Role of platelet glycoprotein IIb/IIIa inhibitors in rescue percutaneous coronary interventions

Anna Sonia Petronio, Marco De Carlo, Roberta Rossini, Giovanni Amoroso, Ugo Limbruno, Nicola Ciabatti, Caterina Palagi, Paolo Caravelli, Mario Mariani

Cardio Thoracic Department, University of Pisa, Pisa, Italy

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In the setting of acute myocardial infarction, thrombolytic therapy fails to restore an adequate epicardial flow in a large number of patients. Although an increasing number of patients undergoes a percutaneous coronary intervention (PCI) after failed thrombolysis, this treatment has been poorly investigated. This review focuses particularly on the safety and prognostic impact of glycoprotein (GP) IIb/IIIa receptor inhibitors after failed thrombolysis.

GPIIb/IIIa inhibitors have been demonstrated to improve the clinical outcome in patients undergoing primary PCI. However, the increased risk of bleeding with the administration of potent antiplatelet drugs after full-dose thrombolytics has limited the widespread use of GPIIb/IIIa inhibitors during rescue PCI. We recently reported that abciximab treatment during rescue PCI has a beneficial effect on the short-term prognosis, without excess bleeding complications. This result can be achieved by using the radial approach, a low-dose weight-adjusted heparin regimen, and by limiting the use of aortic counterpulsation.

In conclusion, in case of thrombolysis failure, patients should be referred to tertiary hospitals where rescue PCI can be performed with expertise.

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Address:

Prof.ssa Anna Sonia Petronio

Emodinamica
Dipartimento
Cardio Toracico
Ospedale Cisanello
Via Paradisa, 2
56124 Pisa
E-mail: a.petronio@mail.ao-pisa.toscana.it

Introduction

The early reperfusion of an occluded artery is the goal of acute myocardial infarction (AMI) therapy. A primary percutaneous coronary intervention (PCI) has been proven to be a successful alternative strategy to thrombolysis, but the latter still remains the most common treatment for patients with AMI. However, in up to 50% of patients thrombolysis fails to achieve an optimal reperfusion (Thrombolysis in Myocardial Infarction [TIMI] flow grade 3), and 20-30% of patients could be referred for "rescue" PCI[1-5]. Although the number of patients undergoing rescue PCI after failed thrombolysis is relatively large, this reperfusion strategy has been poorly investigated, with few data concerning the therapeutic protocols and clinical efficacy of rescue PCI.

Some small studies have been reported, but there is not even a common definition of rescue PCI. The symptom-onset-to-balloon time ranges from 6 to 48 hours, and many studies have pooled together patients with different clinical settings, such as delayed rescue PCI and adjunctive PCI early after thrombolysis[1,6-8].

Initial studies

The most important results reported over the last 10 years are subgroup analyses of large thrombolysis trials. In these trials, the number of patients undergoing rescue PCI, usually in a non-randomized way[9,10], is rather small. In the pre-stent era, the acute angiographic success rate reported for rescue PCI was lower (> 82%) than that of primary PCI (< 96%), but sufficient to demonstrate the feasibility of mechanical reperfusion after thrombolysis.

The RESCUE I trial was the only randomized trial, and included 151 patients with a first anterior AMI randomly assigned to either rescue PCI or conservative therapy. No significant difference was found between the two groups concerning the primary endpoint, which was left ventricular ejection fraction at 30 days. However, at 1 year of follow-up a statistically significant survival benefit was detected in patients undergoing rescue PCI ($p = 0.001$)[8].

Subsequent studies failed to prove the efficacy of rescue PCI. In the TIMI 4 and GUSTO I trials, in spite of a satisfactory angiographic result, the incidence of com-

plications related to rescue PCI was similar to that of patients not undergoing percutaneous intervention. The decrease in adverse events with successful rescue PCI was counterbalanced by the significantly higher incidence of adverse events with failed rescue PCI[9,10]. Considering all patients undergoing rescue PCI (successful or failed), the incidence of an adverse outcome was the same as in patients in whom no procedure was attempted. It should be emphasized that the adverse events experienced by patients with a failed rescue PCI were in part due to acute coronary thrombosis. In the TIMI 4 study, the rate of coronary reocclusion after a successful rescue PCI was 8 vs 5% after successful thrombolysis[9]. However, the incidence of acute coronary thrombosis has been dramatically reduced over the last few years by the improvements in drug therapy and in the technical aspects of PCI.

Contemporary experience

The first studies reporting on rescue PCI were performed in the pre-stent era, but even some subsequent studies had a limited use of coronary stents (29% in the RESCUE II trial)[11]. This is one of the reasons for the high incidence of reocclusion described in both the TIMI 4 and GUSTO I studies[1,9]. Currently, the extensive use of coronary stents and glycoprotein (GP) IIb/IIIa inhibitors has substantially improved the short- and long-term results of interventional cardiology, particularly in acute coronary syndromes. Therefore, the clinical efficacy of rescue PCI needs to be re-evaluated.

The rationale for the use of GPIIb/IIIa inhibitors in rescue PCI is based on their potent antithrombotic effect, which is particularly useful after failed thrombolysis. In fact, thrombolysis has a pro-thrombotic effect due to the release of thrombin from the fibrin network of the thrombus. In turn, thrombin release leads to further thrombin generation, enhanced platelet aggregation, plasminogen activator inhibitor-1 release, and, ultimately, to a state of resistance to fibrinolysis. Thus, even after successful mechanical resolution of the occlusion of the infarct-related artery, the persistence of a pro-thrombotic *milieu* may yield suboptimal results[12]. The platelet GPIIb/IIIa receptor represents the final common pathway in the formation of thrombus. The first available inhibitor of the GPIIb/IIIa receptor was abciximab. Its efficacy in case of a primary PCI has been assessed in many patients[13-15], while only a few studies have considered the use of GPIIb/IIIa inhibitors in the setting of rescue PCI[16-18].

Caution in the use of potent platelet inhibition after failed thrombolysis was prompted by the significant increase in the incidence of major bleeding reported with the association of GPIIb/IIIa inhibitors and thrombolytics[16,19-21]. The benefits of such an association as a primary reperfusion strategy (also called "combolysis") were investigated in the TAMI 8 pilot study[19]. A trend toward an enhanced reperfusion was observed in abciximab-treated patients who, however, experienced a significantly higher incidence of major and minor hemorrhagic events. The IMPACT-AMI and PARADIGM trials confirmed the occurrence of an earlier reperfusion in patients submitted to thrombolysis associated with GPIIb/IIIa inhibitors (respectively eptifibatide and lamifiban), with only a modest increase in bleeding, mainly related to the angiographic access site[22,23]. The high incidence of major bleeding in patients treated with thrombolytics plus GPIIb/IIIa inhibitors might be in part due to the use of full-dose fibrinolytic agents, as described in the PARADIGM study and in the TAMI 8 trial[19,23], and in part to the synergic anticoagulant effect of the two drugs. However, it should be emphasized that in rescue PCI the GPIIb/IIIa inhibitor is administered when the effect of the fibrinolytic agent is significantly reduced or has vanished. On the contrary, the "combolysis" approach in AMI implies the simultaneous administration of the two drugs.

Finally, the few reports on the use of abciximab in rescue PCI all describe a positive effect of abciximab on coronary reperfusion, although in a limited number of patients[16,17,20]. In the subgroup of the EPIC trial, abciximab treatment was associated with a marked reduction (83%) in ischemic complications[20], whereas Ronner et al.[17] showed a trend toward a reduction in the 30-day mortality in patients receiving a GPIIb/IIIa inhibitor.

Personal experience

In the only prospective randomized study on the use of GPIIb/IIIa inhibitors during rescue PCI, we recently reported the efficacy of abciximab in 79 patients randomized to abciximab or placebo before this procedure[18]. The presence of cardiogenic shock (odds ratio 6.8; $p = 0.005$) was an independent risk factor for the occurrence of major adverse cardiac events (MACE, which included death, non-fatal reinfarction, congestive heart failure, target lesion revascularization, and recurrent ischemia) at 6 months of follow-up, while abciximab administration had an independent protective effect (odds ratio 0.15; $p = 0.003$). In addition, the echocardiographic left ventricular wall motion score index showed a significantly better improvement at 1 month of follow-up in patients receiving abciximab.

On the basis of these results, most patients referred to our catheterization laboratory for failed thrombolysis in the last 18 months have undergone rescue PCI following abciximab treatment, if not contraindicated. Over the last 3 years, a total of 153 patients (121 men and 32 women; mean age 62 ± 9 years) were treated in our catheterization laboratory for failed thrombolysis within 24 hours of symptom onset. A mechanical reperfusion attempt after > 24 hours was not considered as rescue PCI. As for the smaller population of our previ-

ously reported study, even in this larger patient cohort the differences in the baseline clinical characteristics between the abciximab and the non-abciximab groups could be due to chance. In particular, the characteristics analyzed were age, sex, diabetes, Killip class, prior myocardial infarction, prior myocardial revascularization, multivessel disease, infarction location, symptom-onset-to-balloon time, and left ventricular ejection fraction. Transient symptom relief after thrombolysis was present in 78 patients (51%), while the remaining 75 (49%) experienced continuous chest pain. An anterior wall infarction was present in 70 patients (46%), while 17 (11.0%) had cardiogenic shock on arrival at our laboratory, with 15 (9.7%) receiving an intra-aortic balloon pump. Ninety-five (62%) patients were treated with abciximab, the intravenous bolus being administered in the referring hospital before transfer to our laboratory. At coronary angiography, a TIMI grade 0, 1, and 2 flow was present in 83 (54%), 44 (29%) and 26 (17%) patients, respectively. Coronary stents were deployed in the majority of patients (88%). There were 4 procedural failures (2.6%), all due to the impossibility of crossing the occlusion with the guidewire. The revascularization attempt was successful in the remaining 149 patients (97.4%), with a post-procedure TIMI grade 3 flow in 137 patients (92%), and a TIMI grade 2 flow in 12 patients (8%). Eight patients (5.2%) died during hospitalization with the in-hospital death rate being significantly higher in patients not receiving abciximab (10.3 vs 2.1%, p = 0.05).

At present, 111 patients (73%) have reached the 2-year follow-up; of these, 79 were included in our previously reported experience. During follow-up, 16 abciximab-treated patients (17%) and 18 non-abciximab-treated patients (31%) experienced MACE, including 2 vs 6 in-hospital deaths, 3 vs 1 late deaths, 1 vs 1 non-fatal reinfarction, 3 vs 3 target lesion revascularizations, 4 vs 5 cases of congestive heart failure, and 3 vs 2 cases of recurrent ischemia, respectively. The actuarial freedom from MACE at 2 years in the overall population was significantly higher in patients receiving abciximab (79 ± 5 vs 68 ± 7%, log-rank test p = 0.03; Fig. 1), thus confirming the results observed at the 6-month follow-up in the prospective randomized trial.

In addition to abciximab use, we investigated the role of other factors which are known to impact on the prognosis after AMI, in particular the time to reperfusion and the TIMI flow grade in the infarct-related artery before PCI.

In our previous experience, patients with MACE at 6 months of follow-up had a longer time from symptom onset to PCI (10.8 ± 7.1 vs 7.8 ± 4.5 hours, p = 0.06), as well as from thrombolysis to PCI (8.6 ± 6.9 vs 5.9 ± 4.7 hours, p = 0.07; unpublished data). In that population, a symptom-to-balloon time of 12 hours was found to be the cut-off value with the highest likelihood ratio for predicting the occurrence of MACE within 6 months, by means of ROC curve analysis. The actuarial freedom from MACE was 83 ± 4% in patients with a symptom-to-balloon time ≤ 12 hours, vs 45 ± 15% in patients with a symptom-to-balloon time > 12 hours (log-rank test p = 0.005; unpublished data). For this reason we recently modified our flow chart for rescue PCI and have decided to perform urgent PCI only within 12 hours of pain onset. Patients with a longer time from symptom onset (12-24 hours) are treated with medical therapy and undergo coronary angiography before discharge if clinically indicated (Fig. 2). In these patients, urgent rescue PCI is performed only in case of cardiogenic shock, hemodynamic instability or severe refractory angina.

In addition to the symptom-to-balloon time, even the thrombolysis-to-PCI time proved to be of prognostic value in the present larger series of patients. In fact, patients remaining event-free at 2 years had an earlier mechanical reperfusion (7.2 ± 4.1 vs 7.8 ± 4.7 hours, p = 0.06). On the contrary, the presence of transient symptom relief and/or ST-segment elevation reduction after thrombolysis was not associated with a better 2-year prognosis.

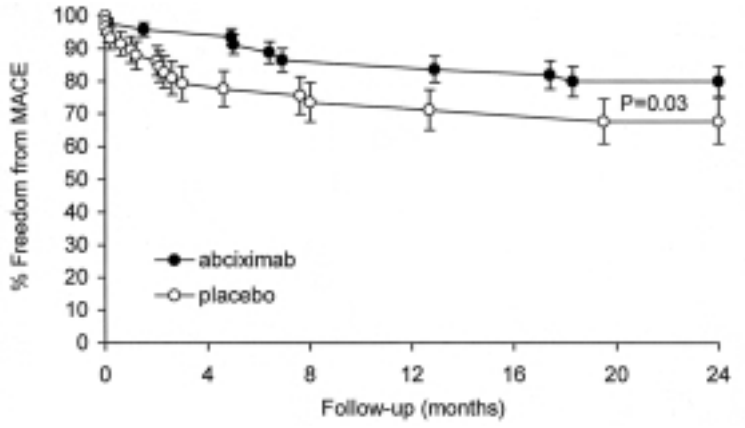

Figure 1. *Actuarial freedom from major adverse cardiac events (MACE) in patients undergoing rescue percutaneous coronary intervention with* (full circles) *or without* (hollow circles) *abciximab administration.*

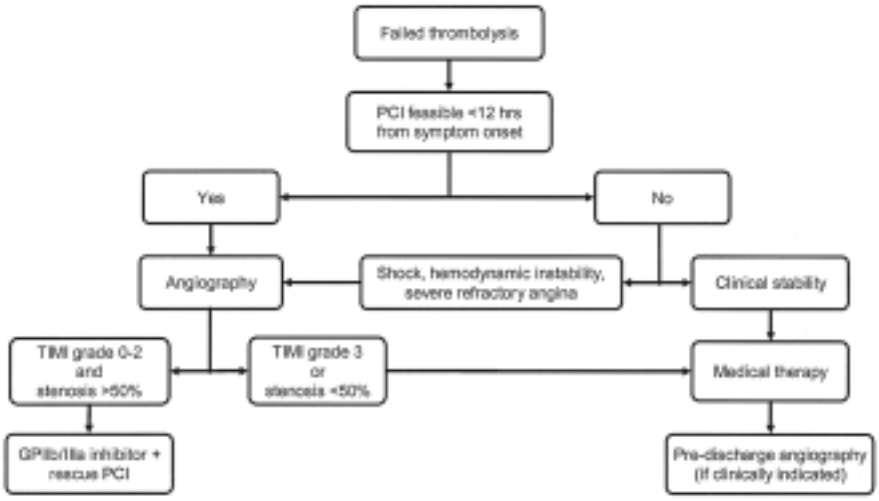

Figure 2. *Therapeutic flow chart for patients with failed thrombolysis at the Cardio-Thoracic Department of the University of Pisa. GP = glycoprotein; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.*

With regard to the TIMI grade flow in the infarct-related artery before intervention, a few studies reported no prognostic benefits of rescue PCI in patients with a TIMI grade 2 flow at initial angiography[11,24]. This finding may be explained by the fact that patients with a TIMI grade 2 flow were at a lower risk of MACE, because thrombolysis achieved a sufficient degree of recanalization. In these lower-risk patients, the benefits of mechanical reperfusion were probably masked by the presence of PCI-related complications. On the contrary, in our experience 16% of patients who had a TIMI grade 2 flow before PCI showed a 2-year freedom from MACE which was not significantly different to that of patients with a TIMI grade 0 or 1 flow (71 ± 13 vs 76 ± 4%, $p > 0.20$). The very low incidence of PCI-related complications makes do that the benefits of this procedure emerge even for this lower-risk subgroup of patients.

Bleeding complications

In rescue PCI, a 2-fold increase in the incidence of major and minor bleeding has been reported for the use of GPIIb/IIIa inhibitors, especially after full-dose thrombolytic therapy (Table I)[16,17,20,21,25]. However, as already outlined, GPIIb/IIIa inhibitor administration during rescue PCI is safer than the simultaneous administration of lytics and GPIIb/IIIa inhibitors as the initial reperfusion strategy. In addition, the drug kinetics of different thrombolytic agents may also play a role in the occurrence of bleeding complications. In fact, while streptokinase persists for a few hours in the circulation, more than 50% of tissue-type plasminogen activator (t-PA) vanishes a few minutes after the end of the infusion.

In our previous experience[18], the increase in the incidence of moderate and minor bleeding, as defined in the GUSTO III study[16], was found to be statistically non-significant in patients treated with abciximab. Abciximab administration was not associated with an increase in life-threatening bleeding. This finding was confirmed in the larger population here described, with a 20% incidence of moderate and minor bleeding in abciximab-treated patients vs 12% in patients not receiving abciximab ($p > 0.20$). Major bleeding (intracranial hemorrhage) occurred in a 77-year-old patient of the abciximab group (1.1%) and in two 65- and 66-year-old patients of the non-abciximab group (3.4%) ($p > 0.20$). The latter finding is in agreement with the data reported from the GUSTO III trial[16] and by Jong et al.[25], according to which the occurrence of intracranial hemorrhage

Table I. Bleeding events in patients undergoing rescue coronary angioplasty with glycoprotein (GP) IIb/IIIa inhibitors.

Authors	No. patients	Lytic	GPIIb/IIIa inhibitor	Major bleeding (%)	ICH (%)
Miller et al.[16]	83	t-PA or r-PA	Abciximab	3.6	0
Ronner et al.[17]	49	SK or t-PA	NR	27	1
Lefkovits et al.[20]	22	NR	Abciximab	24	2
Sundlof et al.[21]	22	t-PA	Abciximab	23	2
Jong et al.[25]	25	NR	Abciximab	12	2

ICH = intracranial hemorrhage; NR = not reported; r-PA = reteplase; SK = streptokinase; t-PA = tissue-type plasminogen activator.

was not increased by abciximab treatment. In addition, in the most recent single-center retrospective study, Ronner et al.[17] reported a slight but not significant increase in the incidence of major bleeding with GPIIb/IIIa inhibitor therapy, without any increase in mortality. In this study, major bleeding was probably related to the frequent use of the intra-aortic balloon pump and to the administration of streptokinase rather than t-PA in almost one third of the patients.

The low incidence of bleeding in our experience is related to various factors. Since moderate and minor bleeding is often related to the arterial access site, we generally prefer the radial approach (68% of rescue PCI patients) and 6F sheaths. In addition, we use low-dose weight-adjusted heparin and insert an intra-aortic balloon pump only in case of hemodynamic instability. Besides, most patients referred to our catheterization laboratory from peripheral hospitals undergo thrombolysis with t-PA (87%) rather than with streptokinase (13%). However, no significant difference in the incidence of bleeding was observed between patients receiving streptokinase or t-PA, even if the thrombolysis-to-PCI time was similar. This finding may be explained by the use of the previously mentioned precautions aimed at reducing the risk of bleeding. Finally, the limited number of patients over 75 years of age (9.6%) in our population may constitute one more reason for the low incidence of bleeding complications.

Conclusions

Primary PCI has been demonstrated to be superior to thrombolysis if performed timely and by experienced personnel. New therapeutic protocols of "facilitated PCI" with low-dose thrombolytics, GPIIb/IIIa inhibitors, and their association are being evaluated to verify whether PCI is better than thrombolysis even for patients requiring transportation to tertiary care hospitals for PCI. However, thrombolysis still remains the most common treatment for AMI, although it fails to achieve reperfusion in 30 to 40% of patients. Thus, a large number of patients are eligible for rescue PCI, which should not be considered as a treatment of secondary importance.

Enough data are available to demonstrate the benefits of mechanical reperfusion when lytic therapy has failed. The use of stents and, more recently, of GPIIb/IIIa inhibitors has reduced the acute complications of the procedure and improved the prognosis. The increase in bleeding complications with GPIIb/IIIa inhibitors is not to be ignored, but may be significantly reduced with an appropriate strategy. In our experience, abciximab treatment prior to rescue PCI improves the clinical outcome at 2 years. In conclusion, in case of thrombolysis failure, patients should be referred to tertiary hospitals where rescue PCI can be performed with expertise.

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