Myocardial revascularization in diabetic patients: current state and future perspectives

Revascularización miocárdica en pacientes con diabetes: estado actual y perspectivas

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Abstract
Diabetes mellitus represents an important risk factor to develop cardiovascular diseases as coronary artery disease, cerebral vascular disease or peripheral artery disease. Diabetic patients have a prevalence of atherosclerosis with significant coronary artery disease ten times higher than in the general population, and the risk of cardiovascular adverse events is two to four times greater. Consequently, cardiovascular diseases and specifically, significant coronary artery disease are the main cause of death in people with diabetes. Prevention and optimal treatment are especially important in this particular population. In this article we have reviewed the current indications for the different techniques of myocardial revascularization, and the future perspectives of these techniques in the treatment of the coronary artery disease in the diabetic patient.

Keywords: myocardial revascularization, diabetes, coronary revascularization surgery, percutaneous coronary intervention.

Introduction
The diabetes mellitus (DM) constitutes at present a public health problem in the developed countries, favored by the new behavior models that include an increase in the caloric intake and the sedentarism, which promotes the onset of obesity and the development of the T2D. Though it is in constant increase, it is estimated that the present worldwide prevalence of this new pandemia is placed in the range of 6-8% of the total population, though there are important geographic differences. As regards to our environment, the prevalence in Spain is estimated also in the range of 7%, though some authors raise this value up to 15% of the population.1

The importance of this syndrome lies in its high association with the cardiovascular disease (CVD). In fact, the American Diabetes Association (ADA) considers the T2D as a cardiovascular disease of metabolic origin,2 that goes beyond the simple glycemic control disorder. Thus, cardiovascular diseases and specifically the ischemic cardiopathy constitute the cause of death in diabetic patients; in particular, they show a cardiovascular disease 2-4 time higher and an attributable mortality to
the coronary arterial disease (CAD) 4 times higher regarding to the non diabetic population. Considering this high cardiovascular risk (CR), the diabetic patient should be considered as a patient in secondary prevention and the same healthy-dietetic and therapeutic measures should be implemented than in patients with previous CVD.

The high CV risk of the diabetes is inherent to the disease itself, though other CV risk factors are also associated to it in a certain extent than in the general population, as the hypertension and the hyperlipidemia. The vascular disease of the DM affects both the vessels of large and mean calibre (macroangiopathy) with a preferable coronary, kidney-related, cerebral and peripheral vascular tree location and the small calibre vessels (microangiopathy), in the kidney, retina and nervous system.

The coronary artherosclerosis of the diabetic patient presents a series of distinctive characteristics compared to the non-diabetic patient. Thus, this is usually more serious, more diffuse, with a lesion of more vessels, a more frequent lesion of the common left coronary trunk artery, a preferable location in the terminal branches with a lower collateral circulation development and, in general, with a higher frequency of complex lesions. A faster progression has also been observed in serial angiographic studies than in the non-diabetic patients. The indications of myocardial revascularization in the diabetic patients are the same ones than in the non diabetic patient, but the results, both of the percutaneous coronary intervention (PCI) and the coronary revascularization surgery (CRS), are worse in the follow-up at mean and short term. The indications of myocardial revascularization in the diabetic patients are the same ones than in the non diabetic patient, but the results, both of the percutaneous coronary intervention (PCI) and the coronary revascularization surgery (CRS), are worse in the follow-up at mean and short term. The indications of myocardial revascularization in the diabetic patients are the same ones than in the non diabetic patient, but the results, both of the percutaneous coronary intervention (PCI) and the coronary revascularization surgery (CRS), are worse in the follow-up at mean and short term. Given the high prevalence and the seriousness of the CAD in the diabetic patient, in the usual practice the clinical cardiologist considers frequently the need of ordering a myocardial revascularization. The present evidence in favor of the different revascularization techniques is checked in this article, as well as the future perspectives.

**Percutaneous coronary intervention in the diabetic patient**

Several studies have proved that the DM exerts a negative role in the results at medium and long term after the percutaneous coronary interventionism (PCI) regarding the patients without DM, and the initial post-interventionism results are similar, in spite that diabetic patients show frequently a more extensive coronary disease. This is due mainly to an increase of the restenosis incidence that can reach, according to the series, up to 60%, with the subsequent need of a new revascularization (either percutaneous or through a CRS). The restenosis is mainly due to three factors: the elastic worsening, the late remodeling and the intimal hyperplasia. After the frequent use of the stent in the usual practice of PCI, the intimal hyperplasia is the main mechanism of the restenosis that, though it has reduced its incidence with the use of the stents, it is still a problem without solution.

This reducing effect of the restenosis after the PCI with stent is observed both in diabetic patients and in non-diabetic patients, but the results are still worse in the diabetic patients, with a higher rate of restenosis and adverse clinical events. The higher incidence of intrastent restenosis (ISR) in these patients is mainly due to the important development of intimal hyperplasia, whose physiopathology is multifactor and to whom hyperinsulemia and hyperglycemia contribute among other factors.

In order to give an answer to this phenomenon and try to reduce the ISR, during the last years, stents have been developed with antiproliferative drugs cover that are released in the intima of the artery in a controlled manner and inhibit the intimal hyperplasia. These are the so-called drug-eluting stents (DES). The drugs that have been first used, and about which most scientific evidence is available, are sirolimus and paclitaxel. Moreover, during the last year’s new prosthesis have appeared with different pharmacological covers, as the everolimus, biolimus, tacrolimus or zotarolimus, all of them with the same purpose of reducing the intimal hyperplasia and the consequent ISR.

The SIRIUS study is the most representative one as regards to those that compare the sirolimus-eluting stents (SES) with the conventional stents (CS). In this study, 1,058 patients have been included from which 26% (279) had diabetes. From them, 131 were treated with SES and the rest with CS. After performing a follow-up of 9 months, the incidence of ISR in the diabetic patients treated with SES was remarkably lower than those treated with CS (17.6 versus 50.5%, p <0.001), but far from the ones registered in the non-diabetic patients treated with SES (6%).
The DIABETES study, also performed with SES but designed for patients with DM, included 160 patients and confirmed also the reduction of the ISR in patients treated with SES versus CS (33.7 versus 7.8%; \( p < 0.001 \)). Unlike the SIRIUS, this benefit was observed both in diabetic patients treated with insulin and in those who are not insulin dependent. In the same line, the TAXUS-IV study performed with paclitaxel covered stents, included 1,314 patients from which 24% had DM, and proved likewise an important reduction of the ISR in these last ones (who received insulin or not) treated with endoprosthesis covered with paclitaxel, but also higher frequencies than the non diabetic patients.

Several studies and records have tried to demonstrate the superiority of one of the two DES in patients with DM, without having at present sufficient data that might show a better behavior of one of the endoprosthesis versus the other.

**Inhibitors of glycoprotein IIb/IIa in the percutaneous coronary interventionism of the diabetic patient**

Different studies have analyzed the efficacy of abciximab, which is an inhibitor of the glycoprotein IIb/IIa, in the reduction of adverse events after PCI of the diabetic patient. In a meta-analysis performed by Deepak et al., which includes the results of the studies EPIC, EPILOG and EPISTENT, abciximab reduced the mortality to one year of a 4.5 to 2.5% (\( p = 0.031 \)) in the diabetic patients, while the reduction in the non diabetic patients did not reach statistical significance (2.6 to 1.9%; \( p = 0.099 \)). It was also observed that the higher benefit was focused mainly in the diabetic patients who had a multivessel disease (7.7% in the placebo group versus 0.9% in the abciximab group; \( p = 0.018 \)).

It has also been speculated that the use of abciximab in the PCI context in the diabetic patient might reduce the restenosis rate and the need of a new revascularization, considering the results obtained from a sub-study of EPISTENT; however, these results have not been confirmed by other studies.

**Multivessel disease in the diabetic patients: coronary revascularization surgery versus the percutaneous coronary interventionism**

The DM is a negative prognosis factor in the patients who undergo a CRS. It has been associated to an increase in the morbimortality after surgery and a higher number of complications at long term, as well as an increase of the occlusion of the coronary grafts. At the end of the 80s and beginning of the 90s, a series of studies have started with the aim of comparing the results of the PCI versus CRS in patients with multivessel disease. None of them was designed specifically for diabetic patients, but conclusions have been taken from the analysis of this group of patients (table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Follow-up time (years)</th>
<th>PCI mortality (%)</th>
<th>CRS mortality (%)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITA-1 (1993)</td>
<td>52 (23 CRS, 29 PCI)</td>
<td>6</td>
<td>6.9</td>
<td>24.2</td>
<td>0.9</td>
</tr>
<tr>
<td>EAST (1994)</td>
<td>59 (30 CRS, 29 PCI)</td>
<td>8</td>
<td>39.9</td>
<td>24.5</td>
<td>0.23</td>
</tr>
<tr>
<td>CABRI (1995)</td>
<td>124 (64 CRS, 60 PCI)</td>
<td>4</td>
<td>22.6</td>
<td>12.5</td>
<td>NR</td>
</tr>
<tr>
<td>BARI (1996)</td>
<td>353 (180 CRS, 173 PCI)</td>
<td>10</td>
<td>55</td>
<td>42.2</td>
<td>0.025</td>
</tr>
<tr>
<td>ARTS* (2001)</td>
<td>208 (96 CRS, 112 PCI)</td>
<td>3</td>
<td>7.1</td>
<td>4.2</td>
<td>0.39</td>
</tr>
<tr>
<td>AWESOME* (2001)</td>
<td>144 (79 CRS, 65 PCI)</td>
<td>5</td>
<td>26</td>
<td>34</td>
<td>0.27</td>
</tr>
</tbody>
</table>

CRS: coronary revascularization surgery; NR: not relevant. PCI: percutaneous coronary interventionism; *PCI studies with stent graft.

One of the most representatives is the BARI study (Bypass Angioplasty Revascularization Investigation) that enrolled 1,829 symptomatic patients with multivessel coronary disease who have been distributed randomly to receive surgical or percutaneous revascularization by means of PCI with cylinder. It has been concluded in this study that in the total population the survival is similar in the patients treated with PCI or with CRS, with a larger need of new revascularization in the group of PCI versus the patients undergoing CRS. If we focus in the diabetic patients (19%), differences have been found in the survival in favor of the CRS group and this has also kept constant over time. Thus, in the BARI study, the survival...
after 5 years of the DM group subject to PCI was of 65.5% versus 80.6% of the patients randomized for CRS (p= 0.003) while after 7 years it was of 55.7% for the PCI and 76.4% for the CRS (p= 0.001); finally, after 10 years of survival of the diabetic patients undergoing PCI was of 45% versus 57.8% of the CRS group (p= 0.025). It is important to point out also that the benefit was reduced to the patients who received at least an internal breast artery during the CRS.

Further on, other studies were designed in which the results of the CRS versus the PCI with stent implants in patients with multivessel disease have been compared. From this group, the ARTS study (Arterial Revascularization Therapy Study) is the most important one. When analyzing the subgroup of patients with DM (280 from a total of 1,205 enrolled), no differences have been observed as regards to mortality when comparing both strategies in the follow-up during one year (the 3.1% in the CRS group versus 6.3% in the PCI group with stent; p= 0.294) and 3 years (4.2% and 7.15% in the CRS and PCI with stent groups, respectively; p= 0.39). As always, the PCI group plus stent need more frequently new revascularization procedures than the CRS group (22.3 versus 3.1% in the first year). The major use of internal breast artery should be pointed out in this study (89%) and the scarce use of glycoprotein IIb/IIIa inhibitors (3.5%).

Considering the results of these studies, there is at present a consensus in which the CRS is generally higher than the PCI in the patient with DM, especially in the common trunk disease of the left coronary artery, when there is a coronary disease with trivascular lesion with added systolic dysfunction, and in the disease of two vessels when the proximal segment of the anterior descending artery is injured.

It has also to be pointed out, as the European Society of Cardiology emphasizes in its last guidelines about diabetes and cardiovascular disease, that when choosing the CRS, arterial grafts should be used and when the indicated treatment is PCI, the use of DES should be chosen and glycoprotein IIb/IIIa inhibitors will be used concomitantly. However, most of these studies will be soon from a decade ago, and during this time both the CRS and the PCI have experienced important technological developments that make difficult that the conclusions taken from these studies can be applied in the current practice.

### Perspectives

At present there are several studies ongoing that compare the results of the CRS and the PCI in diabetic patients and with multivessel disease through the current techniques, that might clarify about which is the best revascularization therapy in these patients. The CARDia study (Coronary Artery Revascularization in Diabetes), conducted in different centers of the United Kingdom and Ireland, included a total of 510 diabetic patients with multivessel disease or complex lesions between January 2002 and May 2007, who have been randomized to perform the CRS or the PCI optimized with stent and abciximab. SES has been implanted to 71% of the patients and CS to the rest. Recently, the results have been known after one year of follow-up. No relevant differences in the primary objective have been found during this time, which was a combination of death, non mortal myocardial infarction (MI) and non mortal cardiovascular stroke (10.2% in the CRS group versus 11.6% in the PCI group; odds ratio [OR]= 1.15; confidence interval (CI) OF 95%: 0.65-2.03; p= 0.063). No differences were either found between both groups if the different components of the primary objective are assessed one by one. As it was expected, differences were indeed found in the need of a new revascularization (9.9% of the patients from the PCI group versus 2% of the group that underwent CRC, OR= 5.31; CI of 95%; 2-14.11; p= 0.001). If a combined objective is analyzed which includes death, infarction, cerebrovascular accident and the need of a new revascularization, there are differences between both groups.
considering this last one (11% in the CRS group versus 17.5% in the PCI group; OR= 1.72; CI of 95%: 1.02-2.8; p= 0.04). There are no differences in the primary objective if only the group of patients undergoing a PCI with SES are evaluated (10.2 versus 10.1% respectively; p= 0.98) nor in a combined objective that includes the need of a new revascularization, notwithstanding that this one was more frequent in the PCI with SES group than in the CRS group, which is probably compensated by a lower number of cerebrovascular accidents (figure 1 and 2). These results have been obtained only after one-year follow-up, so the results should be waited for after 5 years in order observe if they are confirmed.

At present, under enrolment process that started in April 2005, the FREEDOM study (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) financed by the National Heart, Lung and Blood Institute, compares also a strategy of PCI with DES versus CRS in diabetic patients and multivessel disease. This study tries to include more than 2,000 patients, becoming in the largest randomized study on revascularization in diabetic patients.

Also recently the results of the SYNTAX study (Synergy between Taxus and Cardiac Surgery) came forth. This trial included 1,800 patients with trivascular coronary disease or lesion of the common trunk of the left coronary artery assigned to CRS or PCI with paclitaxel-coated stents. The primary objective was a combination of mortality, cerebrovascular accident, MI and the need of a new revascularization. Differences were found after one year in favor of the CRS group versus PCI in the primary objective (12.1 versus 17.8; p= 0.0015). Analyzing the components of the primary objective independently, it can be observed that there are only differences in favor of the CRS in the need of a new revascularization (5.9 versus 13.7%; p <0.0001), being favorable the number of cerebrovascular accidents for the PCI (0.6 versus 2.2%) and the results are comparable as regards to the death and MI. If we focus on the group of patients with DM (452), we find only a major need of revascularization, without differences regarding to death, infarction or cerebrovascular accidents (figure 3).

Conclusions
The DM, regarding to the cardiovascular disease, is associated to an important risk of coronary disease. When this disease appears it is generally serious and shows a multivessel lesion. Both the PCI and the CRS have worse results in diabetic patients compared to the general population. Traditionally, the CRS has been considered as the revascularization choice technique in this type of patients. This is based on the analysis of sub-populations of small number of studies that are not specifically designed for the diabetic patients, that are obsolete at present for not having incorporated the important advances, both technical and pharmacological that have been produced during the last decade (both in the PCI and CRS field).

At present, there are ongoing studies with a great number of diabetic patients, in which the PCI and the CRS are
compared and whose results guide us when deciding about the best revascularization technique for our patients with DM. In any case, it is always important to individualize according to the social situation of each patient, its comorbidity and the health environment when indicating PCI or CRS in the multivessel disease. Moreover, whichever is the chosen revascularization mode, not less important is to follow it with a strict medical treatment with special attention on the metabolic and lipid control, an adequate antiaggregant regime and the optimization in the use of beta blockers and inhibitors of the angiotensin-converting enzyme.

Declaration of potential conflict of interest
D. López Otero, P. Souto Castro, R. Trillo Nouche, B. Cid Álvarez and J.R. González-Juanatey state that there are no conflicts of interest as regards to this article.

Practical considerations

- The ischemic cardiopathy constitutes the main cause of death in diabetic patients, therefore the prevention and the correct treatment of the cardiovascular disease is important.

- The indications of myocardial revascularization in the diabetic patient are the same ones as in the non-diabetic patient. However, the results, both of the percutaneous coronary interventionism and the coronary revascularization surgery are worse in the follow-up at medium and long term.

- It is unknown which of the two techniques offer best results in this pathology. When the coronary revascularization surgery is chosen, arterial grafts should be used. If the indicated treatment is the percutaneous coronary interventionism, the use of drug-eluting stents will be chosen and glycoprotein IIb/IIIa inhibitors will be used concomitantly.

References