

Proximal Left Anterior Descending Coronary Artery Revascularization with Drug-Eluting Stents

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Summary

Objective: To assess the clinical prognosis of patients with coronary artery diseases undergoing percutaneous revascularization with drug-eluting stent implantation in the proximal left anterior descending coronary artery.

Methods: One hundred and seventy consecutive patients with mean age of 65 years, 49 of them females (29%), undergoing implantation of at least one drug-eluting stent in our medical center. The total number of drug-eluting stents implanted was 189, of which 115 (61%) were sirolimus-eluting (CYPHER™) and 74 (39%) were paclitaxel-eluting stents (TAXUS™). In 100 (60%) of the cases, multivessel coronary artery disease was present. In 61 (36%) patients another coronary artery segment was treated in addition to the proximal left anterior descending coronary artery. The mean clinical follow-up period was 11 ± 5 months, and angiographic controls were performed between 6 and 9 months. The final endpoint was a composite of death, acute myocardial infarction and need for reintervention on the anterior descending. The secondary endpoint included the occurrence of restenosis, need for reintervention on the proximal segment of the left anterior descending and stent thrombosis.

Results: The procedure achieved immediate angiographic success in all patients. Two deaths, two acute myocardial infarctions, and two percutaneous coronary reinterventions due to stent thrombosis were recorded during in-hospital stay. At the sixth month of follow-up, an additional cardiac death and three myocardial infarctions were observed; three repeat revascularization procedures were required. Up to the end of the follow-up, three additional deaths, three myocardial infarctions and eight revascularization procedures of the anterior descending, two of them surgical, were verified. Survival free from major adverse cardiac events was 91%. Cardiac mortality was 3%. Binary restenosis in the proximal segment of the left anterior descending coronary artery was 4.1%. Target vessel revascularization-free survival was 94%. No cases of late stent thrombosis were observed.

Conclusion: Percutaneous revascularization of the proximal left anterior descending coronary artery with implantation of drug-eluting stents is a safe and very efficient therapeutic strategy in the short and long terms.

Key words: Angioplasty, transluminal, percutaneous coronary; stent; sirolimus; paclitaxel.

Introduction

The left anterior descending coronary artery is responsible for the blood flow that reaches up to 70% of the left ventricular myocardial mass. As a result, proximal left anterior descending (PAD) coronary artery disease leads to ischemic impairment of a significant myocardial territory, thus contributing to the poor prognosis of individuals with coronary artery disease in this location¹.

Surgical revascularization with internal mammary artery bypass grafts or percutaneous stent implantation have proven to be safe and efficient strategies in the relief of symptoms. However, even considering the advantages of Percutaneous Coronary Intervention (PCI) such as less invasiveness, immediate procedural success, short hospital stay, and quick

recovery, results of multi-center randomized clinical trials (RCT) comparing the two treatment options directly show that patients undergoing surgical revascularization have significantly less need for reintervention in the long term². Despite offering better results than balloon angioplasty, the elective implantation of a conventional (bare-metal) stent is still frequently associated with the need for target vessel revascularization (TVR) due to restenosis, the "Achilles' heel" of PCI.

With the introduction of a new generation of drug-eluting stents (DES), late angiographic restenosis rates have consistently shown to be clearly lower than those observed with bare-metal stent implantation^{3,4}. In recent RCT, the use of DES with Sirolimus and Paclitaxel in the treatment of PAD resulted in low rates of TVR, of 6.0% and 7.9%, respectively^{5,6}, at the end of one year, which leads to the hypothesis that DES will likely reduce or even outweigh the only advantage offered by the surgical treatment of PAD coronary artery disease.

As such, we conducted the evaluation of long-term

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Original Article

clinical prognosis of a consecutive series of patients with coronary artery disease undergoing PCI with DES implantation in the PAD. Simple clinical and angiographic measurements were obtained to provide a basis for comparison with similar studies:

a) Major Adverse Cardiac Events (MACE), a composite of Myocardial Infarction (MI), TVR, and Death;

b) Stent Thrombosis (ST), Target Lesion Revascularization rate (TLR), and, whenever a control coronary angiography was obtained, the In-Stent Binary Restenosis (ISR).

Methods

Patients - By analyzing our center's database, we identified all consecutive patients ("all comers") undergoing PCI of the PAD (segment angiographically defined proximally by the ostium of the anterior descending and distally by the bifurcation with the first septal branch) between July 3, 2002 (date when the first DES implantation was performed in our institution) and August 31, 2004, period in which at least one of the following DES was used:

a) **Cypher™** - A slow-rate release polymer-based Sirolimus-eluting stent 140 $\mu\text{g}/\text{cm}^2$ (Cordis Corp., Miami Lakes, Florida).

b) **Taxus™** - A slow-rate release polymer-based Paclitaxel-eluting stent 1.0 $\mu\text{g}/\text{mm}^2$ (Boston Scientific Corp., Natick, Massachusetts).

Coronary angiography, percutaneous revascularization procedure, angiographic control and in-stent restenosis assessment - Left heart catheterization, whenever possible, was performed via the femoral artery approach. In exceptional cases, due to peripheral vascular disease, it was performed via the radial or brachial artery approach.

All patients underwent anticoagulation with unfractionated heparin, so as to obtain an Activated Clotting Time (ACT) between 250-350 seconds, and between 200-250 seconds when using glycoprotein IIb/IIIa inhibitors.

The use of catheters, guide wires, balloons, PCI procedures (approach of bifurcations, direct stenting, distal protection devices, thrombus aspiration, etc) and coadjuvant pharmacological treatment was left to the surgeon's discretion, following available recommendations.

Angiographic success was defined as a residual angiographic stenosis lower than 20% as assessed by visual estimate, and distal flow equal to or greater than TIMI (Thrombolysis In Myocardial Infarction) grade II.

Patients underwent antiaggregation with both aspirin 150-200mg, id, and Clopidogrel 75mg, id, for at least 90 days. Antiaggregation with aspirin was further indefinitely maintained.

Angiographic control was performed between the 6th and 9th months. In 61 (36%) patients the performance of coronary angiography was associated with their inclusion in clinical trials. The remaining patients were referred to control coronary angiography for the protocol conducted in our center after giving their written consent. At least two orthogonal projections identical to those of the control performed immediately after

stent implantation were obtained. In-stent restenosis (ISR) was considered whenever the percentage of luminal loss in relation to the vessel's reference diameter was greater than 50% using quantitative coronary analysis. The 5mm proximal and 5mm distal to the stent edges were included in the analysis. The ISR was considered focal (single and localized lesion with less than 10mm extension), diffuse (with more than 10mm extension), proliferative (when, in addition to being diffuse, it extended beyond one of the edges of the stent), or occlusive (complete).

Data analyzed - Data concerning the clinical follow-up (in-hospital, at 30 days, at 6 months, and at the last follow-up day, March 31, 2005) were obtained by analyzing database records and by phone contact with all patients included in the study. Angiographic control was performed between the 6th and 9th months after DES implantation. A final endpoint composite of MI, TVR and Death was obtained.

MI was defined by the onset of Q waves or the recording of enzyme elevation of creatine phosphokinase greater than three times the reference values when associated with clinical or electrocardiographic manifestations suggestive of acute myocardial ischemia.

The secondary endpoints included ISR, TLR, and Stent Thrombosis (ST). The latter was considered acute up to 24 hours; subacute between 24 hours and 30 days; and late after 30 days post-procedure.

The following parameters were also analyzed:

a) Demographic parameters: age and gender;

b) Classical cardiovascular risk factors: high blood pressure, diabetes, smoking, dyslipidemia, and family history of early-onset coronary artery disease before 55 years of age in first-degree relatives;

c) Past history of relevant cardiovascular events: myocardial infarction and surgical and/or percutaneous coronary revascularization;

d) Clinical characteristics that indicated PCI: unstable angina, progressive angina, and acute coronary syndrome;

e) Urgency of the procedure: bail out, elective or urgent.

f) Technical and angiographic characteristics of the procedure:

f.1) Type of lesion – de novo versus target lesion treated with PCI or aortocoronary bypass;

f.2) Type of lesion according to the American Heart Association classification

f.3) Use of glycoprotein IIb/IIIa inhibitors, stent diameter, stent length, and procedural success;

g) Left ventricular function (as analyzed by left ventriculography)

Statistical analysis - Quantitative variables were expressed as mean \pm standard deviation, and discrete variables were expressed as percentages. Cumulative analysis of event-free survival was expressed by Kaplan-Meier survival curves. The SPSS 11.0 (Chicago, Illinois) statistical program was used for this analysis.

Results

Characterization of patients and of the revascularization procedure - The description of patients involved in this study is shown in Table 1. Mean age was 65 years. We point out the predominance of males (71%), the previous occurrence of MI in approximately half of the patients evaluated, the high prevalence of diabetic patients (40%; n=58), and a considerable number of patients previously treated with PCI in this segment (18%; n=31). The most relevant clinical and angiographic characteristics and those regarding the percutaneous revascularization procedure are shown in Table 2. The procedure was elective in 47% (n = 79) of the cases. One fourth of the patients were clinically unstable (acute coronary syndrome) and one third had impaired global left ventricular systolic function.

In 40% (n = 70), isolated PAD disease was observed. In 15% (n = 26) of the patients, a coronary lesion located in another segment was treated during the same procedure. The use of glycoprotein IIb/IIIa inhibitors was not frequent. Only 19% (n = 33) of the patients underwent this treatment.

The great majority of the lesions treated were complex: 78% (n = 134) were type B2 or C. One point one DES were implanted per patient, more Cypher™ (61%; n = 115) than Taxus™ (39%; n = 74), with a mean 3.0 ± 0.4mm diameter and mean 21.2 ± 9.5mm length. Angiographic success was achieved in 100% (n = 170). One case of acute thrombosis 10 minutes after PCI was recorded in a patient with MI undergoing rescue angioplasty. No periprocedural deaths were verified.

Clinical and angiographic follow-up characterization - One hundred and sixty nine (99.4%) patients were clinically followed for at least 180 days. Mean follow-up was 333 ± 148 days. Angiographic controls were obtained in 84 (51%) patients between 6 and 9 months. In-hospital and 30-day Outcomes

In addition to the case of acute thrombosis in the operation

Females	49 (29%)
Mean age	65 ± 11 years
Hypertension	92 (54%)
Dyslipidemia	99 (58%)
Smoking	87 (51%)
Diabetes	58 (40%)
Previous MI	80 (47%)
Previous PCI	60 (35%)
Previous CABG	6 (4.0%)
ISR of PAD	31 (18%)
Included in RCT	74 (44%)

MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; PVD - peripheral vascular disease; ISR – in-stent restenosis; PAD – proximal left anterior descending; RCT – randomized clinical trials

Table 1 – Population characteristics (n = 170)

Elective PCI	79 (47%)
ACS	38 (22%)
LVEF < 50%	47 (28%)
Isolated PAD disease	70 (40%)
Multivessel PCI	26 (15%)
Use of GP IIa/IIIb inhibitors	33 (19%)
B2 and C lesions	134 (78%)
Cypher® Stent group	103 (61%)
Taxus® Stent group	67 (39%)
Direct stenting	48 (28%)
Stent length (mm)	21,2 ± 9,5
Stent diameter (mm)	3,0 ± 0,4
Max. implantation pressure	16 ± 3
Angiographic success	170 (100%)
Acute occlusion	1 (0,6%)
Death in operation room	0 (0%)

PCI – percutaneous coronary intervention; ACS – acute coronary syndrome; LVEF – left ventricular ejection fraction; PAD – proximal left anterior descending; GP – glycoprotein

Table 2 - Characterization of clinical and angiographic profiles, and of the percutaneous intervention procedure (n = 170)

room, two other cases of subacute thrombosis (ST) were verified in the setting of primary angioplasty. Of the three ST, two were treated with balloon angioplasty associated with abciximab. One cardiac death resulted from this context immediately prior to reintervention. One additional in-hospital death (0.6%) not related to DES implantation was observed. The patient was a 78-year-old woman with diabetes and previous MI, who had been referred for primary angioplasty because she presented with a three-vessel disease and severe global impairment of the left ventricular systolic function. PCI of the PAD with intra-aortic balloon counterpulsation support was performed, but the patient died in cardiogenic shock at the third day in the coronary unit.

At the 19th day, a percutaneous reintervention in the mid-segment of the AD was performed to treat a de novo lesion, and the good angiographic result of the previous implantation of DES in the PAD was maintained.

Six-month outcomes - An 82-year-old female patient died of acute myocardial infarction at the 77th day. She had a previous history of three-vessel PCI, including multiple percutaneous interventions in the PAD due to ISR.

In-hospital MACE and at 30 days and 6 months of follow-up are described in Figure 1. We point out the relevant role of stent thrombosis in these events. Half of the accumulated MACE (3.6%) at 6 months results from 3 ST (1.8%).

End of follow-up outcomes - After 6 months, the post-PCI coronary angiographies performed in 84 (51%) of the 170 patients included in our series revealed 7 cases of ISR (8.3% of the population undergoing angiographic control and 4.1% of the total population), observed between days 191 and

Original Article

386, and accounting for 43% of the final MACE. Four were located in the proximal edge, two along the stent and one in the distal edge of the stent. In most of the cases the ISR were focal (5 cases). Three patients were asymptomatic. In the management of ISR, 6 patients underwent repeat PAD revascularization (3 with PCI with DES, 1 with balloon PCI, 1 with brachytherapy and balloon angioplasty, and 1 with left internal mammary bypass to the AD), and one patient was only medically treated.

The characterization of ISR, its impact on MACE, and the treatment options available can be observed in Figures 2 and 3.

In addition to the need for repeat revascularization of the PAD due to ISR, an aortocoronary bypass surgery due to progression of the disease located in the common trunk

was performed in a 69-year-old female patient with diabetes treated with insulin, chronic renal failure (CRF), and impaired left ventricular function, who died in the postoperative period in cardiogenic shock.

Two additional deaths occurred. At day 182, a 60-year-old male patient with a previous history of two-vessel revascularization, depressed left ventricular function and severe mitral regurgitation died of a stroke. A 74-year-old female patient with CRF undergoing dialysis and previous 3-vessel percutaneous coronary revascularization died at day 216 of follow-up in the emergency room where she was admitted in cardiac arrest.

In total, 23 events were recorded (6 deaths, 6 MI, 9 PCI, and 2 aortocoronary bypass surgeries) in 15 (9%) of the patients (Fig. 4). The rates of TLR and TVR were 5% and 6%,

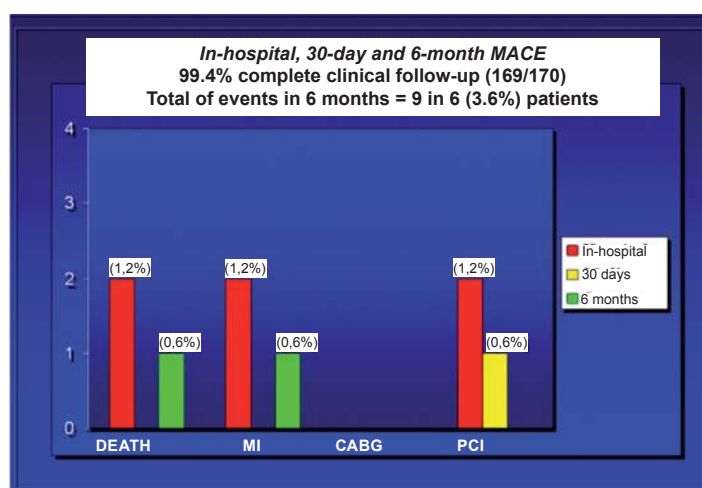


Fig. 1 - In-hospital outcomes, and at 30 days and 6 months of follow-up. MACE (Major Adverse Cardiac Events); MI (Myocardial Infarction); CABG (Coronary Artery Bypass Grafting); PCI (Percutaneous Coronary Intervention)

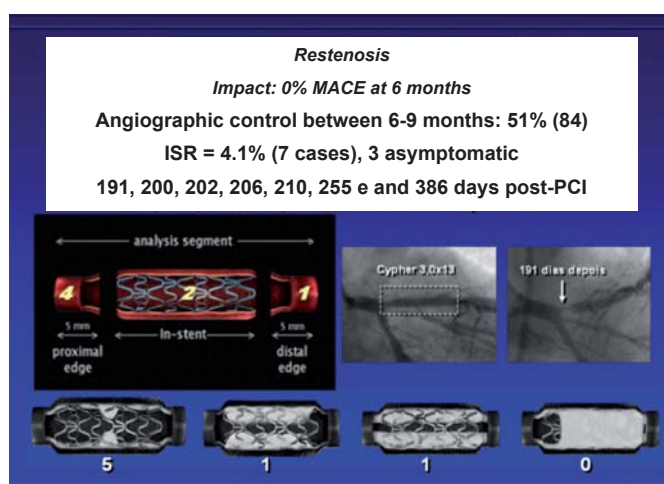


Fig. 2 - Characterization of Restenosis. ISR (In-Stent Restenosis); MACE (Major Adverse Cardiac Events); PCI (Percutaneous Coronary Intervention)

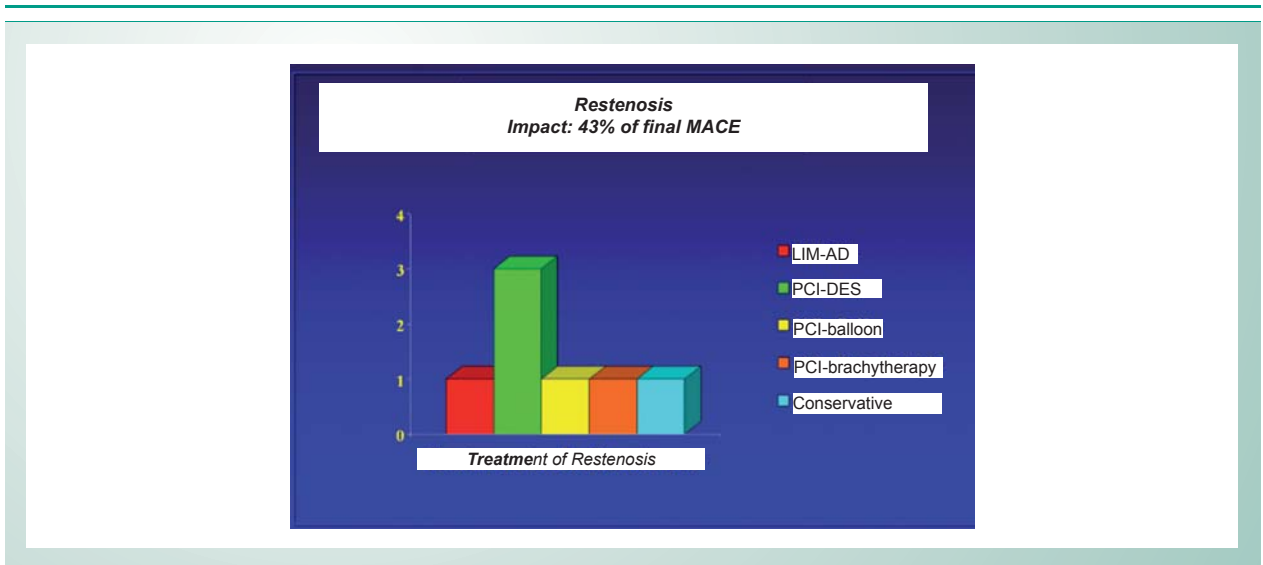


Fig. 3 - Treatment of Restenosis. MACE (Major Adverse Cardiac Events); PCI (Percutaneous Coronary Intervention); LIM-AD (left internal mammary bypass to the anterior descending); DES (drug eluting stents)

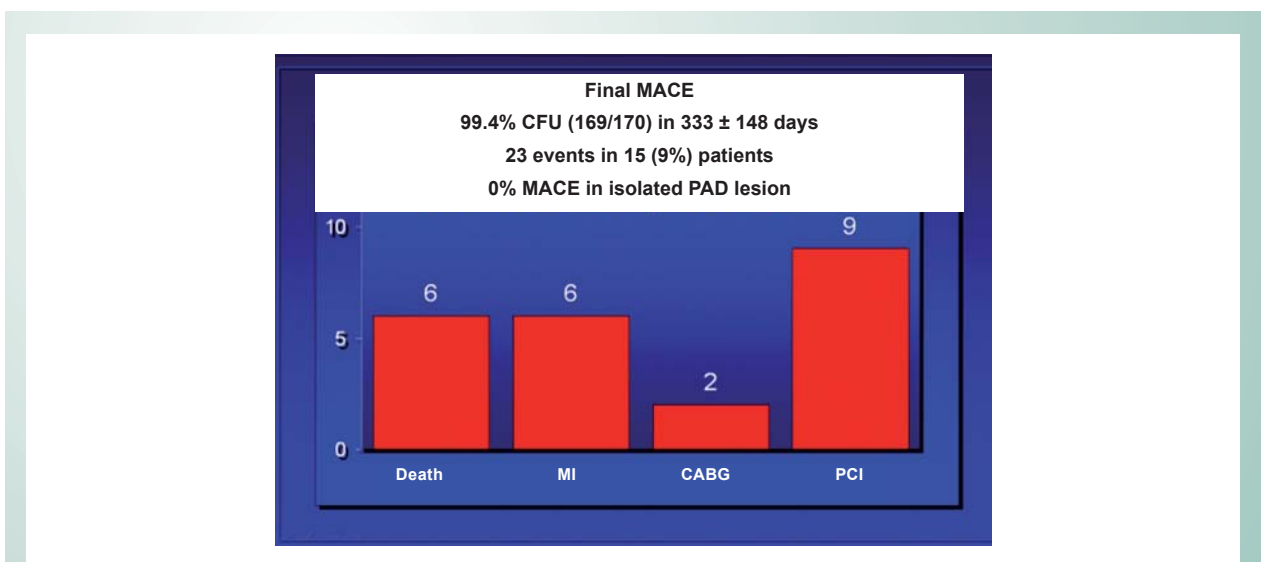


Fig. 4 - Outcomes at the end of the follow-up period. MACE (Major Adverse Cardiac Events); MI (myocardial infarction); CABG (coronary artery bypass grafting); PCI (percutaneous coronary intervention)

respectively. We should point out that in the subgroup of patients with isolated PAD lesion no MACE was observed.

MACE-free survival curves (Kaplan-Meier) are shown in Figure 5.

Discussion

Since September 19, 1977, when Andreas Gruntzig first performed a percutaneous coronary angioplasty (out of curiosity, it was performed in the PAD and after 24 years no signs of significant luminal loss were observed)^{7,8}, percutaneous coronary intervention has tried to gain recognition as the technique of choice for myocardial revascularization. Things were hard at the beginning, because the simple balloon dilatation would cause accidents during the procedure, which

were frequently irreversible (coronary dissection and acute occlusions) and had very high rates (approximately 40-50%) of restenosis in the first year and, consequently, a high need (more than 30%) for repeat target-vessel revascularization⁹.

In the late 1980's, cardiac surgery was the treatment of choice for more complex patients with coronary artery disease (those with diabetes, disease involving the common trunk or PAD, three-vessel disease, ostial disease, chronic occlusions, bifurcations, calcified and long lesion, etc)¹⁰. In the 1990's, bare-metal stents enabled the efficient treatment of acute complications of balloon angioplasty and substantially reduced the advantage of surgery in the treatment of coronary artery disease^{11,12}. In the RCT comparing PCI with bare-metal stent and surgical revascularization, the difference in MI and mortality rates was always consistently zero. However, the

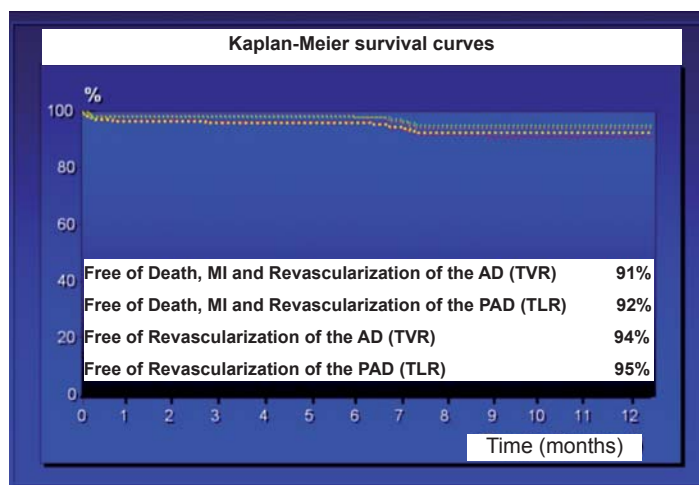


Fig. 5 - Kaplan-Meier Survival Curves. AD (anterior descending); PAD (proximal left anterior descending).

need for repeat procedures for target vessel revascularization remained significantly higher (18% vs. 4.4%; Odds ratio 4.4, 95%CI: 3.3-5.9) in those undergoing percutaneous treatment².

Six RCT¹³⁻¹⁸ comparing left internal mammary (LIM) artery bypass grafts directly with PCI with bare-metal stents were published. In all of them, the TVR rate was significantly higher, reaching 28% for the group undergoing percutaneous revascularization.

In the beginning of this century, a new generation of stents coated with inhibitors of intimal hyperplasia was developed. The first RCT with DES¹⁹ showed excellent results and even editorials were written²⁰ stating that the dream had come true because the first results of this study reported zero percent restenosis! Unfortunately, this phenomenon was soon demonstrated to keep occurring, but now at a quite lower and unprecedented incidence when compared with that obtained with bare-metal stents (3.2% versus 35.4%; $p < 0.001$)³.

After the short and midterm safety and efficacy of these new stents were verified²², some of the setbacks for percutaneous revascularization have been progressively overcome, and studies assessing DES in the treatment of lesions in the common trunk, bifurcations, chronic occlusions, and in sites previously treated with PCI have already been published with encouraging results²³.

However, our discussion is aimed at showing the level of maximum evidence in relation to PAD treatment with these two new stents: two RCT^{24,25} compared the implantation of DES directly with internal mammary artery bypass using a minimally invasive off-pump approach in patients with PAD disease. Both show similar final outcomes with the two strategies: a low MACE and similar TVR rate are observed in one of the studies (1.7% vs. 5.9%), and a slightly less favorable result (although quite better than that observed with bare-metal stents) for PCI in the other study (14% vs. 2%). Final

outcomes of the Sirius and Taxus IV RCT are also available, as regards the subgroup with PAD disease^{5,6}. At the end of one year, the TVR rate is 6.0% and 7.9%, respectively.

In our case series, the cardiac mortality observed (3.0%) was slightly higher than in the RCT, but this fact can be a consequence of the high risk of the patients treated (60% with multivessel disease, 40% diabetics, 28% with impaired left ventricular function, and 18% with previous PCI in the PAD). An explanation for this situation could be the preferential use of DES in patients with these clinical presentations.

The three (1.8%) ST recorded, one acute and three subacute, accounting for half of the MACE at 6 months, were observed with primary angioplasty. In this context, the heavy thrombotic burden related to acute myocardial infarction may have determined the occurrence of these events.

On the other hand, the results regarding MACE-free (91%), TVR-free (94%), and TLR-free (95%) survival are consistent with those obtained in studies that have been conducted with DES in the PAD.

Even when the methodological limitations of our study are considered (a retrospective, non-randomized study without a control group and with only half of the patients undergoing further angiographic control of PCI), we think we can state that PCI in the PAD with DES seems to be a safe and efficient strategy both in the short and the long term, with results comparable to those of surgical revascularization, even when the latter uses the current state-of-the-art technique – a minimally invasive off-pump surgery.

Conclusions

Percutaneous coronary intervention in the proximal left anterior descending artery with implantation of drug-eluting stents showed a low need for TVR (6%) and TLR (5%) in our series of non-selected consecutive patients in the long term. No cases of late stent thrombosis were recorded. Total MACE of

this record (9% at 11 months of clinical follow-up) is consistent with those observed in the large randomized and multi-center studies with drug-eluting stents implanted in the proximal left anterior descending artery. The results shown are likewise comparable with those obtained with surgical myocardial revascularization with internal mammary artery bypass for the anterior descending artery. Thus, the authors conclude that

this is a safe and efficient strategy that can be an alternative to surgical treatment in technically favorable cases.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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