)	0.10
Cost of hospital stay per day mean (SD)	982 (113)	987 (117)	979 (67)	968 (122)	0.28
Overall Cost : Medications and Hospital Stay (Euros)					
Overall cost mean (SD)	6074 (5204)	6676 (6058)	4864 (2881)	5111 (2960)	0.09
Overall cost per day mean (SD)	1140 (176)	1209 (162)	1036 (82)	1010 (148)	0.01

Table 4: Cost analysis.

However, in terms of cardiovascular risk factors our population differed from the population reported in the 2010 nationwide snapshot registry [15]. The percentage of diabetic, dyslipidemic and/or obese patients were comparable, but smokers were more represented in our population (50% versus 40%) and high blood pressure less retrieved (38% versus 47%).

Patients who were not treated with GPI were significantly older. The choice to not administrate GPI have probably been guided first by bleeding avoidance strategies [20,21]. On the opposite, among younger patients, at lower bleeding risk, the choice was oriented toward a more aggressive anti-ischaemic strategy and abciximab was dispensed more willingly.

The prescription of a GPI seems not influenced by the other risk factor, especially diabetes mellitus: the percentage of diabetics was similar in both groups studied. Despite diabetic patients are at higher risk of thrombosis, with a higher platelet reactivity [22], and for which the GPI have been shown a net clinical benefit [23].

The average time between chest pain and coronary angiography was 3.9 hours (+/-2.5 hours). This time was higher in the eptifibatide / tirofiban group compared to the other two groups, particularly among men under 60. These patients, when seen later were less likely treated with abciximab. However, identification of significant thrombotic burden during coronary angiography and their low bleeding risk may have oriented the drug prescription.

We reported that the abciximab group included patients treated earlier with anterior and apical MI locations. In fact, these patients would more benefit of a more aggressive antiplatelet strategy [24,25]. These characteristics are those indicated in the European guidelines [12]. Interestingly electrical diagnosis of MI related to circumflex occlusion may be initially difficult, leading to a delayed medical management. In the present study, patients with occluded circumflex artery had in fact later medical care, and are more represented in tirofiban/eptifibatide treated group.

The radial access is used in 91.2% of patients as recommended guidelines [12]. Although the risk of bleeding is increased with the femoral access [26,27], approach was not a discriminant parameter for the use of GPI.

In-hospital events

The rate of post-MI complications are comparable to data from the French FAST-MI registry [28,29], re-MI in 0.9% of patients (<0.1% in our study), deaths in 5% of patients (2.7% in our study) and transfusion in 3.2% of patients (4.4% in our study). LVEF retrieved in our study was similar to the one reported in the French data 49.7% and 50.4% respectively. Our analysis didn't retrieve any difference among groups regarding in-hospital events. The risk of acute renal failure, left heart failure and recurrence of MI do not differ between the groups with and without GPI, but the number of patients was low.

In our study the use of GPI did not increase the rate of bleeding. The duration of hospital stay was 5.6 days This duration was relatively shorter than those reported in FAST MI [28], 8 days (+/-7.8 days), with 4.4 days (+/-4.2 days) in ICCU. These shorter stays may be related to the fact that we excluded NSTEMI and patients with more severe presentation at admission like cardiogenic shock and cardiac arrested patient. GPI did not change the stay's duration of patients.

Cost

Per patient, the cost of hospital stay was 5426 euros (1008-59583). While no difference regarding hospital stay's cost was found between groups, the overall cost per patient and per day differed between groups. Anticoagulants and antiplatelet drugs have a low price and do not influence. Patients treated with abciximab had the highest overall cost. In our hospital, abciximab's treatment, intra venous bolus and infusion is 915 euros, 197 euros with tirofiban, 235 euros with eptifibatide and 407 euros with bivalirudin. Prices explain the difference in the overall cost, as the hospitalization's duration was similar. An American study [30,31], compared the overall cost for patients with STEMI treated by

angioplasty (associated with GPIIb-IIIa inhibitors or fibrinolysis) to those treated with angioplasty alone. There is no significant difference between groups on this endpoint.

Limits

This study showed limits. First of all, we conducted a retrospective and monocentric analysis with its inherent bias related to patient's recruitment specificity, local practice. Secondly, these results should also be interpreted cautiously in view of the small size of the population. Due to the limited period and the single centre analysis, it was not possible to analyse a temporal trend. Lastly, our records did not include long term parameters. To compare GPI we had only surrogate short term parameters.

Conclusion

Our retrospective monocentric analysis reported that patients to whom GPI were administered were more likely young, with early presentation of an anterior MI related to left anterior descending artery lesion.

No difference between GPI or the no-GPI groups were found regarding in-hospital complications and duration of hospital stay. Solely patients treated with abciximab had a higher cost of overall management.

As registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, in fact our retrospective study met 2012 ESC guidelines [12]. This rational choice of treatment according to patient profile during management of acute MI resulted in event rates, especially haemorrhagic, not different. In these selected indications, small molecules show a better cost-efficacy profiles.

Abbreviated Title

GPIIb/IIIa inhibitors in STEMI: patients' characteristics and cost/efficacy analysis.

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