

Glycoprotein IIb/IIIa Inhibitors in Clinical Practice

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Introduction

Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors were developed in the early 1990's with the purpose of providing maximum platelet aggregation blockade. At first they were used adjunctly with balloon coronary angioplasty to reduce acute occlusion of the vessel treated and its complications such as periprocedural acute myocardial infarction (MI). The dissection of the vessel after balloon dilation in percutaneous coronary intervention (PCIs) occurred in 20 to 25% of the cases, and, as a consequence, acute occlusion developed in 5% of these patients¹. Reduction in platelet aggregation with GP IIb/IIIa inhibitors caused a reduction in major cardiovascular events (death, MI and urgent target vessel revascularization/TVR) after PCI². However, it was the advent of coronary stents, because they reestablish the vessel geometry and "seal" the dissections, which contributed the most to eliminate such complications. GP IIb/IIIa inhibitors, as adjuncts to coronary stents, basically reduced periprocedural MI which occurs due to slow flow phenomena subsequent to platelet embolization ("slow reflow", "no reflow") or secondary branch occlusion.

The good results of initial studies such as EPIC², EPILOG³ and EPISTENT⁴ with the combined reduction of major cardiovascular events (MACEs) determined a growing use of GP IIb/IIIa inhibitors. Since then, different drugs of this class (abciximab, tirofiban and eptifibatide) have been tested in different situations such as elective procedures; acute coronary syndromes (ACSs) with or without ST segment elevation; reduction of coronary restenosis and more recently as a complementary medication to facilitate primary angioplasty.

With the evolution of platelet antiaggregation therapy, new classes of drugs emerged, including thienopyridines. Pretreatment with these drugs before PCI is today mandatory⁵. However, antithrombotic therapy has also evolved and recent studies with bivalirudine⁶ and fondaparinux⁷ currently provide other adjunct therapy options for PCIs.

In this brief review, and according to recent publications and current guidelines, we will establish the role of GP IIb/IIIa inhibitors as an adjunct therapy in PCIs in different scenarios.

Key Words

Platelet aggregation, Glycoprotein IIb/IIIa receptor inhibitors, percutaneous coronary intervention.

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Case Report

Elective percutaneous coronary intervention

The first studies to test the administration of these drugs in elective angioplasties were EPISTENT⁴ (abciximab), ESPRIT⁸ (eptifibatide) and RESTORE⁹ (tirofiban), which showed, however inconsistently, a strong trend towards the reduction of combined events, especially at the expense of non-Q MI (ck-mb elevation more than three times above the upper normality threshold). It is important to note that the use of tirofiban in the RESTORE study did not reach statistical significance levels as to the reduction of MACEs, probably because a sub-dose of the drug was used (fig.1).

Thienopyridines emerged with the evolution of platelet antiaggregant therapy. The issue then was whether pretreatment with these drugs could replace GP IIb/IIIa inhibitors, and whether they would be equivalent in the reduction of periprocedural MI. In this sense, the ISAR REACT I study was published where more than 2,000 low cardiovascular risk patients underwent PCI, and were all treated with 600mg of clopidogrel at least six hours before the procedure. They did not benefit from the addition of abciximab to the association of ASA and clopidogrel, which is the standard therapy in current clinical practice. The final result of this analysis strongly suggest that there is no longer a role for GP IIb/IIIa inhibitors in low risk elective angioplasties¹⁰.

Today in Brazil 5.5% of the PCIs (whether elective or not) are performed under the effect of GP IIb/IIIa inhibitors, according to data provided by CENIC (National Center of Cardiovascular Interventions)¹¹. Despite the high cost of these drugs and the references presented, the latest North American¹² and European¹³ consensuses advocate the use of GP IIb/IIIa inhibitors in elective PCIs under indication IIa, level of evidence B.

Non-st elevation acute coronary syndrome

It can be said that the use of these drugs has become mainstream for patients with moderate to high cardiovascular risk, in acute coronary syndromes with and without ST elevation, where it is known that early intervention with adjunct medication reduces the chances of major cardiovascular events (MACEs).

The benefit of using GP IIb/IIIa inhibitors in non-ST elevation ACSs was proven more than a decade ago with the publication of the CAPTURE¹⁴ study. Patients with non-ST elevation ACS with high cardiovascular risk who were given the drug presented a reduction of the relative risk of major events (death, MI, TLR) of 28.9% as compared with the placebo group at the end of the 30-day period. Such benefit was due primarily to the reduction of periprocedural MI and was only observed in patients with complex lesions (type \geq

Death / MI / TLR 30d	llb/llla	Placebo	P
EPISTENT *	6,4%	12,1%	s
ESPRIT	7,5%	11%	S
RESTORE	10,3%	12,2%	nS
MI EPISTENT *	5,2%	10,3%	s
ESPRIT	6.2%	9.7%	S
RESTORE	4,2%	5,7%	nS
DEATH EPISTENT *	0.5%	1.2%	nS
ESPRIT	0,4%	0,6%	nS
RESTORE	0.7%	0.8%	nS

Figure 1 - Incidence of combined and isolated cardiovascular events in the respective studies; *Data from the EPISTENT study for cardiovascular events within 6 months of follow-up. Data of this study refer to the groups: stent + abciximab and stent + placebo; S = p < 0.05; nS = p > 0.05; MI - Acute Myocardial Infarction; TLR -Target Lesion Revascularization

B2). The following studies: PRISM-PLUS¹⁵, PARAGON-B¹⁶ and PURSUIT¹⁷ have also included patients with the same presentation. When PCI was performed under the effect of GP IIb/IIIa inhibitors, a reduction of relative risk of death or MI by 42%, 35% and 31%, respectively was observed within 30 days as compared with the conservative treatment. With the confirmation of this scientific evidence, the GP IIb/IIIa inhibitors have become major prescription drugs for high risk patients with non-ST elevation ACS.

Just as in elective interventions, the mandatory pretreatment with clopidogrel once again questioned the actual benefit of GP IIb/IIIa inhibitors, now for patients with non-ST elevation ACS. The answer to this question became clear with the publication of the results of the ISAR REACT II¹⁸ study. In a population with high cardiovascular risk (elevation of troponin in 51.9% of the sample and multiarterial disease in 74% of the sample), the sole group of patients to experience a significant decrease in primary outcome (death, MI or TLR) at the end of the six-month period and one-year period was the group with positive troponin (fig.2).

In an era when the reduction of hospital costs has become a key element of new research in progress, the use of a single bolus of GP IIb/IIIa inhibitor was assessed in a recent publication¹⁹. The rationale of such strategy is based on the fact that the literature presents proof that single bolus epitifibatide has a powerful platelet antiaggregation effect without increasing the risks of bleeding²⁰. In an era of ample use of stents under high pressures, with clopidogrel as the standard use, there are few acute thrombus complications such as the abrupt closure of vessel. Currently the average time of a PCI is shorter than one hour in most large centers and, considering the pharmacokinetics of epitifibatide, the platelet antiaggregation should hopefully last at least two to three hours²¹. In the case of abciximab this time could reach six hours. Additionally, early discontinuation of GP IIb/IIIa inhibitor could reduce hemorrhagic complications such as the presence of hematomas in the puncture site. But surely the greater benefit would be the reduction of hospital costs. In the PURSUIT¹⁷ study, the average cost of eptifibatide was 1014 dollars; in ESPRIT⁸, it was 502 dollars and in this analysis it was 59 dollars¹⁹. It could become an attractive alternative if corroborated in large randomized studies.

Some factors such as different designs of studies and the diversity of drugs used pose doubts that prompt the following question: which of the GP IIb/IIIa inhibitors should be used? A significantly larger number of studies with abciximab in ACS, the lesser in vitro affinity of eptifibatide for the glycoprotein IIb/IIIa receptor, and the lack of large randomized studies that compare it directly with the other two drugs of the study (abciximab and tirofiban) and the results at the end of the 30 days of the TARGET²² study, which demonstrated a greater incidence of MACEs in the population that used a 10 μ g/kg bolus of tirofiban as compared with abciximab, all these create a distorted image that abciximab should be the GP IIb/IIIa inhibitor of choice in such situations, and strangely, it has a higher cost. However, the publication of the ADVANCE²³ study and of the TENACITY²⁴ metanalysis, which was interrupted earlier due to financial reasons, when a bolus of $25\mu g/kg$ of tirofiban was used, demonstrated the non-inferiority of this drug relative to abciximab for major outcomes (death, MI and TLR) with a similar profile of safety for 30 days. It is important to note that when non-ST elevation ACS is not followed by invasive stratification, the use of abciximab shows no benefit, as was clearly demonstrated by the GUSTO IV study²⁵. As regards the precise moment to administer the drug (emergency room x hemodynamics laboratory), the ACUITY Timing study²⁶ showed a discrete elevation in ischemic events, with no statistical significance, when a GP IIb/IIIa inhibitor was used in the hemodynamics room as compared with early administration. However, such delay in the administration of the drug resulted in a marked decrease in hemorrhagic events (4.9 x 6.1%; *p* <0,001).



Figure 2 - Kaplan-Meier curve for accumulated incidence of death, MI and target lesion revascularization for both groups under treatment, subdividing patients in two groups: those with and without troponin elevation; Modified from KastratiA, et al¹⁸ JAMA 2006.

With so much proof in the literature, the use of GP IIb/IIIa inhibitors in non-ST elevation ACS is unequivocally a class I indication, level of evidence A, in the absence of clopidogrel, according to the North American consensus¹². When clopidogrel is used, indication of GP IIb/IIIa inhibitors becomes a class IIa indication, level of evidence B. In complex situations, such as the abrupt closure of a vessel; presence of a visible thrombus; and the "no/slow reflow" phenomenon, it is a class IIa indication, level of evidence C, according to the current European guideline^{13,27}. The results of the studies mentioned send out a clear message: the greater the risks, the greater the benefits of the drug. In general, any of the GP IIb/IIIa inhibitors can be used in high-risk patients with non-ST elevation ACS submitted to early invasive stratification.

Acute coronary syndrome with st elevation

ACSs with ST elevation are now an indication IIa (level of evidence B) according to the latest European and North American consensuses for abciximab administration based on metanalyses such as the one conducted by Kandzari et al²⁸ which included the ADMIRAL, RAPPORT, ISAR II and CADILLAC pioneer studies where the most significant variable was a considerable drop in target lesion revascularization within 30 days which was maintained within six months for the group of patients on abciximab. This late warning given by the consensuses might be due to the difficulty in conducting a joint analysis of the different models of studies and their results (fig.3).

The absence of benefits regarding event reduction in the CADILLAC study, where abciximab was always administered

concurrently with PCI, is in contrast with the results of the RAPPORT and ADMIRAL studies. In these studies, the early administration of abciximab occurred in approximately 25% of the patients before they arrived at the hemodynamics laboratory, and, as a result, there was a greater chance of having TIMI III distal flow, which might account for the discrepancy in results²⁸.

Montalescot²⁹ observed in his metanalysis of six studies of ACS with ST elevation (three studies with abciximab and three studies with tirofiban) the role of early administration of GP IIb/IIIa inhibitors (ambulance or emergency department). When compared with the administration in the hemodynamics laboratory, early administration resulted in a higher chance of TIMI III distal flow (20.3% x 12.2% - odds ratio of 1.85; CI 95%, 1.26-2.71; p<0.001) (fig.4). Early administration of the drug in this analysis resulted in a 28% reduction in the relative risk of death as compared with the administration of the drug in the hemodynamics room (4.7% x 3.4%), although this was not statistically significant.

These findings have also been confirmed by a recent study called RELax MI³⁰. It randomized 210 patients with ACS with ST elevation who underwent primary PTCA with early administration of abciximab (emergency room – mean of 55 minutes prior to PTCA) or late administration (hemodynamics laboratory – mean of 14 minutes prior to PTCA – p < 0.001). Primary outcomes included chance of TIMI III epicardial flow, myocardial blush level 2-3 on initial angiography and recovery of left ventricular ejection fraction within 30 days of the event. All the angiographic benefits occurred with greater frequency in the early group (fig.5), and there was also a greater increase



Figure 3 - Odds ratio and confidence interval of 95% for the risks of death, acute myocardial infarction and target lesion revascularization (A), death or infarction (B); with abciximab vs placebo; N - number of patients; Modified from Kandzari DE, et al²⁸ Am Heart J 2004.



Figure 4 - Odds ratio (OR) for TIMI III flow with early vs late administration of GP IIb/IIIa; OR = 1.85 (CI 95%; 1.26-2.71; p < 0.01). Breslow-Day test for heterogeneity; p=0.12; CI - Confidence Interval; Modified from Montalescot G, et al²⁹ JAMA 2004.

in the ejection fraction (8 \pm 7% vs. 6 \pm 7%; p = 0.02) with absolute values of 51 \pm 9% early vs. 47 \pm 10% late (p = 0.01) at the end of the 30-day period.

Srinivas et al³¹ recently published an observational analysis using data from the record of primary angioplasties of New York State. With more than 7,000 patients treated between the years 2000 and 2003, with 78.5% using GP IIb/IIIa inhibitors, the hospital mortality rate dropped from 6.2% to 3%. In the sample assessed, approximately 30% of the patients used abciximab and 46% were given tirofiban or eptifibatide, which is surprising since the latter two only had indication IIb according to the AHA/ACC¹² consensus. Once again, the difficulty in interpreting different studies seems to account for these specific aspects regarding the indication of IIb/IIIa inhibitor as an adjunct to primary PTCA. In our department's experience, at Instituto Dante Pazzanese de Cardiologia, in the period between 2002 and 2007, GP IIb/IIIa inhibitors were used in approximately 5% of all angioplasties. In MI with ST elevation, 30% of the patients who underwent primary angioplasty were given these drugs.



Figure 5 - Epicardial flow according to the TIMI "Thrombolysis in Myocardial Infarction" criterion (left) and level of myocardial blush – MBG (right) on initial angiography in the groups using early and late GP IIb/IIIa inhibitors; Early group with TIMI III flow significantly higher (p=0.001 vs late group), and MBG 3 (p=0.028 vs late group)

Facilitated primary angioplasties

The gold standard for the treatment of ACSs with ST elevation is the fast and effective reperfusion of the target vessel, and several studies in the literature have shown the superiority of primary angioplasty as compared with fibrinolytic medication, as long as it is performed in due time. However, due to a series of factors, this target (< 90 minutes) is hardly ever achieved. The idea then developed that fibrinolytic medication with or without GP IIb/IIIa inhibitors should be administered in the ambulance or emergency rooms, and followed by angioplasty to ensure complete reperfusion. Initially, a series of pilot studies such as TIGER-PA, ON TIME, Sk-EPTIFIBATIDE and SPEED (pilot of GUSTO-IV) showed an increase in the myocardial reperfusion rate with reduction of the platelet thrombus load; but with increased bleeding, especially when GP IIb/IIIa inhibitors were combined with the administration of fibrinolytic drugs^{32,33}. The GUSTO V study, with more than 15,000 patients allocated, assessed the association of abciximab and a sub-dose of reteplase and compared it with a full dose of the latter, and observed that there was no significant difference for the mortality rate within 30 days (5.6 x 5.9%) and one year (8.4% for both groups) and with twice the incidence of intracranial hemorrhage in the population above 75 years (2.1 x 1.1)³⁴. Although there are more than 17 studies in the literature about such strategy, its clinical benefits have not yet proven and the poor results of recent papers, just as the rates of hemorrhage, may be signaling the end of this therapeutic proposal.

The long awaited FINESSE study with 2,452 patients, the largest analysis ever carried out comparing primary PTCA with facilitated angioplasty, was recently published. The primary outcome comprising mortality, ventricular fibrillation and/or heart failure at 90 days has not been statistically different when the following comparisons were made: primary PTCA with GP IIb/IIIa inhibitors in the laboratory vs GP IIb/IIIa inhibitors and a half dose of reteplase pre-laboratory and GP IIb/IIIa inhibitors pre-laboratory vs GP IIb/IIIa inhibitor and a half dose of reteplase pre-laboratory there was a higher incidence (p < 0.005) of major and minor hemorrhage according to the TIMI criterion for the two groups of facilitated angioplasty (GP IIb/IIIa inhibitor pre PTCA and half dose of

reteplase with GP IIb/IIIa inhibitor pre-PTCA) as compared with primary PTCA. These results are not very favorable to this type of strategy³⁵.

Percutaneous coronary intervention in diabetics

Diabetics make up another population to capture the interest of researchers as it is known that they present a greater degree of inflammation and endothelial dysfunction thus creating a favorable environment for the development of coronary artery disease. The platelets of these patients are harder; their membranes have lower viscosity and express a greater amount of glycoprotein IIb/IIIa receptors. This group of patients tends to present a higher rate of mortality and target lesion revascularization within the first year after PCI as compared with the non-diabetic population³⁶. A retrospective sub-analysis of EPISTENT, dealing only with the diabetic population, showed a late reduction in target lesion revascularization in the group that used abciximab³⁷. This hypothesis, however, was not confirmed in the primary outcomes of the ISAR-SWEET study³⁸ which randomized 701 diabetic patients submitted to elective PTCA to receive either abciximab or placebo. In this study, the incidence of death or MI was 8.3% in the abciximab group and 8.6% in the placebo group, with no significant statistical difference between the groups. Almost concurrently, in the DANTE study³⁹, when a group exclusively made up of diabetic patients was reexamined with intracoronary ultrasound six months after the elective angioplasty, no effect on the decrease of the restenosis rate was observed in the group that used abciximab (fig.6).

However, in a population of higher risk diabetics, the administration of abciximab has demonstrated an impact on the reduction of events. Montalescot et al. in a recent metanalysis of ACS with ST elevation⁴⁰, observed, at the end of a three-year follow-up, a fourfold incidence of death and MI in diabetics as compared with non-diabetics. The administration of abciximab to this population of diabetics provided marked benefits on the reduction of cardiovascular outcomes.

Another metanalysis of six studies⁴¹, in patients with non-ST elevation ACS, demonstrated that diabetic patients also present benefits from the administration of GP IIb/IIIa



Figure 6 - Cumulative distribution for minimum luminal diameter pre-treatment, post-treatment and within a six-month follow-up for the control and abciximab groups; mm – millimeters; Modified from Chaves AJ, et al³⁹ Circulation 2004.

inhibitors. Among more than 6,000 patients included, platelet antiaggregation therapy with GP IIb/IIIa inhibitors demonstrated a reduction in mortality at 30 days from 6.2% to 4.6% (relative reduction of 0.74; [confidence interval of 95% 0.59-0.92]; p = 0.007). Although the studies have observed a protective action for these patients, there is no specific indication so far from the North American and European consensuses regarding the administration of GP IIb/IIIa inhibitors specifically to the diabetic population.

New Alternatives

In the pursuit of the ideal antithrombin medication to treat ACSs, new drugs were tested such as fondaparinux and bivalirudine (direct inhibitors of thrombin), with a profile of higher safety relative to the incidence of hemorrhagic events when compared with the standard therapy, i.e., the association of heparin and GP IIb/IIIa inhibitors as adjuncts to PTCA.

Bivalirudine, previously administered only as an alternative to patients who developed heparin-induced immune thrombocytopenia was tested initially in the REPLACE 2 study⁴². Bivalirudine, associated with the judicious use of GP Ilb/IIIa inhibitors, has proven its non-inferiority relative to the association of unfractioned heparin (UFH) - GP IIb/IIIa inhibitors in elective and urgent PCIs with equivalent results within one year for all subgroups assessed, and a lower incidence of major hemorrhage during hospital stay (2.4% x 4.1%; p < 0.001). It is important to highlight that there was a trend towards mortality reduction in the group using bivalirudine, although with no statistical significance (fig.7).

The results of ACUITY⁶, a recent study, demonstrated non-inferiority of the isolated administration of bivalirudine as compared with associations of UFH - GP IIb/IIIa inhibitors and bivalirudine - GP IIb/IIIa inhibitors relative to ischemic events with a marked reduction of major hemorrhagic events in patients with non-ST elevation ACSs, regardless of the administration of thienopyridines (fig.8). The results of its subanalysis, ACUITY-PCI⁴³, although still posing questions relative to the groups of patients who did not use thienopyridines prior to PCTA and those with positive troponin, where the isolated use of bivalirudine demonstrated a trend towards higher ischemic events (with no statistical significance) provides a new option to treat high risk non-ST elevation ACSs (indication IIA – level of evidence B)⁴⁴, especially when the risk of hemorrhagic events is significant (elderly patients, females and low weight patients).

Fondaparinux, another drug with direct action on thrombin, also demonstrated superiority when compared with low molecular weight heparins in the OASIS-5⁷ study (ACS without ST elevation) and OASIS-6⁴⁵ (ACS with ST elevation), relative to major cardiovascular outcomes (death, MI and TLR) and, especially, a marked reduction in the incidence of major and minor hemorrhage. The two studies together included more than 20.000 patients, but the results about the incidence of MACEs could not be extrapolated to the group submitted to PCI. The incidence of catheter thrombosis in the OASIS-5 study for the group on isolated fondaparinux was well above that of the group on low molecular weight heparin (1.3% x 0.6%). However, such problem seems to be solved if another drug with anti-Ila activity (UFH or bivalirudine)⁴⁴ is added during PCI, without increasing the risk of bleeding.

Conclusion

In view of the evidence presented, the use of GP IIb/IIIa inhibitors has become extremely rational in recent years. They are currently administered only in cases of ACSs with and without ST elevation (with markers of high risk such as positive troponin), with the consensuses still advocating



Figure 7 - Cumulative incidence of acute myocardial infarction and new target lesion revascularization; Modified de Lincoff AM, et al42 JAMA. 2003.

the administration of tirofiban and eptifibatide in strategies that are initially conservative. Issues relating to cost and incidence of hemorrhagic events which are directly related to an increase in mortality rate during hospital stay have opened the way for studies with new drugs which show promising results. the early administration of abciximab before arrival to the hemodynamics laboratory in ACSs with ST elevation and a single bolus of eptifibatide in elective PCIs can justify future changes in guidelines. The administration of drugs of this group should be accompanied by an adjusted dose of UFH for PCI (mean of 70UI/kg) in order to reduce the chance of hemorrhagic events. Cases with high risk of

Some new options for GP IIb/IIIa inhibitors, such as

thrombotic complications such as complex anatomies are also an alternative for these drugs. The doses of eptifibatide (Cr Cl < 50ml/min) and tirofiban (Cr Cl < 30 ml/min) should be adjusted whenever necessary for renal failure. When bivalirudine is the anticoagulant of choice for PCl, GP IIb/IIIa inhibitors should not be administered, whereas with fondaparinux GP IIb/IIIa inhibitors can be one of the alternatives of association in case early PCl is performed. Despite recent updates in consensuses, these drugs are not vet available in Brazil

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