Does Abciximab Improve the Prognosis of Diabetics After Percutaneous Coronary Intervention?

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Introduction and objectives. It is known that the outcome of percutaneous coronary intervention is worse in diabetics than in non-diabetics. The aim of our study was to determine whether abciximab therapy could improve clinical outcome in an unselected diabetic population that underwent percutaneous coronary interventions.

Material and methods. We analyzed retrospectively 198 diabetic patients who underwent PTCA from January 1997 to January 2000. Seventy-three patients (36.7%) were treated with abciximab and the remaining 125 patients (63.3%) did not receive abciximab. The mean follow-up was 12.6 months. The events considered were death, non-fatal myocardial infarction, any revascularization procedure (including the target vessel), and hospital admission for unstable angina.

Results. Patients who received abciximab had more frequent previous myocardial infarction (67.1 vs. 52.8%; p = 0.04), worse left ventricular function (0.53 vs. 0.59%; p = 0.02), more frequent angiographic thrombus (67.1 vs. 36.8%; p < 0.001), more complex lesions (B2/C) (76.4 vs. 55.8%; p = 0.004), and less frequent location in left anterior descending artery (34.2 vs. 60.8%; p = 0.002). The indication for PTCA in patients who received abciximab was most often related to myocardial infarction. There were no differences between the groups in sex, age and distribution of diabetes treatment. Events were more frequent in diabetics not treated with abciximab than in those who were treated with abciximab (38 vs. 22%; p < 0.037). The patients not treated with abciximab suffered more frequently target vessel revascularization (22.7 vs. 7.2%; p < 0.007). There were no significant differences in the frequency of death or non-fatal myocardial infarction, but hospital readmissions for unstable angina were significantly more frequent in diabetics not treated with abciximab (29.1 vs. 15.9%; p = 0.045). Multivariate analysis identified abciximab as a predictor of the absence of complications during follow-up (OR: 0.45; p = 0.03).

Conclusion. Abciximab treatment seems to reduce events in unselected diabetic patients undergoing percutaneous coronary intervention, particularly target vessel revascularization.

Key words: *Coronary angioplasty. Diabetes mellitus. Revascularization. Prognosis.*

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¿El abciximab mejora el pronóstico de los diabéticos tras la intervención coronaria percutánea?

Introducción y objetivos. Se sabe que los pacientes diabéticos tienen peor pronóstico tras la intervención coronaria percutánea que los no diabéticos. El propósito de nuestro estudio fue determinar si el tratamiento con abciximab puede mejorar los resultados clínicos en una población diabética no seleccionada.

Material y métodos. Analizamos retrospectivamente a 198 pacientes diabéticos sometidos a intervención coronaria percutánea (ICP) desde enero de 1997 a enero de 2000. Setenta y tres pacientes (36,7%) fueron tratados con abciximab y los restantes 125 (63,3%) no recibieron abciximab. El seguimiento medio fue de 12,6 meses. Consideramos como episodios: la muerte, el infarto no fatal, cualquier revascularización (incluyendo el vaso diana) y el ingreso hospitalario por angina inestable.

Resultados. Los pacientes que recibieron abciximab tenían mayor incidencia de infarto de miocardio previo (67,1 frente a 52,8%; p = 0,04), peor función ventricular izquierda (0,53 frente a 0,59%; p = 0,02), mayor incidencia de trombo angiográfico (67,1 frente a 36,8%; p < 0,001), mayor incidencia de lesiones complejas B2/C (76,4 frente a 55,8%; p = 0,004) y menor proporción de afectación de la coronaria descendente anterior (34,2 frente a 60,8%; p = 0,002). La indicación de angioplastia en los pacientes con abciximab se relacionaba en mayor medida con el ingreso hospitalario por infarto agudo de miocardio. No había diferencias entre los grupos respecto al sexo, edad y distribución del tratamiento diabético. Los episodios fueron más frecuentes en los diabéticos que no recibieron abciximab frente a aquellos que lo recibieron (38 frente a 22%; p < 0,037). Asimismo, los pacientes que no recibieron abxicimab necesitaron más revascularización del vaso diana (22,7 frente a 7,2%; p < 0,01) du-

rante el seguimiento. No hubo diferencias significativas en lo concerniente a la muerte e infarto de miocardio no fatal, pero sí en la necesidad de ingreso hospitalario por angina inestable (29,1 frente a 15,9%; p = 0,045). El uso de abciximab era un factor predictor de ausencia de complicaciones en el seguimiento (OR = 0,45; p = 0,03).

Conclusiones. El tratamiento con abciximab podría reducir los episodios a medio plazo en los diabéticos sometidos a intervención coronaria percutánea especialmente debido a una menor necesidad de revascularización en el seguimiento en una población no seleccionada.

Palabras clave: *Angioplastia coronaria. Diabetes mellitus. Revascularización. Pronóstico.*

INTRODUCTION

A high percentage of patients who undergo percutaneous coronary intervention procedures are diabetic. It is known that this type of patient has a higher morbidity-mortality rate following coronary revascularization, whether it is percutaneous or surgical, than non-diabetic patients.[1-4] Even now, in the era of the stent, worse results are observed in diabetic patient groups.[5,6]

Powerful plaque inhibition with glycoprotein IIb/IIIa inhibitors has been shown to improve the results following percutaneous coronary invervention (PCI),[7-11] and this effect may be even greater in diabetic patients, as the changes in plaque function may be 1 of the mechanisms responsible for worse results in the diabetic population.[12]

Recently, the clinical results of the subgroup of diabetic patients in 3 large tests that used abciximab (EPIC, EPILOG and EPISTENT) were analyzed, and a decrease in the mortality rate of patients who received anti IIb/IIIa versus diabetics who did not receive it was observed.[13] The aim of our study was to analyze our series of diabetic patients and observe the medium-term clinical results with regard to whether or not abciximab treatment was used.

MATERIAL AND METHODS

Study population

Between January, 1997 and January, 2000 198 consecutive diabetic patients underwent PCI in our unit with angiographic success. Of these, 73 patients (36.7%) received concomitant abciximab treatment, and the remaining 125 patients (63.3%) did not. We selected those patients with a prior diagnosis of diabetes mellitus, who were already being treated with insulin, or oral agents, or whose diabetes was controlled by diet. The patients were considered diabetic if they had been diagnosed previously, if they had been in treatment with oral anti-diabetic medication or insulin, or if they presented with elevated glycemic values during hospital admission, with at least 2 fasting test results being greater than 200 mg/dL. The decision to use abciximab after coronary angioplasty was made according to the criteria of the interventionist in the face of the conventional complications of angioplasty, visible angiographic thrombus, bifurcated lesions with a non-protected branch, or high-risk clinical criteria.

Procedure protocol

Conventional angioplasty and stent implantation was performed by the technique habitually used in our laboratory. The balloon procedure was considered optimum when residual stenosis of less then 30% was achieved, with a TIMI flow rate of III. The stent was implanted by high pressure inflation according to the judgment of the hemodynamic specialist until an adequate angiographic result was obtained. Abciximab was administered in a bolus of 0.25 mg/kg, followed by perfusion of 8 to 10 U/kg/minute for 12 hours post-procedure. The perfusion was begun in an elective manner before performance of the angioplasty if the lesion to be treated was known to have unfavorable anatomical characteristics,according to clinical criteria, or during the procedure in the presence of conventional angioplasty complications or with the presence of a visible angiographic thrombus or bifurcated lesions with an unprotected branch. In the same manner, intravenous heparin at a dose of 70 U/kg was used before dilatation. All patients received 200 mg of aspirin per day. Those patients who had stent implantation also received 250 to 500 mg of ticlopidine, according to body weight, for 30 days. Intracoronary nitroglycerin was also administered to all patients before coronary dilatation during the procedure, according to the judgment of the surgeon and before the final control angiography. Revascularization was considered complete if all vessels of a caliber greater than 2 mm were dilated, and revascularization was considered incomplete if the vessels of greater than 2 mm were not revascularized.

Follow-up

Follow-up was performed either n the physician´s practice or telephone interview. Mean clinical follow-up of patients was 12.6 months. After angiographic success of the procedure had been achieved, the following were considered cardiac events: death due to cardiac causes (all deaths being considered of this type unless death by another mechanism was proven), non-fatal myocardial infarction (anginous pain for more than 30 minutes with an elevation of total plasma creatinine to double the laboratory proscribed limits), the need for a new revasculatization (whether PCI or by

TABLE 1. **Patient baseline clinical characteristics**

	Diabetes+ abciximab (N=73)	Diabetes– abcimixab (N=125)	*P*
Age	64±7.9	65±8.2	.44
Men	41 (56.2)	82 (65.6)	.18
Risk factors			
Hypertension	42 (57.5)	66 (52.8)	.51
Smoking	31 (42.5)	55 (44)	.83
Hypercholesterolemia	30 (41.1)	51 (40.8)	.96
Type of diabetes			.29
Diet-controlled	17 (23.3)	41 (328)	
Oral agents	35 (47.9)	57 (45.6)	
Insulin	21 (28.8)	27 (21.6)	
EF	0.53±0.17	0.59±0.14	.028
Previous infarct	49 (67.1)	66 (52.8)	.049
Indication for PCI indication	.005		
Stable angina	8 (11)	22 (17.6)	
Unstable	20 (27.4)	56 (44.8)	
Myocardial infarction	45 (61.6)	47 (37.6)	
Previous PCI	1 (1.4)	6 (4.8)	.20
Previous cardiac surgery	2 (2.7)	6 (4.8)	.47

Data is expressed as the number of patients and the percentage of the total in parentheses or as mean±standard deviation. PCI indicates percutaneous coronary intervention; EF, ejection fraction.

TABLE 2. **Patient baseline angiographic characteristics**

	Diabetes+ abciximab (N=73)	Diabetes– abciximab (N=125)	*P*
Complete revascularization			.37
Yes	38 (52.1)	73 (58.4)	
No	35 (47.9)	52 (41.6)	
Dilated vessel			.002
Diagonal AD	25 (34.2)	76 (60.8)	
RC/PD	40 (54.8)	32 (25.6)	
CX/OM	8 (11)	17 (13.6)	
AHA/ACC lesion			.004
A/B1	17 (23.6)	54 (44.2)	
B2/C	55 (76.4)	68 (55.8)	
Thrombus	49 (67.1)	46 (36.8)	.0001
Peri-procedure diameter	0.59±0.41	0.71±0.43	.079
Post-procedure diameter	2.90±0.65	2.89±0.54	.92
Lesion length	14.55±7.90	13.93±7.15	.58

The data is expressed as the number of patients with the percentage of the total in parenthesis or as mean±standard deviation. AD indicates anterior descending coronary; CX, circumflex; OM, obtuse marginal; RC, right coronary; PD, posterior descending.

coronary surgery) including of the target vessel, as well as hospital admission for unstable angina.

Statistical analysis

For data analysis we used the SPSS (Statistical Package for Social Sciences, version 8.0 for windows) statistical package. The quantitative variables appear as mean±standard deviation (SD). The qualitative values appear as percentages. To compare the qualitative variables, we used the χ^2 test (or Fisher test, if the expected frequencies were <5). The quantitative variables were compared using the Student *t* test. We used multivariate logistical regression analysis to evaluate the factors that contributed to the final goal in both groups. The variables included in the logistical regression model were age, ventricular function, indication for angioplasty, involvement of the descending anterior artery, and the use of abciximab. A test was considered statistically significant when $P<.05$.

RESULTS

Baseline clinical characteristics of both groups are shown in Table 1. There was no difference with respect to age or sex. Both groups had a very similar cardiovascular risk profile. In the abciximab group, there was a higher percentage of insulin-dependent patients (28.8% versus 21.6%), and in the group without abciximab there was a greater number of patients with diet-controlled diabetes (32.8% versus 23.3%), ($P=.29$). The indication for percutaneous coronary revascularization was related to complications following an infarct in 45 diabetics treated with abciximab (61.6%); 30 presented with residual post-infarct ischemia (either spontaneous of after ergometry); 9 had cardiac insufficiency; 4 in recovery chest angioplasty, and in 2 patients primary angioplasty was performed secondary to fibrinolysis being contraindicated.

The patients who received abciximab had worse left ventricular function (0.53 versus 0.59) and greater infarct frequency (recent or old) (67.1% versus 52.8%; $P<.049$). In the same manner, diabetics treated with abciximab had more complex lesions, smaller luminal diameter, and less involvement of the anterior descending artery (Table 2).

Similar medium-term follow-up was carried out for both groups of 12.6±9.7 months; follow-up was completed for 88.7% of the diabetic patients who received abciximab and for 90.8% of patients who did not (90.4% overall). We found a reduction in episodes per patient during this period in the patients treated with abciximab (38% versus 22%; $P<.037$) (Table 3). There was no significant difference with regard to mortality rate (7.3% versus 5.8%) and non-fatal infarct (3.2% versus 6.8%) between the 2 groups, but we did find there was a significant difference in the need for hospital admission due to unstable angina, which was 29.1% in those patients who did not take abciximab and 15.9% in those who did ($P=.045$), and the need for revascularization of the target vessel, which decreased

TABLE 3. **Episodes on follow-up**

	Diabetics treated with abciximab	Diabetics not treated with abciximab	*P*
Episodes	16 (22)	47 (38)	.037
Death	4 (5.8)	8 (7.3)	.9
Non-fatal infarct	1 (1.4)	2 (1.8)	.9
Admitted for unstable angina	11 (15.9)	32 (29.1)	.045
Revascularization of any type	7 (10.1)	27 (24.5)	.02
Revascularization of the target vessel	5 (7.2)	25 (22.7)	.01

The data is expressed as the number of patients and the percentage of the total is given in parenthesis.

TABLE 4. **Multivariate analysis of predictive factors of episodes during follow-up**

	Odds ratio (95% CI)	*P*
Age	0.98 (0.94-1.03)	.59
LVEF	0.99 (0.97-1.01)	.49
Post-infarct PCI indication	0.92 (0.81-1.05)	.25
PCI of anterior descending	1.07 (0.83-1.39)	.57
Use of abciximab	0.45 (0.21-0.94)	.03

LVEF indicates left ventricular ejection fraction; PCI, percutaneous coronary intervention.

from 22.7% in those patients not treated with abciximab to 7.2% in those treated with abciximab (*P*<.01). There were no differences between the 2 groups with respect to the use of coronary stents, this device being used in 86.2% of the cases where abciximab was not administered and 84.7% of cases where it was administered, with the same significant difference with regard to major clinical episodes in favor of the group treated with abciximab (39.6% versus 23.7%; *P*<.04), and a lesser need for revascularization of the target vessel on follow-up (21.9% versus 6.8%; P<.01). On multivariate analysis (Table 4) the use of abciximab is shown to be a protective factor with regard to complications on follow-up (OR=0.45; P=.03).

DISCUSSION

Diabetic patients have particular characteristics that differentiate them from other patients with ischemia. The greater age of diabetic patients and the greater number of risk factors associated with the disease, as well as the increased difficulty of revascularizing all the arterial territories and the increased progression of heart disease, means that diabetic patients with ischemic heart disease have a worse long-term prognosis than non-diabetic patients.[14] The progression of coronary disease in these patients seems to be related to multiple factors such as hematological anomalies (increased plaque aggregation, increased synthesis of procoagulant factors such as fibrinogen, factor VII, and von Willebrand factor, and fibrinolysis attenuated by the increase in type I plasmagenic inhibitor),[15] endothelial dysfunction with increased risk of vasospasm and coronary thrombosis, and it has even been suggested that exogenous insulin could have a deleterious effect, as in *in vitro* studies elevated concentrations of insulin induce the formation of atheromatous plaques.[16]

Although it has been established that following balloon angioplasty diabetic patients have a higher incidence of re-stenosis due to greater neointimal hyperplasia and a higher mortality-morbidity rate as compared to non-diabetic patients,[17] there is no conclusive evidence that these differences are maintained following placement of a coronary stent. Some authors have reported a greater rate of re-stenosis in diabetic patients,[18] but others have not found diabetes to be a predictive factor of re-stenosis when a stent is used.[19] They have associated the poor prognosis of diabetic patients after PCI exclusively to those who are insulin-dependent[20] and to incomplete percutaneous revascularization.[21-23]

We found a significant difference in the combined clinical objective on follow-up (38% in patients who received abciximab versus 22% in those who did not; P=.037), ane a decrease in the necessity for revascularization of the target vessel (22.7% versus 7.2%; *P*<.01) at medium-term follow-up of 12.6 months. There were no differences between the 2 groups with regard to mortality rate or non-fatal myocardial infarct. The small size of both groups made it difficult to obtain results in this sense, a situation that also occurred in the substudy of diabetic patients in the EPISTENT study,[10] while in the metaanalysis of the EPIC, EPILOG, and EPISTENT studies,[24] of 1462 diabetic patients treated with abciximab in the 3 studies they found a significant decrease in the mortality rate of diabetic patients treated with abciximab, which was decreased in non-diabetic patients taking placebo.

The use of abciximab is associated with the presence of angiographic thrombus on coronary angiography. We found a similar incidence of acute complications (acute non-fatal myocardial infarct) in the group treated with abciximab in spite of there being a greater incidence of angiographic thrombus. Although the presence of angiographic thrombus has traditionally been related to a greater incidence of complications during percutaneous coronary intervention, the situation has changed considerably since the advent of the coronary stent and anti- IIb-IIIa agents. Alfonso et al[25] showed the efficacy of the coronary stent for treatment of lesions containing a thrombus, obtaining an immediate angiographic success rate of 96%, although with a rate of myocardial infarct without Q-wave of 6%, the majority with data indicating distal embolization. On

the other hand, Musa Khan et al[26] classified 2099 consecutive patients in the EPIC study in 3 groups according to whether they had a lack of, the possibility of, or clear evidence of angiographic thrombus. Although they found a greater percentage of acute occlusion in the presence of thrombus, at 6 months follow-up there were no differences in the combined clinical outcome (death, acute myocardial infarct [AMI], need for revascularization), and the benefit of treatment with abciximab was observed in the 3 groups. Ellis et al[27] analyzed the combined data from the EPIC and EPILOG studies with the aim of evaluating whether a differential effect existed with abciximab as a function of the baseline characteristics of the lesion treated, and they found a benefit in all groups, but particularly in more complex lesions such as type B or C in which the risk of death, AMI, or urgent revascularization was reduced by 7.6% and 5.8%, respectively. It is worth considering the possibility of an added effect of the physical phenomenon of «sealing» of the thrombus by the stent together with the effect of abciximab on possible distal embolization and the consequent improvement in microcirculation, something that Neumann et al[28] already demonstrated in the context of AMI, where they found an improvement in the peak velocity of coronary flow measured with a Doppler guide after administration of papaverine in patients treated with abciximab with regard to those who did not receive the drug.

We found a significant decrease in the need for revascularization of the target vessel (RTV), which was, respectively, 7.2% and 22.7% in patients who received and did not receive abciximab ($P<.01$). The need for RTV has been considered equivalent to re-stenosis, given that the patients were not routinely studied from an angiographic point of view. In the substudy of diabetic patients in the EPISTENT study, which included 491 paients divided into the 3 types of treatment (balloon angiography+abciximab, stent+ placebo, and stent+abciximab) there was a decrease in RTV from 16.6% in the stent plus placebo group to 8.1% in the stent plus abciximab group ($P=.021$). Nevertheless, such a decrease was not found in the general group of patients in the EPISTENT study; nor was it found in other studies with anti-IIb-IIIa in the field of interventional cardiology, with the exception of the EPID study at 3 years, findings that were not confirmed in later studies of treatment with abciximab or other anti-IIb-IIIa agents. The excessive intimal hyperplasia seems to be the cause of the increased re-stenosis seen in diabetic patients both in the context of balloon angioplasty and after stent implantation;[29] although in the ERASER study,[30] which evaluated the possible effect of abciximab on the decease in re-stenosis, they did not encounter differences between the different groups in plaque volume measured by intravascular echocardiography, although it must be pointed out that there were only 19 diabetic patients in the study so that it was not possible to reach conclusions regarding this type of patient. Perhaps in the diabetic patient, with a greater tendency toward aggregation, a potent IIb-IIIa receptor inhibitor could reduce the presence of non-occlusive peri-procedure thrombi that in turn, could influence neointimal proliferation on follow-up.[31] If this is the case, we could hope for a similar effect on the diabetic population with other anti-IIb-IIIa agents such as tirofiban y eptifibatide. Another possible mechanism could be the inhibition of abciximab, different from the other anti-IIb-IIIa agents, of the $\alpha_v\beta_3$ receptor of vitronectin,[32] which would impede both neointimal prolifertion and the migration and production of extracellular matrix. The long-term results in the diabetic population of studies with eptifibatide (ESPRIT) and tirofiban (TARGET) will indicate whether this is an exclusive effect of abciximab or it can be extended to other anti IIb-IIIa agents.

Study limitations

This is a longitudinal study of an observational character and it is subject to its own design limitations. There is no homogeneity between the groups compared, although the tendency to present characteristics that classically are considered unfavorable for PCI is close to abciximab treatment. No data exists regarding glycemic control in these patients and its possible influence on the results.

CONCLUSION

Abciximab improves the prognosis of a non-selective diabetic population subjected to PCI. This improvement is achieved along with a lesser need for revascularization of the target vessel during follow-up.

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