Coronary Angioplasty in Diabetic Patients. Current and Future Perspectives

Joaquín J. Alonso, Juan M. Durán, Federico Gimeno, Benigno Ramos, Ana Serrador and Francisco Fernández-Avilés

Instituto de Ciencias del Corazón (ICICOR). Hospital Universitario de Valladolid. Valladolid. España.

It has been estimated that 15-25% of patients who undergo percutaneous or surgical coronary angioplasty are diabetics. The indications for coronary revascularization and initial results of the procedure do not differ substantially between patients with diabetes mellitus and non-diabetics. However, the long-term results of both percutaneous and surgical coronary angioplasty are less favorable in diabetics in terms of mortality and the need for new revascularization procedures.

The development and widespread use of stents and glycoprotein IIb/IIIa receptor inhibiting drugs have improved the clinical evolution of diabetics treated with angioplasty. Currently available data show that the administration of glycoprotein IIb/IIIa inhibitors to patients undergoing coronary angioplasty is especially useful in diabetics and improves short-term and long-term results, decreasing one-year mortality by 45%. There seem to be indications for the routine use of glycoprotein IIb/IIIa inhibitors in diabetics treated with angioplasty. While the use of stents has improved long-term and short-term results in diabetics, the success rates of angioplasty in diabetics are still lower than in non-diabetics. Diabetes is still an independent predictor of restenosis and long-term events after stenting interventions.

Analysis of the studies comparing percutaneous and surgical revascularization in diabetic patients with multivessel disease shows that surgery is superior in terms of long-term mortality and need for new revascularization procedures. Stenting has improved, but not substantially, the results of multivessel angioplasty in diabetics. Therefore, the indications for angioplasty in multivessel diabetes should be evaluated individually.

Factors that contribute to the less favorable post-angioplasty evolution of diabetic patients are more rapid progression of atherosclerosis and, especially, a higher rate of restenosis. New angioplasty techniques, such as brachytherapy and drug-eluting stents, are likely to significantly improve the results of percutaneous interventions in diabetics, thus allowing the indications for angioplasty in diabetics to be extended even further in the near future.

Key words: Diabetes. Coronary angioplasty stent. Coronary surgery. Glycoprotein IIb/IIIa inhibitors.

Angioplastia coronaria en el paciente diabético. Situación actual y perspectivas futuras

Se estima que un 15-25% de los pacientes en los que se indica angioplastia o cirugía coronaria son diabéticos. Las indicaciones de revascularización coronaria y los resultados iniciales de ésta en los pacientes con diabetes mellitus no difieren sustancialmente de los no diabéticos. Sin embargo, los resultados a largo plazo, tanto de la angioplastia coronaria como de la cirugía, son peores en los diabéticos en términos de mortalidad y de necesidad de nuevos procedimientos de revascularización.

El desarrollo y la expansión del uso del stent y de los fármacos que inhiben los receptores IIb/IIIa de las plaquetas han mejorado la evolución clínica de los diabéticos tratados con angioplastia. Los datos disponibles en el momento actual revelan que el uso de los inhibidores de la glucoproteína IIb/IIIa en el contexto de la angioplastia coronaria es especialmente beneficioso en los diabéticos, mejorando los resultados a corto y largo plazos y reduciendo la mortalidad al año en un 45%. Su utilización rutinaria en los diabéticos que son tratados con angioplastia parece indicada. El stent, aunque ha mejorado los resultados a corto y largo plazos en los diabéticos, no ha podido igualar los resultados de la angioplastia a los de los no diabéticos. La diabetes continúa siendo un factor predictor independiente de reestenosis y de acontecimientos a largo plazo tras angioplastia con stent.

El análisis de los estudios que han comparado la revascularización percutánea y quirúrgica en los pacientes diabéticos con enfermedad multivascular demuestran que la cirugía es superior en términos de mortalidad y necesidad de nuevos procedimientos de revascularización a largo plazo. El stent ha mejorado, pero no parece haber cambiado sustancialmente los resultados de la angioplastia multivaso en los diabéticos. Por tanto, las indicaciones...
de angioplastia en los diabéticos multivaso deben consi-
derarse de forma individualizada.

Los factores determinantes de la peor evolución post-
angioplastia de los pacientes diabéticos son la más rápi-
da progresión de la arteriosclerosis y, sobre todo, la ma-
yor tasa de reestenosis. Las nuevas técnicas de angioplastia, como la braquiaterapia o los stents liberado-
dores de fármacos que inhiben la hiperplasia intimal es pro-
bable que mejoren significativamente los resultados del
intervencionismo percutáneo en los diabéticos y permiti-
tan, en un futuro próximo, la expansión de indicaciones de angioplastia en éstos.

Palabras clave: Diabetes mellitus. Angioplastia corona-
ria. Stent. Cirugía coronaria. Inhibidores de la glucopro-
teína IIb/IIIa.

INTRODUCTION

The relation between diabetes and coronary artery
disease is marked by two circumstances: the high inci-
dence of coronary artery disease in diabetic patients
and its poor prognosis in diabetics compared to non-
diabetics. It is estimated that more than 50% of adult
diabetics have significant coronary atherosclerosis,
a prevalence 10 times greater than that of the general
population, which is about 2%-4%.1,2 In fact, at pre-
sent diabetes is considered not only a risk factor, but
also a marker of cardiovascular disease from the point
of view of prevention. Consequently, the recommen-
ded prevention interventions are the same for diabetics
as for patients with coronary artery disease.3,4 Diabetes
not only increases the incidence of coronary disease,
but also contributes to a less favorable prognosis.
Thus, cardiovascular mortality is twice as frequent in
diabetic men and four times as frequent in diabetic
women. In general, if we analyze any subgroup of dia-
betics with coronary artery disease, they have a worse
long-term clinical evolution in terms of cardiovascular
morbidity and mortality.2,3 These factors, together with
the high prevalence of diabetes in the industrialized
world, have made the association of diabetes and is-
chemic heart disease a serious public health problem
in these countries, a frequent cause of disability
among the citizens of these countries, and a major ex-
pense for health resources (in the U.S., it has been cal-
culated that diabetics use one-fourth of the Medicare
budget).

A topic that has received much attention in recent
years is coronary revascularization in diabetic patients.
The high incidence of coronary artery disease in dia-
betics, and its greater extension and severity, mean
that coronary revascularization is considered in many
of these patients. The proportion of diabetics among
patients who undergo revascularization is high and it
is calculated that 15%-25% of the patients in which
percutaneous or surgical revascularization is indicated
are diabetics.2,3 The interest in revascularization in dia-
betics not only is due to its frequency, but also to two
other factors. The first is related with the results of
both angioplasty and coronary surgery, which are less
favorable in diabetics, and the second with the contro-
versy regarding the suitability of percutaneous revas-
cularization for diabetics with multivessel disease.6,8
This subgroup of patients is the only one in the general
population of patients with ischemic heart disease in
which percutaneous revascularization is associated
with a greater long-term mortality than surgical revas-
cularization.

Nevertheless, the continuous advances that are ap-
ppearing in the field of coronary angioplasty are im-
proving results, even in unfavorable subgroups like
diabetes, and expanding the indications. Paradigms
of this progress are the development and dissemina-
tion of the use of stents and glycoprotein IIb/IIIa inhibi-
tors, the availability of techniques that inhibit inti-
mal hyperplasia, the main factor responsible for intra-stent restenosis in diabetics, such as intracor-
monary brachytherapy and, more recently, coated stents
that release drugs to inhibit the proliferation of smo-
th muscle cells. Due to these advances, percutaneous
coronary revascularization in diabetic patients is a
continuously evolving area of cardiological therapeutic
rather that requires frequent updates. The fundamental
aims of this update are to review the indications for
revascularization in diabetic patients with coronary
artery disease, analyze the results of percutaneous re-
vascularization in diabetics, especially in comparison
with surgical revascularization, and evaluate the futu-
re expectations for new devices.

INDICATIONS FOR REVASCULARIZATION
IN DIABETIC PATIENTS WITH CORONARY
ARTERY DISEASE

The indication for any intervention should be based
on an analysis of the evidence of its influence on mor-
tality, the clinical evolution, and short and long-term
quality of life. Coronary revascularization has been
shown to be useful in reducing mortality and impro-
ving quality of life in many clinical situations and di-
verse angiographic contexts. The indications for coro-
nary revascularization were recently reviewed by the
Sociedad Española de Cardiología in various docu-
ments, but the specific subgroup of patients with dia-
abetes has not been examined in depth.9,10

Indications for revascularization in diabetic
patients with stable chronic ischemic heart
disease

Coronary revascularization is a useful tool for im-
proving the prognosis and controlling symptoms in
some groups of patients with coronary artery disease.\textsuperscript{11-13} In fact, there is a clear surgical indication in patients with acute angina in spite of adequate medical treatment, regardless of the number of diseased blood vessels. This indication is also valid in diabetic patients, but limited by the fact that, as is well known, the perception of ischemia is sometimes altered by diabetic neuropathy. Diabetics with asymptomatic acute ischemia or atypical clinical manifestations are not uncommon.\textsuperscript{2,3} For that reason, the evaluation of revascularization indications in asymptomatic or mildly symptomatic patients is especially interesting. These indications have been analyzed in many studies. The overall evidence obtained from evaluating these studies has allowed scientific societies and expert groups to issue recommendations on the indications for revascularization based on the clinical manifestations and anatomy of each patient.\textsuperscript{9,15} Generally speaking, benefits have been shown in terms of mortality in patients with significant disease of the coronary trunk, three vessels, or one or two vessels with involvement of the proximal portion of the anterior descending coronary artery, especially if left ventricular ejection fraction is abnormal or there is extensive ischemia. The validity of these studies has been questioned because they were carried out in the 1980s. The surgical or angioplasty technique used in most cases, and especially the medical treatment, were substantially different from those now used. Nevertheless, because of the consistency of the results they are still considered applicable and valid.\textsuperscript{14,15}

The morbidity and mortality of surgery has always been found to be higher in diabetics compared with non-diabetics.\textsuperscript{16,17} However, although most studies did not specifically analyze the benefit of revascularization in diabetic patients, they did demonstrate that the effectiveness of revascularization was always greater in patients with more extensive coronary artery disease and/or a more impaired left ventricular function. Indeed, among diabetics there is a greater proportion of patients with these characteristics and, therefore, a larger number of patients than could potentially benefit from surgery. Thus, in 317 diabetic patients over the age of 65 years in the CASS study,\textsuperscript{16} after a mean follow-up of 13 years the mortality was 57\% greater than in the 1843 matched non-diabetics. Nevertheless, the benefit of surgery in relation to medical treatment was similar to that of non-diabetics, so surgery was associated with a reduction in mortality of 44\%. To summarize, there is a general consensus that surgical revascularization prolongs the life of diabetics with acute coronary disease so, consequently, it seems reasonable to order examination to detect extensive ischemic heart disease in diabetics, in which it is common.

\textbf{Indications for revascularization in diabetic patients with acute coronary syndrome without ST-segment elevation}

The management of acute coronary syndrome without elevation of the ST segment has recently changed as a result of the publication of two large clinical trials that have compared an aggressive strategy, consisting of coronaryography and early revascularization, with conservative management guided by ischemia. In both studies (FRISC II and TACTIS-TIMI-18)\textsuperscript{18-21} an early invasive strategy in patients with acute coronary syndrome without ST-segment elevation reduced the incidence of major cardiac events at 1 year and at 6 months, respectively. The clinical impact of the two studies has been so important that it has forced both the ACC/AHA and Sociedad Española de Cardiología to update their guidelines for clinical practice in the management of acute coronary syndrome.

In the FRISC II study,\textsuperscript{18,20} 2457 patients with acute coronary syndrome without ST-segment elevation, with ST-segment depression or an increase in CK-MB or TnT (>0.10) were randomized to receive either an invasive strategy (1222 patients) consisting of catheterization and revascularization in the first 7 days, or noninvasive management in which revascularization was indicated for refractory angina or ischemia in the exercise stress test. Of the 1222 patients assigned to invasive therapy, angioplasty was performed in 522 patients (43\%) (a stent was used in 61\% of the procedures and abciximab in 10\%) and surgery in 430 patients (35\%). Within one year, the invasive strategy was associated with a reduction in mortality of 43\% (RR, 0.57; 95\% CI, 0.36-0.90) and in myocardial infarction of 26\% (RR, 0.74; 95\% CI, 0.59-0.94). In the FRISC II study, 298 patients (12\%) were diabetics (154 in the invasive group and 144 in the conservative group). The invasive strategy reduced the 1-year mortality in diabetics by 38\% (RR, 0.62; 95\% CI, 0.31-1.24) and the incidence of death or infarction by 30\% (RR, 0.70; 95\% CI, 0.47-1.04). These figures were similar to those observed in non-diabetics. In addition, in diabetics that received invasive treatment a decrease in the need for medication and improvement in symptoms was observed at 6 months (RR, 0.59; 95\% CI, 0.49-0.64). In summary, the findings of this study are consistent with the idea that invasive management that includes revascularization, if indicated and feasible, for high-risk acute coronary syndromes is clinically more beneficial than the classic conservative strategy guided by the presence of ischemia, even in diabetic patients.

The findings of the other study (TACTICS)\textsuperscript{22} confirm those of the previous one. This clinical trial included 2220 patients with acute coronary syndrome (unstable angina or acute myocardial infarction without ST-segment elevation) and high risk (positive markers of myocardial damage, changes in the ST segment or
T wave, or previous history of coronary artery disease). All were treated with the glycoprotein IIb/IIIa inhibitor tirofiban and then assigned randomly, as in the FRISC II study, to either a non-invasive strategy guided by the development or detection of ischemia or invasive management consisting of catheterization and revascularization in the first 48 h. Of the 1114 patients assigned to the interventional group, 41% underwent angioplasty and 20%, coronary surgery. The incidence of death or reinfarction at 6 months decreased by 26% and the rate of occurrence of the main endpoint (death, reinfarction, or readmission for acute coronary syndrome) also decreased by 22% (OR, 0.78; 95% CI, 0.62-0.97). Of the 2220 patients included, 28% were diabetic. In these patients, the incidence of death, reinfarction, or readmission for acute coronary syndrome decreased by 28% in the patients assigned to the interventional strategy (28% in the invasive group and 20% in the non-invasive group; \( P<0.05 \)). In non-diabetic patients, the reduction was not significant (16.4% vs 14.2%). That is to say, the benefits of the study were observed mainly in diabetic patients. The conclusions of this study are consistent with the above results and confirm that diabetics with acute coronary syndrome benefit from a strategy that includes early appropriate revascularization. It is more complicated to decide on the type of revascularization, surgery, or angioplasty in the context of multivessel disease, as we will see below. In general, and with the present techniques, angioplasty is recommended in single-vessel disease and surgery in multivessel disease, assuming that at least the anterior descending coronary can be revascularized with mammary artery and the surgical risk is not raised by coexistent comorbidity factors.

### Indications for revascularization in diabetic patients with acute coronary syndrome and ST-segment elevation

The results of the DANAMI II study, which have been recently communicated, have confirmed the findings of the meta-analyses of Weaver et al and Michels et al, which demonstrated that primary angioplasty is the reperfusion method of choice in patients with acute myocardial infarction and ST-segment elevation whenever it can be performed quickly (within 3 h) by an experienced team. This and other studies, like the recently published CADILLAC study, have clarified doubts about the effectiveness of stents that emerged with the results of the Stent-PAMI study, in which stent implantation was not found to be more beneficial than balloon angioplasty. The results of primary angioplasty with stent implantation in the DANAMI II study were better than those of thrombolytic treatment. In the CADILLAC study, angioplasty with a stent was associated with a lower need for new revascularization procedures during follow-up.

There is little information about the results of primary angioplasty in diabetic patients. The reason for this probably lies in the fact that most of studies that have compared primary angioplasty with thrombolysis have been small, which has precluded the analysis of subgroups. The only study that has evaluated primary angioplasty in diabetics is the angioplasty substudy of GUSTO IIb. In this clinical trial, 177 diabetics and 961 non-diabetics with acute myocardial infarction were distributed randomly to primary angioplasty or thrombolysis with the accelerated alteplase schedule. The diabetics had clinical and angiographic characteristics (more severe stenosis and worse flow) that were less favorable than those observed in non-diabetics. Nonetheless, the success rate of the procedure in patients assigned to angioplasty was similar (diabetics 70%, non-diabetics 72%). The clinical results at one month of diabetics and non-diabetics were similar, so the incidence of death, reinfarction, or disabling stroke was reduced by 38% (OR, 0.62; 95% CI, 0.41-0.96) in non-diabetics and 30% in diabetics (OR, 0.70; 95% CI, 0.29-1.72). Therefore, the available data, although scant, suggest that primary angioplasty is as effective in diabetics as in non-diabetics, and better than thrombolysis.

Although diabetics treated with primary angioplasty and stent had a less favorable clinical evolution at 6 months than non-diabetics, and diabetes has been demonstrated to be an independent predictive factor of thrombotic stent occlusion, the data available for primary angioplasty with stent confirm the usefulness of this device in diabetics with acute myocardial infarction. The incidence of cardiac events (death, reinfarction, disabling stroke, and need for revascularization of the treated vessel) at 6 months in the 135 diabetic patients included in the STENT-PAMI study was lower in the patients assigned to stent implantation than in those assigned to balloon angioplasty (20% vs 30%), especially in non-insulin-dependent patients (12% vs 28%; \( P=0.44 \)).

Therefore, given the information available, it can be said that primary angioplasty with stent implantation is the reperfusion strategy of choice in diabetic patients with acute myocardial infarction and ST-segment elevation. In these cases, aside from exceptions, there is no doubt that angioplasty should be performed after coronary angiography, if possible with stent implantation in the causal lesion. Surgery should only be considered in patients in which the artery responsible for infarction is not susceptible to angioplasty, has a large dependent myocardial territory, and can be performed immediately. Scant information is available regarding the best strategy in cases in which angioplasty of the causal artery only achieves partial revascularization. Depending on individualized analysis of each case and the experience of each group, revasculariza-
tion may be completed by angioplasty in the same act or in a second stage, patients may be controlled with medical treatment, or revascularization may be completed surgically in a second intervention.

**GLYCOPROTEIN IIb/IIIa INHIBITORS IN ANGIOPLASTY IN DIABETICS**

The development and availability of drugs that block platelet IIb/IIIa receptors is an important advance in the pharmacological treatment of angioplasty. The administration of these potent platelet antiaggregants in angioplasty has substantially improved its short and long-term results, which is why its use in angioplasty is increasing. The group of patients that probably have benefited most from glycoprotein IIb/IIIa inhibitors are diabetics, both in the case of angioplasty in a stable context and in acute coronary syndrome. Currently, three drugs of this group are used: abciximab, the best known and most often used, eptifibatide, and tirofiban.

Abciximab was first used in the context of coronary angioplasty and its effectiveness has been confirmed in several studies that have involved a large number of patients in diverse clinical contexts of ischemic heart disease. The results obtained in diabetic patients have been analyzed in a meta-analysis of the three main clinical trials (EPIC, EPILOG, and EPISTENT). The EPIC Study included 2099 patients in which high-risk angioplasty was indicated. It was considered a high-risk intervention because it was carried out in the context of unstable angina, acute myocardial infarction in evolution, or in lesions with a complex morphology. EPILOG recruited 2792 patients undergoing elective or emergency angioplasty and EPISTENT included 2399 patients who were randomized to treatment with abciximab as well as the angioplasty technique (stent or balloon). The three studies included a total of 1462 diabetics and the results revealed a clear benefit of treatment with abciximab: the 1-year mortality was 4.5% in the patients who were assigned randomly to abciximab and 2.5% in patients assigned to the control group ($P=0.03$). That is to say that the use of abciximab in diabetics was associated with a reduction in the 1-year mortality of 45%. This reduction in mortality was greater than that obtained in the overall group (diabetics and non-diabetics), which was 36% when adjusted to a Cox regression model (hazard ratio [HR], 0.64; 95% CI, 0.46-0.90; $P=0.01$). A reduction in mortality with abciximab was observed in 462 diabetics, whether insulin-dependent (abciximab, 4.2%; placebo, 8.1%; $P=0.07$) or non-insulin-dependent (abciximab, 1.8%; placebo, 2.7%; $P=0.34$). Nevertheless, the most interesting finding was that the reduction in mortality was especially important in two diabetic subgroups of interest: diabetics undergoing multivessel percutaneous revascularization (abciximab, 0.9%; placebo, 7.7%; $P=0.02$) and diabetics with insulin resistance syndrome (abciximab, 2.3%; placebo, 5.1%; $P=0.04$). Two findings underline the special benefit of abciximab in diabetics: in diabetics undergoing angioplasty and treated with abciximab (2.5%), the 1-year mortality equaled that of nondiabetics treated with placebo (2.6%). If diabetics are excluded from the meta-analysis, the difference in mortality between those treated with placebo or abciximab is not significant (2.6% vs 1.9%; $P=1$). Therefore, it seems that the reduction in mortality in the patients included in the meta-analysis treated with abciximab takes place fundamentally as a result of the benefit that it produces in diabetics (Figure 1). Abciximab also reduced the incidence at one year of the endpoint formed by mortality, the incidence of myocardial infarction, or the need for a new revascularization of the treated vessel in 15% (abciximab, 29%; placebo, 34%; $P=0.02$). This reduction took place at the expense of a decrease in mortality and the incidence of infarction.

The good results of prophylactic treatment with abciximab in diabetic patients in the context of angioplasty have also been confirmed with glycoprotein IIb/IIIa inhibitors that have a structure different from that of abciximab, like tirofiban, eptifibatide, or even lamifiban. In the context of acute coronary syndrome without ST-segment elevation, a meta-analysis of six studies that analyzed the influence of the use of glycoprotein IIb/IIIa inhibitors on the clinical evolution at 30 days has been published recently. Of the 6458 diabetic patients included in the six studies, 1279 were treated with coronary angioplasty. The associated use of glycoprotein IIb/IIIa inhibitors in these patients with acute coronary syndrome without ST-segment elevation treated with coronary angioplasty reduced the 30-day mortality from 4% to 1.2%, that is to say, by 70% (OR, 0.30; 95% CI, 0.14-0.69). The results were homogeneous in all the studies, which all showed that the use of these antiaggregant drugs in diabetics treated with angioplasty was associated with a decrease in mortality, as can be seen in Table 1.

The use of glycoprotein IIb/IIIa inhibitors, specifically abciximab, in the context of acute myocardial infarction treated with primary stent angioplasty in diabetic patients has not been specifically analyzed in adequate studies. In the general population, the results of a recent meta-analysis of the three main studies of angioplasty with stent implantation, associated or not with abciximab (CADILLAC, ISAR II, and ADMIRAL), suggest that their use is beneficial, reducing the incidence of adverse cardiac events in the intermediate term. The incidence of death or reinfarction at 6 months was 3.9% vs 7.1% in those not treated with abciximab (OR, 0.53; 95% CI, 0.34-0.84). It is likely that the results in the subgroup of diabetics are at least similar to those of the general population with acute myocardial infarction.
In the context of stent angioplasty, eptifibatide has demonstrated its effectiveness in reducing events in the short, intermediate, and long term in both acute coronary syndrome and stable ischemic heart disease. The meta-analysis of Bhatt et al.,\(^{32}\) extensively commented above, compiled information about the diabetics in the EPIC, EPILOG and EPISTENT studies. This meta-analysis demonstrated that the association of abciximab to angioplasty with stent implantation reduced the 1-year mortality in diabetics from 4.6% to 1.3% (\(P = .04\)), which equalized the mortality in diabetics and non-diabetics (1.3%) (Figure 1). In the context of scheduled stent angioplasty, the ESPRIT study (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) demonstrated the effectiveness of eptifibatide in reducing events at 48 h, 30 days, 6 months, and 1 year.\(^{35-37}\) This study included 2064 patients in which angioplasty was scheduled, who were assigned randomly to placebo or eptifibatide treatment (which began before stent implantation and was maintained for 48 h). The results were consistent with those of previous studies, so that the incidence of death or reinfarction decreased by 37% at 1 year in patients treated with eptifibatide (HR, 0.63; 95% CI, 0.48-0.83). The incidence of the combined endpoint of mortality, non-fatal infarction, or revascularization of the treated lesion was significantly lower in patients treated with glycoprotein IIb/IIIa inhibitors (17.5% vs 22.1%; HR, 0.76; 95% CI, 0.63-0.93; \(P = .007\)). This reduction in events was greater in diabetics (a 32% reduction at 1 year in the incidence of death or reinfarction in non-diabetics and of 42% in diabetics). However, because of the sample size (only 419 patients were diabetics) the difference was not statisti-

Table 1. Thirty-day mortality in diabetic patients with acute coronary syndrome treated with coronary angioplasty with or without glycoprotein IIb/IIIa inhibitors associated

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Randomized to GP IIb/IIIa</th>
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</thead>
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<tr>
<td>PURSUIT</td>
<td>457</td>
<td>2.4%</td>
</tr>
<tr>
<td>PRISM</td>
<td>147</td>
<td>0%</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>107</td>
<td>0.7%</td>
</tr>
<tr>
<td>GUSTO IV</td>
<td>239</td>
<td>1.2%</td>
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<tr>
<td>PARAGON A</td>
<td>45</td>
<td>0.7%</td>
</tr>
<tr>
<td>PARAGON B</td>
<td>284</td>
<td>0.7%</td>
</tr>
<tr>
<td>Total</td>
<td>1274</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

GP IIb/IIIa indicates glycoprotein IIb/IIIa inhibitors. Taken from Roffi et al.\(^{33}\)

Fig. 1. One-year mortality in diabetic and non-diabetic patients treated with angioplasty, depending on whether or not they received abciximab and stent implantation (taken from Bhatt et al\(^{32}\)).
RESULTS OF CORONARY ANGIOPLASTY IN DIABETICS

Results of coronary balloon angioplasty

Percutaneous revascularization in diabetics has been an object of study since the technique was first used in 1977. The results of all the studies have coincided. In the main studies that have analyzed balloon angioplasty in diabetics, it was observed homogeneously that the clinical and angiographic profile of the diabetics was unfavorable in relation to that of non-diabetics. These less favorable clinical and angiographic characteristics do not seem to influence the angiographic success rates, which were similar in diabetics and non-diabetics. Nevertheless, the initial results and, above all, the long-term results were worse in diabetic patients.

In the Registry of the National Heart, Lung and Blood Institute, the results of balloon angioplasty were specifically compared between 281 diabetics and 1833 non-diabetics. The diabetics were older, had more comorbidity, were more often women, and had more extensive and diffuse coronary disease. The initial angiographic success rate and degree of revascularization (complete vs incomplete) were similar, but the incidence of the endpoint formed by mortality, infarction, or the need for urgent revascularization during hospitalization was 11% in diabetics and only 6.7% in non-diabetics (P<0.001). The mortality and incidence of infarction in the hospital phase were greater in diabetics, especially diabetic women, who had a mortality of 8%. The long-term evolution (Table 2) was clearly unfavorable in diabetics: the adjusted mortality at 9 years was twice as high in diabetics (36% vs 18%; RR, 1.82; 95% CI, 1.41-2.34), the incidence of infarction was 60% higher (29% vs 19%), and the need for new revascularization procedures was greater in diabetics (33% more required new angioplasty and 19% more needed coronary surgery in the follow-up than in non-diabetics). The second classic study analyzed the experience of Emory University. At this center, in the period between 1980 and 1990, elective angioplasty was performed in 1133 diabetic and 9300 non-diabetic patients. As in the previous study, the diabetics were older and more frequently women than the non-diabetics; likewise, their functional class was worse and the history of previous infarction, multivessel disease, hypertension, obesity, or heart failure were more frequent in the diabetics. The clinical and angiographic results after angioplasty were good and similar in diabetics and non-diabetics. There was a low incidence of major adverse events (3%), although a tendency to a greater mortality and the development of infarction was detected in patients with insulin-dependent diabetes. The situation was clearly different in the long term (5 years). Survival was significantly lower in diabetics (89% vs 93%), as was the percentage of patients who did not develop infarction (81% vs 89%) or require coronary surgery (77% vs 86%) or new angioplasty (57% vs 68%) during follow-up. At 5 years, only 36% of the diabetics remained alive without presenting an infarction or requiring revascularization. The studies made in patients with multivessel disease have demonstrated similar findings: a similar mortality and rate of intrahospital events between diabetic and non-diabetic patients, but a greater long-term incidence of cardiac events and mortality (Table 2). Thus, for example, in the BARI study 170 diabetics with multivessel disease and 734 non-diabetics were randomized to angioplasty. The intrahospital mortality was similar, 0.6% for diabetics and 1.2% for non-diabetics, as was the incidence of death or infarction (diabetics, 2.4%; non-diabetics, 3.1%). Nevertheless, at 5 years the mortality was 5 times greater in diabetics (20.6% vs 4.8% in non-diabetics). The rate of myocardial infarction was 37% greater in diabetics during follow-up. It seems clear, therefore, that similar initial results can be expected from angioplasty of diabetics and non-diabetics, but the long-term clinical evolution is much less favorable in terms of the incidence of infarction, need for new revascularization procedures, and mortality.

The question that immediately arises after knowing the natural history of angioplasty in diabetics is: Is this unfavorable evolution due to a very high rate of restenosis or to a more rapid progression of arteriosclerosis in the untreated segments than in non-diabetics? In the light of the present evidence, both phenomena are involved in the mechanisms that explain the less favorable prognosis of angioplasty in diabetics. Different studies have consistently found higher rates of clinical and angiographic restenosis in diabetics. Rozenman et al observed an incidence of restenosis of 35% in non-diabetics and 61% in insulin-dependent diabetics. In the angiographic analysis of 320 patients in the BARI study at 5 years, the incidence of restenosis was 27% in lesions in non-diabetics and...
43% in patients with diabetes ($P=.01$). In addition, the available data demonstrate that the progression of the disease is greater in healthy or significantly injured segments in diabetics. In the last commented study, Barsness et al$^{45}$ detected a greater rate of appearance of significant new injuries at 5 years in diabetics (3% vs 2%; $P=.002$). Analysis of the patients of the CA-BRI study $^{46}$ demonstrated that the degree of revascularization and extension of coronary disease were similar in diabetics and non-diabetics. Consequently, this factor was not responsible for the less favorable evolution of diabetics. The investigators of this study could only attribute the evolution to a greater progression of coronary disease in the native arteries or grafts. The investigators from the EAST study reached similar conclusions.$^{41}$ In this study, the survival curves of diabetic and non-diabetics patients treated with angioplasty separated later (as of 5 years), suggesting that the progression of coronary disease was responsible in large measure for the worse prognosis of diabetic patients.

Therefore, balloon angioplasty in diabetic patients is associated with less favorable intermediate and long-term results than angioplasty in non-diabetics. This is due to a greater incidence of restenosis and a greater progression of coronary arteriosclerosis in untreated segments.

**Results of coronary stent angioplasty**

The stent is considered the greatest advance in coronary angioplasty since Grüentzig performed the first angioplasty in 1977. The stent has been shown to reduce the incidence of restenosis in a large variety of lesions and to improve the short, intermediate, and long-term clinical results of coronary angioplasty.$^{47-57}$ Consequently, stent angioplasty has become the most frequently used percutaneous coronary revascularization technique. The findings of the registry of the Working Group of Hemodynamics of the Sociedad Española de Cardiología reported for 2000 indicated that stents have been used in Spain in at least 22 580 angioplasties (77% of the total). This expansion is due not only to its good clinical results but, above all, to the fact that it is a very operative technique.

What has the stent contributed to angioplasty in diabetics? The stent has improved the initial and long-term results and has reduced the incidence of restenosis in relation to conventional angioplasty. Nevertheless, it has not managed to achieve the same results as obtained in non-diabetics: the rate of restenosis and incidence of long-term events, although lower than with balloon angioplasty, are still high and the results are less favorable than expected.

The subanalysis of 92 diabetics in the STRESS I and II studies$^{40}$ compared the clinical effectiveness and rate of restenosis at 6 months between patients randomized to balloon angioplasty or stent angioplasty. It demonstrated that stents in diabetics are associated to a greater initial rate of angiographic success, with a greater initial gain (1.61 mm vs 1.06 mm; $P<.001$) and success rate (stent, 100%; balloon, 82%; $P<.01$). In the long term, stents were accompanied by a lower incidence of restenosis at 6 months (24% vs 60%; $P<.01$) or need for new revascularization of the treated vessel (13% vs 31%; $P=.03$). The experience obtained in a non-randomized study by the French group of Lille$^{60}$ was similar; stent implantation reduced the incidence of restenosis from 63% to 25% and the rate of complete occlusion from 14% to 2%. The findings are similar for Spanish studies. Navarro et al$^{61}$ demonstrated that the use of stents reduced the incidence of clinical restenosis more than two-fold. Nevertheless, except in isolated studies,$^{62}$ the rate of restenosis in diabetics continued to be high in unselected patients and diabetes is still an independent predictive factor of restenosis.$^{63-67}$ Elezi et al$^{63}$ observed an incidence of restenosis in diabetics of 37.5% vs 28.3% in non-diabetics ($P<.001$). Kastrati et al$^{62}$ demonstrated in a series of 1349 patients that diabetes increased the risk of reste-
nosis by 86% (OR, 1.86; 95% CI, 1.56-2.16) and the need for a new revascularization procedure by 45% (OR, 1.45; 95% CI, 1.11-1.80). In our experience, an angiographic re-evaluation was performed at 6 months and patients were clinically followed up (median of 4 years). In the cohort of 981 consecutive patients treated with stent implantation, including 128 diabetics, the adjusted incidence of angiographic restenosis was 38% greater in diabetics, with a restenosis rate of 39% in diabetics and 26% in non-diabetics (P=.008). As in the study by Kastrati et al, diabetes was a strong independent clinical predictor of restenosis (Figure 2).

From a clinical point of view, diabetics have a less favorable evolution than non-diabetics in the intermediate and long term. At 5 years, the incidence of clinical events in our series was 39% higher in diabetics (HR, 1.39; 95% CI, 1.02-1.90). Diabetes, along with hypertension and multivessel disease, was an independent predictor of the long-term evolution (Figure 3). The results of other studies are similar. At 1 year, the diabetics analyzed by Elezi et al had a lower event-free survival than non-diabetics (73.1% vs 78.5%; P<.01). The mortality after a mean follow-up of 18±10 months was 4 times greater in diabetics (8.1% vs 2.1%; P=.03) and the need for revascularization of the treated lesion was 35% greater in the series of Paschal et al.

The influence of the type of diabetes (type 1 vs type 2) on the results of stent angioplasty has also been analyzed. Although Schofer et al did not find differences in the incidence of angiographic restenosis, the Washington group, in the largest study published, observed that the clinical evolution of non-insulin-dependent diabetic patients is similar in the short and intermediate term to non-diabetics. However, insulin-dependent diabetics had clearly worse short and intermediate results than non-diabetics.

### MECHANISM OF RESTENOSIS IN DIABETICS

Restenosis, together with the frequent impossibility of achieving complete revascularization of all ischemic territories and faster progression of arteriosclerosis, have been identified as factors in the less favorable clinical evolution of diabetics treated by balloon angioplasty or stent implantation. Restenosis has a key role. This complication is conditioned by three phenomena: the immediate elastic recoil, unfavorable late remodeling, and intimal hyperplasia. In particular, hyperplasia is the predominant mechanism of restenosis in angioplasty with stent implantation. Reduction of the incidence with stenting seems to be due fundamentally to its capacity to prevent immediate elastic recoil and achieve favorable arterial wall remodeling. Nevertheless, the implantation of a stent increases intimal hyperplasia, the third mechanism involved in the restenotic process, which becomes the main mechanism responsible for restenosis in lesions with stents. The final balance of the three effects in most patients treated by stent implantation is a larger final and long-term luminal diameter and a lower incidence of restenosis.

Metabolic, hematological, and biological abnormalities inherent to diabetics probably participate in the complex combination of mechanisms that occur after vascular aggression and are involved in restenosis. In diabetics it has been possible to demonstrate by intravascular ultrasound studies that restenosis is due fundamentally to intimal hyperplasia, which is greater than in non-diabetics in both balloon angioplasty and stenting. Therefore, two factors that increase intimal hyperplasia coincide in diabetics: diabetes per se and stent implantation, which is why the final result might not be as favorable as in non-diabetics. The increased hyperplasia in diabetic patients can be measured by the hyperinsulinemia, as determined by the insulin resistance of type 2 diabetics, and other metabolic disorders of diabetics that involve the re-
nination of arteriosclerosis, intimal hyperplasia, and thrombosis induced by hyperglycemia per se. Another mechanism involved is the greater probability of diabetics to develop thrombotic phenomena and occlusion of the treated lesion. Hyperinsulinemia, lipid disorders, and disturbances in the activity of PAI-1, which are common in diabetics, favor the progression of arteriosclerosis, intimal hyperplasia, and thrombotic disturbances. Although much remains to be learned about the pathophysiology of restenosis in diabetics, the available information suggests that stent-based methods that reduce intimal hyperplasia should be sought. This would lead to less restenosis and, undoubtedly, a more favorable clinical evolution than what can now be expected.

REvascularization in the diabetic patient with multivessel disease. RESULTS OF ANGIOPLASTY AND CORONARY SURGERY

Advances in angioplasty in the 1980s have made it possible to approach patients with multivessel disease percutaneously. At this time, a series of clinical trials were designed and carried out to compare coronary balloon angioplasty and surgery in patients with 2 or 3-vessel disease or with acute stenosis of the proximal portion of the anterior descending artery. The results of these studies, considered together in a meta-analysis published in 1998, demonstrated that the short and long-term results were similar in terms of mortality and the incidence of non-fatal infarction. Nevertheless, the need for new revascularization procedures was much greater in patients assigned randomly to angioplasty. These conclusions seem valid for all the subgroups of patients with multivessel disease, except diabetics. The BARI study showed that the 5-year mortality in diabetics assigned to revascularization by angioplasty was almost 4 times greater (20.6% vs 5.8% in those assigned randomly to surgery). Although the design of this analysis in the subgroup of diabetics was carried out at the end of the patient inclusion period, which is a limitation, it ignited an intense controversy that still goes on and leads many cardiologists to advise against angioplasty in diabetics with multivessel disease.

What was learned in the BARI study was used to publish many papers that analyzed the problem parting from the data of clinical trials or cohort studies (Table 3). The majority confirmed that the prognosis was worse in diabetic patients with multivessel disease treated with angioplasty. The largest experiences come from two non-randomized studies made by the University of Emory and the Northern New England Cardiovascular Study Group. In the first study, the adjusted mortality in a 10-year follow-up was 35% greater in insulin-dependent diabetic patients with multivessel disease treated with angioplasty (63%) than in those who underwent coronary surgery (53%; P = .04). In the second study, the mortality was 49% greater (HR, 1.49; 95% CI, 1.02-2.17) in diabetics who underwent angioplasty than in those who underwent surgery. The analysis of the 125 diabetics of the CABRI study demonstrated that the 4-year mortality was almost two-fold greater in the patients randomized to percutaneous revascularization than to surgery (22.6% vs 12.5%; RR, 1.81; 95% CI, 0.80-4.08). In the 8-year follow-up of 90 diabetic patients of the EAST study, it was observed that the survival of diabetics assigned to angioplasty was significantly lower than in those randomized to aortocoronary bypass surgery (60.1% vs 82.6%; P = .02). The data from the 7-year follow-up of the BARI study also confirmed the better prognosis in terms of survival of diabetics assigned to surgery (76.4%) vs angioplasty (55.7%; P = .0011). Only two large cohort studies demonstrated a similar 5-year mortality in diabetics with multivessel disease treated with either angioplasty or surgery. These two studies are the analysis of the Duke University database and the registry of the BARI study, which included patients who met the inclusion criteria of this clinical trial and were registered and followed up. Their treatment was not assigned randomly.
but established by the cardiologist and/or surgeon with the patient. The explanation of this apparent paradox is based on the main characteristic that differentiates the design of the two types of studies: patient selection. Whereas in the BARI clinical trial the revascularizing strategy was assigned randomly, in the patients of the BARI registry and Duke University database, the physician and surgeon of each patient selected the treatment that seemed most suitable for each case. This methodological bias explains the difference and is an interesting clinical finding. In at least 2 out of 4 observational studies, adequate patient selection could ensure acceptable long-term results.

Analysis of these data has some limitations, principally related to the angioplasty technique (stents and glycoprotein IIb/IIIa inhibitors were not used) and surgery (little use of arterial grafts). These points could be relevant. For example, in the BARI study, the benefit observed in surgery was obtained only in patients in which internal mammary artery was used.\(^\text{78,83}\) Nonetheless, the data available from studies in which effective techniques from current practice have been used do not differ substantially from the information obtained from references for older trials and registries. The ARTS Study\(^\text{87}\) of 1205 patients with multivessel coronary disease compared the strategy of stent angioplasty (600 patients, including 112 diabetics) with coronary surgery (605 patients, including 96 diabetics). The intrahospital evolution of 208 diabetics revealed no significant differences between the patients randomized to surgery and angioplasty with stent implantation, which showed a similar intrahospital survival free of coronary events (surgery, 91%; stent angioplasty, 90%; \(P=.7\)). Nevertheless, at 1 year the need for new revascularization procedures was significantly greater in the patients assigned to stent implantation (22% vs 3.1%; \(P<.001\)), with a tendency to a greater mortality (6.3% vs 3.1%). The event-free survival of the patients assigned randomly to stent implantation was 63% vs 84% (\(P<.001\)) for those randomized to surgery. Diabetes continued to be an independent predictor factor of events in this study, which were twice as frequent at 1 year (OR, 2.1; \(P=.001\)).

While awaiting the long-term results of the ARTS and other studies that include not only stent implantation but also glycoprotein IIb/IIIa inhibitors in the protocol, it seems clear that, in general, the long-term results of coronary revascularization in diabetics are better when surgical procedures are used instead of angioplasty.

### CONTROVERSY REGARDING INDICATIONS FOR CORONARY ANGIOPLASTY IN DIABETICS

Based on the above discussions, in what diabetics can coronary angioplasty be indicated? We know that angioplasty in diabetics has initial results that are very similar to those of non-diabetics. Even in patients with multivessel disease, the short-term results do not differ from those of surgery. Nevertheless, even with stenting, coronary angioplasty in diabetics is associated with a less favorable long-term evolution than in non-diabetics and to worse results than surgery in multivessel patients. These worse results are due, in good measure, to the greater incidence of restenosis. We also know that intra-stent restenosis is greater when other factors are associated, like small vessel size and the presence of residual stenosis and long lesions.\(^\text{64,65}\) In general, the sum of the factors that independently influence an event result in an effect of much greater magnitude than the expected sum of the factors. This also occurred in our case. Thus, in the study by Elezi et al\(^\text{63}\) the incidence of restenosis in non-diabetics was 28% and in diabetics, 38%. However, if we analyze the rate of restenosis in diabetics, it is evident that it was 49% in those with an arterial diameter of less than 3 mm, but only 27% in diabetics with an arterial diameter of 3 mm or more, which was similar to the overall result in non-diabetics. Another factor that we must be aware of is that the results of angioplasty are always worse in insulin-dependent diabetics.\(^\text{69,84}\)

Therefore, it seems reasonable to perform angioplasty in diabetics who have an indication, as described in the second section of this article, and stable di-

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>No.</th>
<th>Mortality, %</th>
<th>Follow-up, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARI</td>
<td>Randomized</td>
<td>173</td>
<td>44</td>
<td>7</td>
</tr>
<tr>
<td>BARI</td>
<td>Registry</td>
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<td>14</td>
<td>5</td>
</tr>
<tr>
<td>EAST</td>
<td>Randomized</td>
<td>29</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>CABRI</td>
<td>Randomized</td>
<td>62</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Weintraub et al</td>
<td>Observational</td>
<td>834</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Niles et al</td>
<td>Registry</td>
<td>1593</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 3. Long-term mortality in diabetics with multivessel disease treated with angioplasty or coronary surgery
sease or unstable single-vessel disease, in which sur-
genous effectiveness in diabetics is in the process of ev-
operation of restenosis because of its capacity to inhibit cell pro-
clinical effectiveness in diabetics is in the process of eval-
Firstly, it should be considered in diabetic patients, par-
etically non-insulin-dependent diabetics, preferen-
tivality in diabetics treated with angi-
pilation, with results that sometimes cannot be descri-
Intracoronary brachytherapy

Intracoronary brachytherapy reduces the incidence of re-
most important effect takes place during the phase of
nital angioplasty, such as arterial diameter of less than 3 mm,
rapy and stents coated with proliferation inhibitors
inhibition of neointimal proliferation. Clinical trials of
Angioplasty with stents that release inhibitors
Intracoronary brachytherapy and, above all, stents
At present, brachyther-
ies remaindered that, even
y and stent implantation.
The second situation is surgery associated with
Without balloon angioplasty, the initial complication
mortality or infarction) are less with angioplasty than
Therefore, in patients with a high risk for
revascularization is inevitably indicated, it seems rea-
neointimal hyperplasia) could be
os, acute angina or extensive ischemia, in which
restenosis (reduction of intimal hyperplasia) could be

THE NEAR FUTURE OF PERCUTANEOUS REVASCULARIZATION IN DIABETICS

Although the present of percutaneous revasculariza-
tions that release drugs that inhibit intimal hyperplasia.
Restenosis has been the main limitation of coronary
aly and G2, causing cell death or, more frequently,
ology (de novo restenosis) and, above all, restenosis

Angioplasty with stents that release inhibitors of intimal hyperplasia

The publication in June 2002 of the results of the
sterone therapy and, in fact, increased it. The development
Revascularization in Diabetic Patients
plasia may make it possible to eliminate or greatly re-
duce the main limitation of angioplasty: restenosis.95
This is what was discovered in the RAVEL study.96
The first experimental studies demonstrated that ra-
 pamycin (sirolimus) also impeded T-cell proliferation
and the proliferation and migration of smooth muscle
cells (a fundamental phenomenon in postangioplasty
intimal hyperplasia). Based on these observations, a
stent coated with rapamycin was that was slowly released
was developed. This stent was applied in 30 patients in
São Paulo97 and in 15 patients in Rotterdam.98 None of
the patients developed restenosis and only one patient
died as a result of cerebral hemorrhage, one had suba-
cute occlusion, and one had an infarction at 14
months. These spectacular results motivated the RA-
VEL study. In this study, 238 patients were assigned
randomly to angioplasty with a standard stent or with
a stent coated with sirolimus. The results impressed
the scientific community. None of the patients in the
group randomized to sirolimus-coated stents devel-
oped restenosis, vs 26% of those that received the stan-
dard stent. The rate of major cardiac events at 1 year
was 5.8% in the coated stent group vs 29% (P<.001)
in the control group. In the 19 diabetic patients treated
with sirolimus-coated stents, restenosis was not obser-
ved. Other studies (ELUTES, TAXUS) with stents co-
ated with inhibitors of myoimal proliferation (taxol,
paclitaxel) have demonstrated less favorable, but still
encouraging, results. As a result, new questions must
be asked: does this type of stent prevent or delay re-
estenosis? Will it increase the incidence of late thrombotic
occlusion? Is it safe in acute coronary syndrome? We
should have answers to these questions in the near fu-
ture.

It is very likely that the development of these devi-
ces will substantially change and improve the results of
angioplasty, particularly in diabetics. This will
make new studies necessary, especially in the context
of multivessel disease, whose results will require a re-
examination of revascularization strategies in dia-
etics, thus further expanding the use of percutáneas

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