INTERVENTIONAL CARDIOLOGY

Drug-Eluting Stents in Patients With Left Main Coronary Lesions Who Are Not Candidates for Surgical Revascularization

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Introduction and objectives. Surgical revascularization is the treatment of choice in patients with left main coronary artery stenosis. Conventional stents are not a valid alternative because of the rate of restenosis and sudden cardiac death. Drug-eluting stents, which reduce the rate of restenosis, may represent an alternative to cardiac surgery. The objective of this study was to describe the results with drug-eluting stents in patients with left main coronary artery stenosis who were poor candidates for surgical revascularization.

Patients and method. We prospectively followed a consecutive series of patients who were poor candidates for surgical revascularization and were treated with implantation of a drug-eluting stent in the left main coronary artery between May 2002 and April 2004. In-hospital and long-term results were analyzed. Follow-up included angiographic and intravascular ultrasound (IVUS) studies.

Results. Forty-two patients (25 men, 59.5%) with a mean age of 70.1 (10.5) years were studied. Fourteen (33%) had diabetes, and 7 (16.7%) had a protected left main coronary artery. The reasons for ruling out surgery were poor distal vessels in 19 (45.2%), previous surgery in 9 (21.4%), age in 6 (14.3%), primary angioplasty in 5 (11.4%), and other reasons in 3 (7.2%). Four patients (9.5%) died before discharge, three of them after primary angioplasty. No in-hospital revascularization procedures were needed. Median follow-up time was 288 days; mean follow-up time was 315 (241) days. Another four patients died after discharge (9.5%) on days 5, 24, 34, and 115. Angioplasty was repeated in one patient, and another was referred for heart transplantation.

Conclusions. Drug-eluting stents represent a valid alternative in patients with left main coronary artery stenosis who are poor candidates for surgical revascularization. Randomized studies with a longer follow-up should be performed to evaluate their benefits in patients eligible for surgery.

Key words: *Left main coronary artery. Stent. Coronary angioplasty. Revascularization.*

Stent liberador de fármacos en lesiones de tronco coronario izquierdo en pacientes no candidatos a revascularización quirúrgica

Introducción y objetivos. La cirugía es el tratamiento de elección de la estenosis del tronco. Los *stents* convencionales no son una alternativa debido a la reestenosis e incidencia de muerte súbita. Los *stents* liberadores de fármacos, al disminuir la reestenosis, pueden ser una terapia válida. El objetivo del estudio es describir los resultados del *stent* con liberación de fármacos en pacientes con lesión en tronco no candidatos a tratamiento quirúrgico.

Pacientes y método. Se analizó la evolución de una serie de pacientes consecutivos no candidatos a cirugía a los que se implantó un *stent* liberador de fármacos entre mayo de 2002 y abril de 2004 por lesión en el tronco. Se analizaron los resultados intrahospitalarios y a largo plazo. Se realizó un seguimiento angiográfico y con ultrasonidos intracoronarios.

Resultados. Se estudió a 42 pacientes, con una edad de 70,1 ± 10,5 años, 25 (59,5%) varones, y 14 (33%) diabéticos; 7 (16,7%) tenían tronco protegido. El motivo de imposibilidad de cirugía fue por malos vasos en 19 (45,2%) casos, cirugía previa en 9 (21,4%), edad en 6 (14,3%), angioplastia primaria en 5 (11,4%) y otras causas en 3 (7,2%) pacientes. Cuatro (9,5%) pacientes fallecieron antes del alta; a 3 de ellos se les practicó una angioplastia primaria, y no hubo necesidad de nueva revascularización. La mediana de seguimiento fue de 288 días (media, 315 ± 241). Otros 4 (9,5%) fallecieron después del alta, en los días 5, 24, 34 y 115. Se repitió la angioplastia en un caso y en otro se practicó un trasplante.

Conclusiones. Los *stents* liberadores de fármacos representan una alternativa para los pacientes con lesiones en el tronco que no son candidatos a cirugía. Se deberían hacer estudios aleatorizados con seguimiento a largo plazo para valorar su validez en pacientes elegibles para cirugía.

Palabras clave: *Tronco coronario. Stent. Angioplastia coronaria. Revascularización.*

INTRODUCTION

Left main coronary artery (LMCA) disease occurs in 5% of the patients with stable angina and 7% of those with recent myocardial infarction.[1] It is found in 3%-5% of the coronary angiographies carried out for chest pain or heart failure.[2] Since the publication of the Veterans Administration Cooperative Study, revascularization surgery has been the treatment of choice[3] with an associated mortality <5%.[4,5] Although the number of percutaneous coronary interventions (PCI) has increased exponentially,[6] LMCA lesions continue to be treated surgically[7,8] due to restenosis, its clinical consequences and, above all, to the high number of cardiac events after PCI.

In 2001, Sousa[9-11] published the first series of patients treated with sirolimus-eluting stents, reporting a zero rate of restenosis and the virtual absence of intimal proliferation in the follow-up with intravascular ultrasound (IVUS). Later studies, and those involving paclitaxel-eluting stents, confirmed these results.[12-19] Although initial drug-eluting stents (DES) studies were done in patients with selected lesions, in current practice their use is more widespread and the promising results make it possible to consider extending their indications to patients who previously were not candidates for PCI.[20] Although the use of DES could involve an estimated 20% reduction in the number of surgical interventions,[21] this percentage could be greater due to the exclusion, in the study mentioned, of lesions that in the future could also be managed with these devices.

Percutaneous coronary interventions in LMCA lesions are gradually beginning to be done with DES. Published data are still scarce,[22-28] but the results obtained are beginning to lead to changes in the guidelines.[29] The purpose of this study is to describe the results of implanting DES in patients with LMCA lesions who were poor candidates for surgical revascularization.

PATIENTS AND METHOD

Patients

This was a prospective study of all the patients with LMCA lesions treated with DES in 2 centers between May 2002 and April 2004. Indications included all types of coronary disease, including myocardial infarction. In all cases, except for emergencies, the therapeutic options were assessed during a medico-surgical group meeting and patients with contraindications for surgery were scheduled for PCI.

Procedure

The stents used were Cypher® (Cordis Corp. Johnson & Johnson) and Taxus® (Boston Scientific Corporation). The choice of the type of stent, the technique (direct or with predilatation), and the use of abciximab or an intraaortic balloon pump depended on the operator. A loading dose of 300 mg clopidogrel was administered 48 h before PCI to all patients, except in the emergency cases. A pre- and postintervention electrocardiogram was done and we measured creatine kinase (CK) and CK-MB fraction 8 h and 24 h after the procedure. At discharge the patients were prescribed 100 mg of acetylsalicylic acid daily on a permanent basis, and 75 mg clopidogrel daily, initially for 3 months and subsequently for 6 months depending on changes in the protocol. Informed consent was obtained for PCI in all cases.

Follow-up

A prospective clinical follow-up by telephone was done every month and initially at 6 months at the clinic. From the 16th patient onwards follow-up was carried out every 4 months. In addition, all patients underwent clinical follow-up before drafting the report thus providing us with the maximum follow-up time. Deaths were classified as cardiac and non-cardiac. Those due to indeterminate causes were considered cardiac.

Angiographic and IVUS follow-up was scheduled initially at 6 months, but was subsequently brought forward to 4 months. The quantitative analysis of the lesions was done offline with a previously validated margin detection system (CAAS II®, V4.1.1. Pie Medical Imaging, Maastricht, The Netherlands). For the IVUS study ClearView® and Galaxy® 2 systems were used with Atlantis SR Plus® 40 MHz catheters (Boston Scientific Corporation).

Definitions

Surgical contraindication. After evaluation in the medico-surgical group meeting, the case was considered to be at high risk or there was diffuse disease in distal vessels <1.5 cm diameter.

Calcification. Mild: single or multiple image of non-linear well-defined calcium density, located on the target lesion. Moderate: image of linear calcium density, located on one side of the target lesion and

TABLE 1. **Clinical Characteristics of the Patients (n=42)**[*]

	Number	Percentage
Age, years[†]	70.1±10.5 (44-85)	–
Males	25	59.5
DM	14	33.3
AHT	20	47.6
Hypercholesterolemia	26	61.9
Smoking	19	45.2
Previous AMI	18	42.9
Previous PCI	8	19
Previous surgery	11	26.2
Protected LMCA	7	16.7
Diseased vessels		
Two vessels	15	35.5
Three vessels	27	64.3
Ventricular dysfunction		
No	15	37.5
Light, 46%-60%	11	26.2
Moderate, 30%-45%	13	31
Severe, <30%	3	7.1
Abciximab	27	64.3
Shock	6	14.3
Balloon pump	19	45.2
Indications		
Angina	35	83.3
Primary or rescue	5	11.9
AMI and later ischemia	2	4.8
Reason for rejecting surgery		
Poor vessels	19	45.2
Reintervention	9	21.4
Age	6	14.3
Primary PCI	5	11.9
Other	1	7.2

*RS indicates revascularization surgery; DM, diabetes mellitus; AHT, arterial hypertension; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention.
†Mean ± standard deviation (range).

non-visible under detailed fluoroscopic imaging. Severe: linear calcium density image located on both sides of the target lesion and visible under detailed fluoroscopic imaging.

Myocardial infarction. Elevated CK equal to or more than twice the normal value.

Protected left main coronary artery. Presence of at least one patent bypass graft to the left coronary artery.

Restenosis: Stenosis ≥50% at follow-up, measured via quantitative analysis.

Distal location. Need to cover the circumflex artery with the stent.

Two-vessel disease. Left main coronary artery disease without lesions >50% in the right coronary artery, regardless of the state of the anterior descending coronary artery or circumflex artery.

Three-vessel disease. Left main coronary artery disease with lesions >50% in the right coronary artery, regardless of the state of the anterior descending coronary artery or circumflex artery.

TABLE 2. **Characteristics of the Lesions (n=42)**[*]

	Number	Percentage
Location		
Ostial	5	11.9
Medial	8	19
Distal	20	47.6
Diffuse	9	21.4
Calcification		
Absent	12	28.6
Light	9	21.4
Moderate	11	26.2
Severe	10	23.8
Restenosis	4	9.5
ACC/AHA		
A	1	2.4
B1	3	7.1
B2	18	42.9
C	20	47.6
Reference diameter, mm	3.09±0.32	-
Previous stenosis, %	–	77.6±12.3
Pre-PCI MLD, mm	0.82±0.42	–
Length, mm	8.7±4.2	–

*ACC/AHA indicates American College of Cardiology and American Heart Association; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and qualitative variables as absolute value and percentage. Student's t test was used to compare means and χ^2 for proportions. Data were analyzed with SPSS version 12.0 for Windows.

RESULTS

The 42 patients that composed the study population were treated with DES in the LMCA between May 2002 and April 2004 in the 2 centers. The mean age was 70.1±10.5 years and 33% were diabetic. The indication was primary PCI in 5 cases (11.9%) and 6 (14.3%) were in shock. Eleven (26.2%) patients had a history of previous surgical revascularization but only 7 (16.3%) had protected LMCA. Patient characteristics are presented in Table 1.

Angiographic characteristics of the lesions are shown in Table 2. Despite being short lesions, a large number of them were complex; 88% were type B2 and C, mainly due to being calcified, their ostial location or bifurcation disease of the anterior descending coronary artery or circumflex artery. Four of these involved restenosis of a previous stent.

The results of the procedure are shown in Table 3. Four patients died before discharge. One patient was a 73-year-old with an ejection fraction of 25% and severe mitral regurgitation who was not a candidate for surgical revascularization due to poor distal beds, nor

was there any possibility of valve replacement due to severe ventricular dysfunction. The procedure ended successfully but it was impossible to remove the balloon pump. Ten days later, severe right leg ischemia occurred due to the balloon pump, thus entailing an embolectomy. The patient died of acute pulmonary edema. The other 3 patients were undergoing primary PCI for cardiogenic shock. The first was an 85-year-old patient with a severely calcified left main coronary artery, peripheral vascular disease, and acute pulmonary edema, in whom a balloon pump could not be deployed, and who died 1 h after PCI. The second was a 69-year-old patient with a history of previous extensive acute myocardial infarction (AMI) and severe ventricular dysfunction 1 year before the current episode, who presented cardiorespiratory arrest at home entailing prolonged resuscitation. In addition to a stent in the LMCA, 2 stents were implanted in the descending anterior coronary artery. A subsequent computerized tomography showed severe anoxic encephalopathy with cerebral edema. The patient died 10 days after PCI. The third patient was undergoing primary PCI and died of hemorrhagic complications. No infarctions or need for new revascularization took place before discharge.

Median follow-up time for discharged patients was 288 days (mean, 315±241). Of the 38 patients discharged, 4 died during follow-up, all from cardiac causes. The procedures were elective with a favorable hospital course. The first was a 72-year-old patient admitted for previous extensive AMI and with an ejection fraction of 33% who died 5 days after discharge due to acute pulmonary edema. The second patient, 70 years old with an ejection fraction of 48%, died 24 days later due to possible anterior reinfarction. A second Cypher® stent had been implanted over 1 implanted 10 months before for restenosis. The third patient, 75 years old with a systolic function of 33%, died 34 days later also due to possible anterior reinfarction. The last was an 83-year-old woman with an ejection fraction of 49% who died of sudden death 4 months after the procedure. In one patient, PCI was repeated and a Cypher® stent was implanted again. This was the patient who died 24 days after discharge following the second procedure. Finally, 1 patient needed heart transplantation 6 months after PCI due to a very depressed ejection fraction with dyspnea despite the percutaneous treatment.

Data on patients who had angiographic and IVUS follow-up is presented in Table 4. Angiographic and IVUS follow-up was done in 25 of the 34 patients who survived for more than 4 months. Of the 9 remaining patients, 6 refused follow-up catheterization due to age (79.6±3.2 years), and the other 3 still have not completed the follow-up period. In the first 16 cases, coronary angiography was carried out at 6 months. In the

TABLE 3. Procedure Outcome (n=42)*

	Number	Percentage
Procedural success	41	97
Post-PCI reference diameter, mm	3.13±0.29	–
Post-PCI MLD	2.96±0.35	–
Post-PCI stenosis	–	4.3±7.2
Stent length, mm	14.4±7.5	–
Nominal stent diameter, mm	3.02±0.30	–
2.5	6	14.3
2.75	2	4.8
3	25	59.5
3.5	9	21.4
Pressure, atm	14.70±2.8	–
Direct stenting	12	28.6
Number of stents per lesion		
One	40	95.5
Two	1	2.4
Three	1	2.4
Need for postdilatation	7	16.7
Stenting the circumflex artery	24	57.1
Occlusion of circumflex branch	1	2.4
Type of stent		
Cypher	30	71.4
Taxus	12	18.6

*MLD indicates postintervention minimum lumen diameter: PCI, percutaneous coronary intervention.

TABLE 4. Follow-up With Angiography and IVUS

Angiography	
Reference diameter, mm	3.22±0.34
Minimum lumen diameter, mm	2.97±0.36
Stenosis, %	7.7±7.8

IVUS	
Reference diameter, mm	3.34±0.48
Minimum lumen diameter, mm	2.72±0.51
In-stent area, mm^2	6.66±1.92
Vessel reference area, mm^2	15.03±4.36

remaining patients, this was anticipated at 4 months to detect possible restenosis earlier. Underexpansion of the stent was found in 16 (70%) patients; thus, from the thirty-second patient onward, we began to use IVUS for the implantation. Restenosis was found in one patient, with no cases of poor apposition.

DISCUSSION

In the Spanish Society of Cardiology guidelines, PCI in favorable lesions and with protected LMCA or in cases of unprotected LMCA and high surgical risk constitute a class IIa indication.[8] In this study we analyzed the results of DES in patients with LMCA lesions who were poor candidates for surgical revascula-

rization. The most important finding is the favorable outcome in selected patients, as well as the unfavorable evolution of the patients with doubtful indications for percutaneous revascularization or PCI for acute AMI. The use of a suitable technique is particularly decisive in this type of intervention. Finally, distal location requiring stenting the circumflex artery does not seem to add to the risk.

In-Hospital Mortality

As in previous series,[24-28] in-hospital evolution of the elective patients was very favorable and the deaths occurring before discharge cannot be directly related to DES. In the only case where PCI was not primary, this was caused by a reduced ejection fraction and severe mitral regurgitation due to the aortic balloon pump. In the other cases, as well as in published series,[22,30-33] in-hospital mortality was very high (50%) in the patients in the acute phase of infarction and with LMCA lesions, thereby demonstrating the seriousness of the situation.

Out-of-Hospital Mortality

Survival was similar to previous series,[31,34-36] as was mortality which was greater in the first months.[36-39] In our series, the 4 deaths after discharge and before 4 months could have been due to 3 causes:

1. Low ejection fraction: this was around 30% in 2 of the patients. This could have contributed to the event, especially in one of them, where the diagnosis was acute pulmonary edema. This factor can also induce cardiac arrhythmias contributing to mortality.[31]

2. Progression of the disease. This is a very significant cause of mortality in the first months.[40] In our series, despite DES being used, the first patients were scheduled for angiographic follow-up at 6 months, and therefore this cannot be ruled out as a cause of death in the 4 patients who died. This has been previously described.[41]

3. Finally, subacute and late thrombosis could have contributed to mortality. Two of the patients died 24 and 34 days following implantation. As neither correct expansion nor stent apposition was verified via IVUS at the end of the procedure, the involvement of a thrombotic mechanism cannot be ruled out. On the other hand, combined antiplatelet therapy was maintained for only 3 months in the first cases. Following the appearance of cases of late thrombosis,[42-44] current recommendations indicate extended combined antiplatelet therapy in patients with DES for 6 months minimum, although some authors state that until the situation is better understood, this should be maintained indefinitely.[43] Thus, in our series, late thrombosis could have contributed to mortality in the patient who

died 4 months after the procedure, given that aspirin was the only medication administered. In any case, this series involved patients with a high baseline risk, of whom only eight (19%) could be considered as low risk for PCI according to the criteria used by Tan et al.[37]

Reference and Stent Diameter

According to previous studies, post-PCI minimum lumen diameter is an independent predictor of events,[45-51] and, among other factors, depends on the reference diameter. In our series the reference diameter was 3.09±0.32 mm, and stents more than 3 mm were only used in 20% of patients. In other published series reference diameters were greater.[25,27,28] Several factors might have influenced the choice of the stent diameter. First, a high percentage of patients were elderly with very diffuse disease in whom it was impossible to implant stents with a larger diameter. Second, in up to 7 patients, overdilatation with a higher caliber balloon was required as a stent with a suitable diameter was unavailable. Finally, this series does not represent the total set of patients treated with PCI in the LMCA in these 2 centers, since patients in whom the reference diameter was greater than 4 mm were treated with conventional stents.

Revascularization During Follow-up

Only 1 patient required revascularization. This is a much lower frequency than in other series with conventional stents.[34,36] This decrease in the rate of restenosis can be attributed to the effects of DES. However, given the late timing of angiographic follow-up, this could have been underestimated and may have manifested as sudden death in some of the early deaths, especially in the patient who died in the fourth month. In one study, restenosis was considered the cause of sudden death in 9% of the patients.[40] In our series, the first cases were scheduled for follow-up at 6 months, but subsequently this was brought forward to 4 months, in line with previous studies[37] that stress the need for early detection of restenosis. There is still a lack of data to assess whether a later angiographic follow-up is also advisable. This is an important issue and should be clarified in future studies, since, on the one hand, it is already known that DES[52] show a late restenosis pattern. On the other hand, this pattern might require a greater number of follow-ups in the first year, although in some cases this would take place in elderly patients or in those with a poor baseline situation. Until objective data become available, decisions regarding the timing of follow-up should be tailored according to the patient's characteristics.

The Importance of Using IVUS for Implantation of DES in the LMCA

Previous studies have demonstrated that up to 80% of implanted stents are not expanded correctly despite appearing to be so under angiography.[53] The relevance of the final diameter after implantation on the event rate is well known.[29,46-51] Hong found that IVUS provided better help in LMCA lesions compared to other lesions[54] which could be due to the frequent presence of calcium. However, other authors have obtained very satisfactory results without IVUS.[28,35] In our series, IVUS was not used during implantation in the first 32 patients. However, we used it systematically after the thirty-second patient due to underexpansion being found in up to 70% of patients when following previously accepted criteria.[55] This effect may have been heightened because of the advanced age of the patients who therefore had a higher calcium content. Due to the high percentage of severe calcification (24%) and not having used rotational atherectomy, the inflation pressures required were very high (16 ± 2.1 atm). Furthermore, IVUS can help in the choice of stent, given the difficulties in ascertaining the reference diameter.[30,41] In a study of LMCA lesions, the post-PCI IVUS area was the only predictor for new revascularization.[56]

Location of the Stenosis

Unlike other series,[57] in our study lesions were treated in all locations, including distal ones affecting the origin of the circumflex artery. This fact may have had more impact in the past when the stents available were less sophisticated.[41] We did not find differences between the different types of anatomies regarding the outcomes of the procedure nor in the long-term. In 1 case, the approach from the beginning was to treat both arteries (anterior descending coronary and circumflex artery) with DES. In the remaining patients, the technique used was to implant the stent in the LMCA and the origin of the anterior descending coronary artery and to treat the circumflex artery later with a new stent if necessary. Using this approach, there was only 1 case of occlusion of a small, non-dominant circumflex artery. Despite the lack of data from other studies, and given the higher rate of restenosis at bifurcations,[41] DES probably contribute to better outcomes in this type of anatomy.

Advisability of Using DES in LMCA Lesions

Although in general no relationship has been found between restenosis and mortality,[58] in the LMCA restenosis can manifest as sudden death.[39,40] Thus, although in our area finances constrain the general use of DES,[59,60] and although models are being created to optimize the benefits of DES,[61] given the limited number of patients with these characteristics and the fatal outcome of restenosis, we consider that DES should be used in all LMCA lesions undergoing PCI, provided the diameter allows for this. Since, to date, there have been no random studies on LMCA lesions which compare DES with conventional stenting, it seems reasonable to expect a decrease in mortality in this subgroup of patients with the new devices.

Study Group Proposal for PCI With DES in the LMCA

We suggest the use of PCI for LMCA lesions in emergency cases (primary and rescue percutaneous transluminal coronary angioplasty) and in patients with excessively high surgical risk. Given the low numbers of these kinds of patients and the fatal outcome of restenosis, we believe that DES should be used in all these patients. Based on the findings on stent underexpansion during follow-up, we believe postintervention IVUS is advisable to ensure correct apposition of the stent to the vessel wall. Finally, based on previous protocols,[37] angiographic follow-up should be scheduled at 3 or 4 months. Studies with longer follow-up could help us make decisions regarding whether a later follow-up would be necessary due to the different behavior of restenosis with DES compared to conventional stenting.

Limitations

The causes of out-of-hospital death were inferred from family reports and emergency teams, but were not verified via catheterization studies or autopsy findings; thus, there could be some bias.

A high percentage of patients included in this series had associated extracardiac disease, very advanced age and reduced ventricular function. In many cases consensus regarding the advisability of interventions in these types of patients can be difficult and many factors, including social ones, have an influence on decision-making. Decisions regarding PCI in this series were individually based, but we cannot objectively provide substantial reasons to support this type of intervention in general. This study cannot provide any data regarding the advisability of later angiographic follow-up and, due to the baseline characteristics of these patients, it is probably appropriate to treat each case individually.

The study protocol did not include use of IVUS during implantation in the first cases. The involvement of stent thrombosis due to underexpansion or malapposition in some of the events cannot be ruled out and thus better outcomes may have been obtained with the systematic use of ultrasound techniques.

CONCLUSIONS

Drug-eluting stents offer an alternative for patients with lesions in the left main coronary artery who are poor candidates for revascularization surgery. The immediate outcome of interventions in acute myocardial infarction are far worse than those in elective cases. The mortality rate found in this series of patients in the first months may not necessarily be reproduced in patients without contraindications for surgery; thus, studies with a long follow-up should be undertaken before recommending this as the treatment of choice in patients with LMCA lesions.

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