

Platelet Antiaggregation Treatment in the Aftermath of GUSTO IV, TARGET, TACTICS, and CURE Trials

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Various clinical studies have shown that the risk associated with acute coronary syndrome can be reduced by pharmacological treatment with platelet glycoprotein IIb-IIIa receptor inhibitors. The treatment with these drugs is beneficial in conjunction with conventional medical treatment, during angioplasty and in patients undergoing aortocoronary bypass, as indicated by the results of the CAPTURE, PRISM, and PURSUIT studies. However, shortly after the European Society of Cardiology recommended systematic use of glycoprotein IIb-IIIa inhibitors in the management of high-risk patients, the report of negative results in the GUSTO IV and TARGET trials caused this position to be reconsidered. The need for studies to better characterize the mechanism of action of these antithrombotic agents is evident. Studies *in vitro* have demonstrated that prolonged treatment with these drugs can cause patients to remain outside the therapeutic range by causing platelet receptors to change configuration and have more affinity for fibrinogen. In view of these findings, the results of the GUSTO IV and TARGET studies, far from demonstrating the ineffectiveness of the antiplatelet aggregation agents, could be interpreted as a failure in the design of the therapeutic strategy. On the other hand, the results of the CURE study provide new evidence of the benefits of the use of clopidogrel in patients with acute coronary syndrome undergoing medical or revascularization treatment (PCI-CURE group). The debate about the usefulness of platelet glycoprotein IIb-IIIa inhibitors, alone or in combination with clopidogrel in certain circumstances remains open. The evidence available to date is inconclusive and the guidelines for the management of patients with acute coronary syndrome should be updated.

Key words: *Revascularization. Tirofiban. Abciximab. Clopidogrel.*

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Tratamiento antiagregante plaquetario después de los resultados de los estudios GUSTO IV, TARGET, TACTICS y CURE

Diversos estudios clínicos han demostrado que es posible reducir el riesgo asociado al síndrome coronario agudo mediante el tratamiento farmacológico con inhibidores de la glucoproteína plaquetaria IIb-IIIa. El tratamiento con estos fármacos ha resultado ser beneficioso en asociación con el tratamiento médico convencional, durante la angioplastia e, incluso, en pacientes que se someten a un *bypass* aortocoronario, tal y como se desprende de los estudios CAPTURE, PRISM y PURSUIT. Sin embargo, poco después de que la Sociedad Europea de Cardiología recomendara el uso sistemático de los inhibidores anti IIb-IIIa en el tratamiento de pacientes de alto riesgo, la publicación de los resultados negativos obtenidos en los ensayos GUSTO IV y TARGET hizo replantear la conveniencia de su uso, y puso de manifiesto la necesidad de realizar estudios para caracterizar mejor el mecanismo de acción de estos agentes antitrombóticos. Algunos estudios realizados *in vitro* han demostrado que el tratamiento prolongado con estos fármacos puede ocasionar que los pacientes queden fuera del rango terapéutico al hacer que los receptores plaquetarios cambien su configuración y se vuelvan más afines al fibrinógeno. A la vista de estos datos, los resultados de los estudios GUSTO IV y TARGET, lejos de demostrar la ineficacia de los antiagregantes plaquetarios, pueden interpretarse más bien como el fracaso en el diseño de la estrategia terapéutica. Por otra parte, los resultados del estudio CURE aportan nuevas evidencias sobre los beneficios del uso del clopidogrel en pacientes con síndrome coronario agudo sometidos a tratamiento médico o revascularización (subgrupo PCI-CURE) y dejan abierto el debate sobre la conveniencia de usar los antiagregantes plaquetarios inhibidores de la glucoproteína IIb-IIIa, solos o en combinación con clopidogrel en determinadas circunstancias. Las evidencias disponibles hasta la fecha no permiten tomar una decisión al respecto, y parece necesario actualizar las directrices sobre el tratamiento de los pacientes con síndrome coronario agudo.

Palabras clave: *Revascularización. Tirofiban. Abciximab. Clopidogrel.*

INTRODUCTION

The classification of acute coronary syndromes is currently based on electrocardiographic criteria. Thus, we speak of syndromes that are accompanied by persistent ST-segment elevation (once known as Q-wave infarction) and syndromes that are not accompanied by persistent ST-segment elevation. These syndromes are subdivided into two groups, unstable angina and non-Q-wave infarction, which have a similar clinical presentation but differ with respect to the release of serum markers of cell damage (CPK-MB and troponins).

According to the guidelines of the European Society of Cardiology, patients with acute coronary syndrome without ST-segment elevation should be classified as patients at high risk of suffering acute myocardial infarction and/or death and patients at long-term risk. The factors that determine that patients are at a high risk are: *a)* the presence of recurrent ischemia in spite of treatment; *b)* ST-segment depression; *c)* dynamic changes in the ST segment; *d)* troponin elevation, and *e)* presence of thrombi in the angiography. Patients at long-term risk are those that have certain clinical markers that accompany underlying coronary artery disease (age, previous history of myocardial infarction, diabetes), biological markers (reactive C protein) or angiographic markers (depressed left ventricular function and extension of the vascular disease). According to the results of the FRISC study, ST-segment depression and troponin T values are the two most powerful predictors of the occurrence of death due to cardiac causes.¹

The risk associated with acute coronary syndromes can be reduced with inhibitors of platelet IIb/IIIa glycoprotein. Diverse clinical studies, like CAPTURE, PRISM and PURSUIT, have shown that these drugs can reduce the risk of myocardial infarction by up to 40% when they are given before the percutaneous intervention and by up to 50% when given during the intervention. In addition, they significantly decrease enzyme release after intervention.² Nevertheless, after stent implantation, treatment with IIb/IIIa inhibitors does not produce any additional benefit. The relevance of the decrease in enzyme release is demonstrated by the many studies that correlate increased enzyme levels during percutaneous intervention with the appearance of microinfarctions as long as 10 months after the intervention. Greater enzyme release is associated with a worse patient prognosis. In such cases, magnetic resonance imaging techniques have documented the development of microinfarctions distal to the stent.³ In many cases, these microinfarctions are small enough not to compromise left ventricular function, but they can be a substrate for future ventricular arrhythmias.

The effectiveness of IIb/IIIa platelet aggregation inhibitors and, specifically, tirofiban, has been demon-

strated in three different therapeutic strategies: *a)* during medical treatment (as long as it is associated with conventional medical treatment); *b)* during angioplasty, and *c)* in patients who undergo aortocoronary bypass, according to findings from the PRISM-PLUS study. On the other hand, the results of the EPISTENT study show that the association of stent implantation with abciximab treatment can significantly reduce the percentage of patients with myocardial infarction or death at 6 months of follow-up compared with patients who received placebo after stent implantation or were randomized to angioplasty and abciximab treatment. Similar results were obtained in the ESPRIT study, although in this case the selected population had a lower risk.

In view of the abundant evidence available in 2000 on the benefits of treatment with IIb/IIIa inhibitors, the European Society of Cardiology made recommendations for the treatment of acute coronary syndrome that included this therapy. According to these recommendations, patients who do not present persistent ST-segment elevation should be treated with aspirin, heparin, beta-blockers, and nitrates, in addition to being stratified into high-risk and low-risk patients. Low-risk patients could be treated conservatively with relative safety. Treatment with IIb/IIIa inhibitor drugs, coronary angiography, and revascularization were indicated in high-risk patients whenever possible. The relative simplicity of this protocol and the clarity with which the European Society of Cardiology stratified the treatment of patients by risk were obscured shortly after these guidelines were made public because their appearance coincided with the publication of the results of two very conflictive and controversial studies: GUSTO IV and TARGET. The appearance of the results of these studies has made it necessary to reconsider the role of IIb/IIIa platelet inhibitors and how best to investigate their mechanism of action.

THE FAILURE OF THE GUSTO IV AND TARGET STUDIES

The GUSTO IV study was a large clinical trial that included more than 7000 patients with acute coronary syndrome that received medical treatment. The patients were randomly assigned to three groups: a placebo group, a group that received abciximab for 24 h and a group that received abciximab for 48 h. In addition, in all cases conventional medical treatment was given and interventions were advised against. This study failed and the mortality was exactly the same in all groups at 30 days (Figure 1). In order to explain the discrepancy between the actual results of this study and abundant evidence suggesting that positive results would be obtained, it is necessary to understand the mechanism of action of the IIb/IIIa inhibitors. In this sense, studies *in vitro* of models demonstrate that bin-

ding of these inhibitors to platelets induce a conformational modification in the membrane receptor that switches it from an inactive to an active configuration. In the presence of the inhibitor, the active form remains blocked by the drug, but when the inhibitor is absent, the receptor (which is in its active form) can bind more easily to fibrinogen and trigger platelet aggregation.⁴ This is what may occur when the abciximab infusion is sufficiently prolonged. The results of flow cytometry, which have demonstrated that increasing IIb/IIIa inhibitor concentration paradoxically increases the percentage of platelets bound to fibrinogen, support this hypothesis (Figure 2).

No data directly demonstrating this phenomenon in humans exist, but there is evidence suggesting that prolonged abciximab infusion in patients undergoing angioplasty can cause the drug concentration to fall outside therapeutic range. The therapeutic goal of these drugs is to achieve 80% to 100% inhibition of platelet aggregation. Nevertheless, according to data from the Cleveland Clinic of the U.S., a large percentage of patients who receive this treatment as a bolus followed by infusion do not attain the therapeutic minimum and are therefore not necessarily protected. In addition, the longer that infusion is prolonged, the larger the proportion of patients who are outside therapeutic range will be. If a certain degree of proinflammatory activity by abciximab is added to this, the negative results of the GUSTO IV study can be understood.

In my opinion, the GUSTO IV study does not indicate drug failure, but rather poor therapeutic use of the IIb/IIIa inhibitors and a failure of strategy. If there had been an additional group with an invasive strategy, the increase in incidents after 48 h probably would have been avoided. The GUSTO IV study exemplifies the failure of the medical approach to treating acute coronary syndrome because we now know that revascularization is the best way to proceed.

The second setback in relation to the IIb/IIIa inhibitors came from the TARGET study, which hypothesized that tirofiban could be as effective and safe as abciximab. This study raised many expectations, especially if we consider that tirofiban is 4 times less expensive than abciximab. As is well known, this hypothesis was not corroborated and tirofiban was found to be clearly inferior to abciximab. To a certain degree, this negative result was not surprising. According to the study published by Steinhubl et al,⁵ when the antiplatelet aggregant capacity of three different drugs with IIb/IIIa inhibitor activity, abciximab, tirofiban and eptifibatide, was compared over time, tirofiban produced a platelet inhibition of $47 \pm 40\%$ at 24 h of administration versus $75 \pm 14\%$ by abciximab and $77 \pm 21\%$ by eptifibatide. In addition, it is likely that after the injection of a bolus of tirofiban followed by infusion, most of the patients did not reach the therapeutic

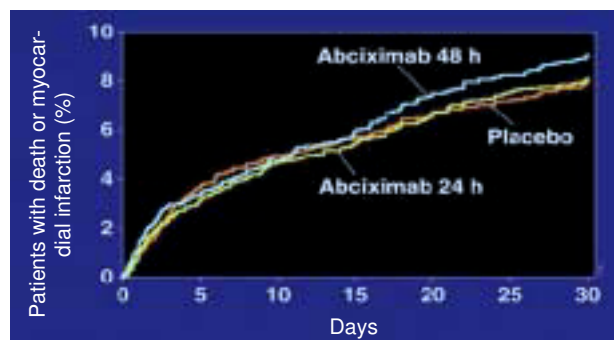


Fig. 1. Incidence of death or myocardial infarction at 30 days of follow-up in patients with acute coronary syndrome who were randomized to receive abciximab treatment for 24 h or 48 h, or placebo, according to the results of the GUSTO IV study. Contrary to what was expected, the incidence of episodes was no lower than in the patients who were treated with IIb/IIIa platelet aggregation inhibitor.

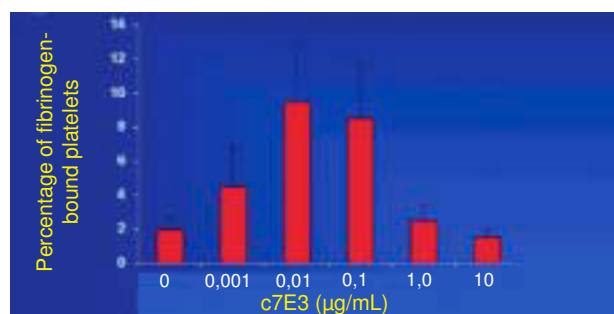


Fig. 2. Percentage of platelets bound to fibrinogen in the presence of increasing concentrations of c7E3 (abciximab), analyzed by flow cytometry. As can be appreciated in the graph, when the concentration of the IIb/IIIa platelet inhibitor is increased it has the paradoxical effect of stimulating platelet binding to fibrinogen. This effect could explain the discrepancy between the results obtained in different clinical trials that have demonstrated the effectiveness of inhibitors of IIb/IIIa platelet receptors as treatment for acute coronary syndrome. (Taken from Peter K et al.⁴)

tic range in the critical period in which incidents occur. In view of what is now known, it could be speculated that a double bolus of tirofiban might achieve a superior therapeutic effectiveness and protective effect in these patients. However, this hypothesis has to be verified and the decision to undertake the TARGET 2 study has already been made. The analysis by subgroups of this study is shown in Figure 3.

EVIDENCE IN FAVOR OF EARLY INTERVENTION: TACTICS-TIMI 18 STUDY

The TACTICS-TIMI 18 trial was designed to test, not a pharmacological treatment, but the strategy of early revascularization compared with a conservative strategy in the treatment of acute coronary syndrome. For many years, until the results of the FRISC II study became available, interventionism had fallen into dis-

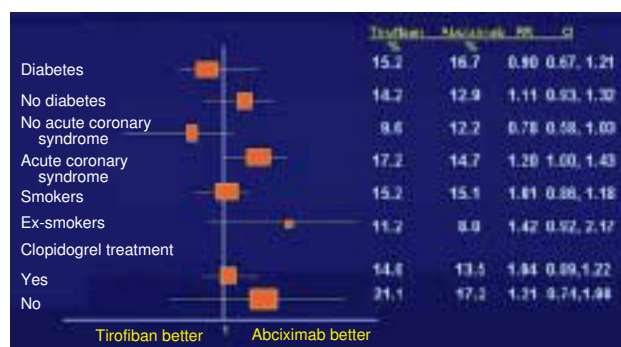


Fig. 3. Results of the analysis by subgroups of the TARGET study at 6 months of follow-up. In this study, the effectiveness of tirofiban versus abciximab in the treatment of acute coronary syndrome was compared. In spite of the expectations that arose about tirofiban, this drug was less effective than abciximab in practically all the subgroups of patients in the study.

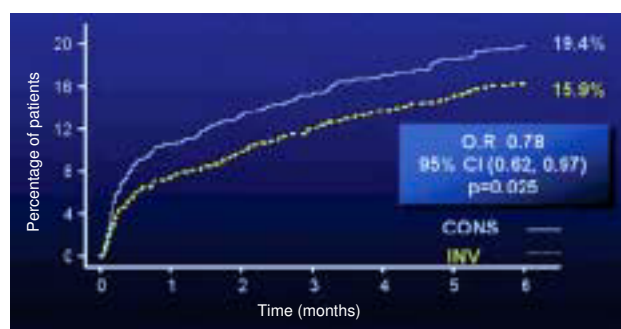


Fig. 4. The rate of myocardial infarction, hospital readmission, and mortality at 6 months of follow-up, according to the results of the TACTICS-TIMI 18 study, which compared the effectiveness of an early invasive strategy (yellow line) to conservative therapy (white line) in the treatment of acute coronary syndrome. Early intervention significantly decreased the rate of long-term episodes in these patients.

favor because there was no evidence that the invasive strategy had any advantage. The need for a clinical study to confirm the findings of FRISC II motivated the TACTICS-TIMI 18 study in which the patients were randomized to two groups: a group that underwent early revascularization and a group that received conservative treatment. Angiography was performed in practically all the patients and revascularization or medical treatment was applied whenever possible. In the group treated conservatively, revascularization was only performed if there was recurrence of episodes or confirmed recurrent ischemia.

The design of the TACTICS-TIMI 18 study was very similar to that of the FRISC II study, with the exception that, regardless of the group to which they were randomized, all the patients were treated with tirofiban and an invasive strategy was used in the first 24-48 h. In the FRISC II study, only 10% of the patients received IIb/IIIa inhibitors and revascularization was performed up to day 12.

The results of the TACTICS-TIMI 18 study revealed that at 6 months of follow-up, mortality, myocardial infarction, and the readmission rate were 20% lower in the group that received early revascularization (Figure 4). This trial served to definitively validate the policy of performing immediate revascularization in these patients. It is important to emphasize that the patients who benefited most from an early aggressive strategy were those of the high-risk group (patients with ST-segment depression). Likewise, the analysis by subgroups demonstrated that early intervention significantly improved the long-term recurrence rate. The patients who underwent intervention in the first 4-12 h had a lower rate of readmissions than those who were intervened in 12-24 h or 24-48 h. The worse prognosis was for the group that underwent intervention more than 48 h after the appearance of symptoms.

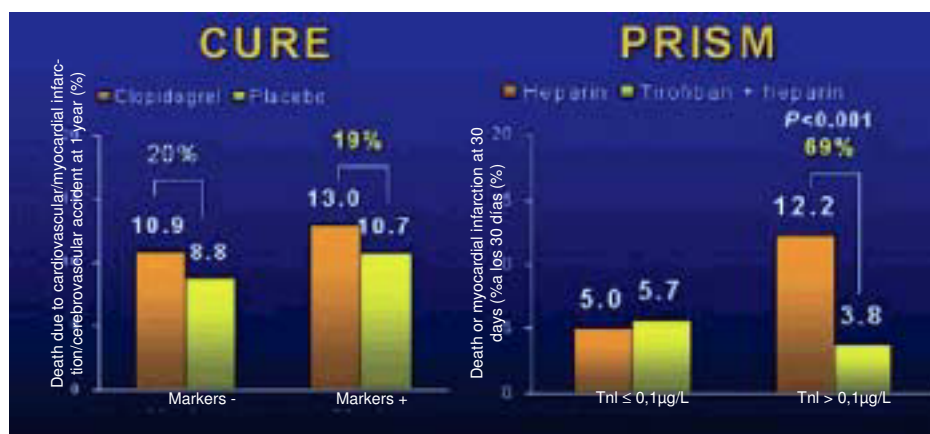
Finally, if we compare the results of the TACTICS-TIMI 18 and FRISC II studies, the lower incidence of episodes in the initial phase of the TACTICS study (linked to enzyme release induced by invasive measures), which confirmed the protective effect of tirofiban during interventionist management compared with low-molecular-weight heparin.⁶

As could be expected, the cost of the initial hospitalization was higher in the invasive group, but the overall cost decreased significantly due to the lower incidence of readmission.

BENEFITS OF CLOPIDOGREL TREATMENT: RESULTS OF THE CURE STUDY

This clinical trial collected data from more than 12 000 patients with acute coronary syndrome who were randomized into two treatment groups: a placebo group (that received conventional medical treatment, including aspirin) and a group treated with clopidogrel in addition to conventional treatment. Surprisingly, the curves of episode incidence (mortality, myocardial infarction, and cerebrovascular accident) in these two groups began to diverge significantly from the first days of randomization in favor of the group that received clopidogrel. It is important to remember the characteristics of the population included in the CURE trial: a low-risk population in which only 25% of the patients presented an elevation of the markers of cell death. In addition, treatment with clopidogrel produced an absolute decrease in risk in all the patients without any subgroup benefiting distinctively. The differences between the results of the CURE study and those of the PRISM study are shown in Figure 5. Considering that in the PRISM study treatment with tirofiban/heparin only benefited the subgroup of patients with elevated serum troponin (>0.1 µg/L), whereas clopidogrel was effective in all the groups, it can be concluded that the mechanism of action of these antithrombotic drugs is completely different.⁷

Fig. 5. Effect of clopidogrel treatment (CURE study, graph on left. Taken from Cure Investigators. N Engl J Med 2001) and tirofiban/heparin treatment (PRISM study, graph on right. Taken from Heeschen et al.⁷) on the risk of cardiovascular disease, myocardial infarction, or cerebrovascular accident at one year of follow-up in patients who did not have elevation of serum markers of cell death (bars on the left) and those that did have elevation of the markers of cell death (bars on the right). The results demonstrate the effectiveness of clopidogrel in reducing risk in both groups of patients, whereas the tirofiban/heparin association only reduced risk in the patients who had an elevation of troponin I of more than 0.1 µg/L.



It has been known for years that the more effective that an antithrombotic treatment is, the greater the risk of hemorrhagic complications. It is not strange, therefore, that the group that received clopidogrel presented a significant increase in the risk of bleeding. The problem arises in patients who must be referred for surgery because the risk of hemorrhage is excessive for 5 days after treatment is discontinued. Therefore, if treatment has not been discontinued for more than 5 days, all surgery except emergency procedures is contraindicated.

PCI-CURE is a subgroup of 2658 patients who represent approximately 25% of all the subjects included in the CURE study and underwent revascularization by percutaneous intervention. These patients came from both treatment groups of the CURE study: one group received placebo (in addition to conventional medical treatment) and the other group received clopidogrel. Patients were randomized openly and were treated with a thienopyridine for 30 days after the percutaneous intervention. After this period, they returned to placebo or clopidogrel as initially randomized.⁸

The result of PCI-CURE is not related with the intervention, which is the same in both groups, but with previous treatment with clopidogrel. The curves of the incidence of episodes during follow-up began to diverge in favor of the group that received clopidogrel immediately after the intervention, and remained divergent at 400 days of follow-up. The reduction of risk in patients undergoing coronary intervention in the different periods of follow-up of the PCI-CURE subgroup are shown in Figure 6. It should be noted that no greater risk of hemorrhage was detected in the subgroup of patients included in the PCI-CURE study.

CLINICAL IMPLICATIONS

It is difficult to discuss the clinical implications of results that have been obtained in diverse trials and in the light of what we now know about antiplatelet ag-

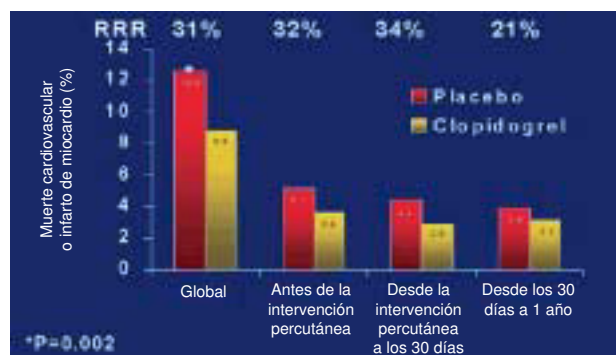


Fig. 6. Incidence of death due to cardiovascular causes or myocardial infarction in patients treated with clopidogrel before undergoing percutaneous revascularization (PCI-CURE subgroup of the CURE trial). Observe that clopidogrel treatment reduced the risk in the period before the intervention (32% risk reduction), 30 days after the intervention (34% risk reduction), and in the period from 30 days to 1 year after the intervention (21% risk reduction). The overall reduction in coronary risk was 31% in patients who received clopidogrel before revascularization. (Taken from Mehta et al.⁸)

gregants, IIb/IIIa inhibitors, revascularization, and the general treatment of acute coronary syndrome. From the many findings of these clinical studies we can conclude that clopidogrel has been shown to be effective in all the subgroups of patients without exception (possibly somewhat less in diabetics), independently of their risk classification. When surgery is scheduled 5 days after discontinuing treatment, there is no greater risk of hemorrhage. It also seems clear, in view of the analysis of the patients included in the PCI-CURE subgroup, that pretreatment with clopidogrel improves the prognosis of patients who undergo percutaneous revascularization.

Does this mean that all patients diagnosed as acute coronary syndrome without ST-segment elevation should receive clopidogrel? What, then, is the role of the IIb/IIIa platelet inhibitors? How should these two

drugs be combined? The difficulty of responding to these questions shows that the debate remains open. On the basis of the evidence available at present, we cannot make any decision. There is an urgent need to review and update guidelines for the treatment of acute coronary syndrome in order to optimize as far as possible the treatment of patients.

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