Long-Term Follow-Up of Patients with Proximal Left Anterior Descending Coronary Artery Stenosis Treated with Stent

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Introduction and objective. Patients with lesions of the proximal left anterior descending coronary artery are a special high-risk group. In the present study we analyzed the efficacy and safety of coronary stenting in such lesions and the factors related to a less favorable prognosis in long-term follow-up.

Methods. Ninety-eight consecutive patients with severe left anterior descending artery stenosis were enrolled, all with coronary angioplasty and elective stenting. Clinical follow-up was carried out annually in all patients by personal interview or telephone contact. The incidence of death, new infarction, anginal status, and new revascularization procedures was registered. Clinical, angiographic, and procedural variables were analyzed to identify predictors of long term prognosis.

Results. Mean follow-up was 38 ± 11 months. There was only one major periprocedural complication, which required urgent surgery. Five deaths were registered, 3 of non-cardiac and 2 of cardiac origin. Twenty-five patients developed angina and 11 underwent a new revascularization of the proximal left anterior descending coronary artery (6 surgical and 5 angioplasty). Two patients had new anterior myocardial infarction. At 60 months the major cardiac event-free rate was 83.7% and the cardiac death-free rate was 98%. The use of two stents and the association of diabetes-hypertension-hypercholesterolemia were associated with a less favorable prognosis in our population.

Conclusions. Stenting of left anterior descending coronary stenosis was safe and effective in a long-term analysis. The survival rate was high and the incidence of new revascularization was low.

Key words: Coronary disease. Stents. Prognosis. Survival. Follow-up studies.

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Seguimiento a largo plazo de pacientes con estenosis de la arteria coronaria descendente anterior proximal tratadas con stent

Introducción y objetivo. Las lesiones de la arteria coronaria descendente anterior proximal suponen un subgrupo de especial riesgo. El objetivo del presente estudio fue determinar la seguridad y efectividad del tratamiento con stent de dichas lesiones a largo plazo, así como los factores pronósticos asociados.

Métodos. Se incluyó un total de 98 casos consecutivos con afección grave de la descendente anterior proximal, a quienes se realizó angioplastia con implantación electiva de stent. Se realizó un seguimiento clínico anual, y se registró incidencia de muerte, nuevo infarto de miocardio, tratamiento farmacológico asociado y necesidad de nueva revascularización.

Resultados. El seguimiento medio fue de 38 ± 11 meses. Se registró un solo caso de complicación grave durante el procedimiento, que requirió cirugía coronaria urgente. Se registraron 5 fallecimientos, tres de origen no cardíaco y dos de origen cardíaco. Veinticinco pacientes presentaron clínica anginosa, de los cuales 11 fueron remitidos para nueva revascularización de la descendente anterior proximal, seis con cirugía con arteria mamaria interna y cinco con nueva angioplastia. Dos pacientes presentaron infarto anterior en el seguimiento. A los 60 meses, la probabilidad de permanecer libre de acontecimientos cardíacos mayores fue del 83.7% y la supervivencia libre de muerte de origen cardiaco fue del 98%. La utilización de 2 stents y la presencia conjunta de diabetes-hipertensión-hipercolesterolemia se asociaron a una peor evolución.

Conclusiones. El tratamiento con stent de las lesiones de la arteria descendente anterior proximal es seguro y efectivo a largo plazo mostrando tasas elevadas de supervivencia y baja incidencia de nuevas revascularizaciones.

INTRODUCTION

Stenosis of the proximal segment of the anterior descending coronary artery (pAD) is a special subgroup of ischemic heart disease, given the high-risk profile that these lesions have alone or in the context of multivessel disease. The quantity and quality of myocardium at risk, which depends on the pAD permeability, makes a more aggressive therapeutic approach necessary. Ultrasound studies in vivo of this type of lesions have shown that vessel involvement is predominantly eccentric. This would explain the worse results obtained after percutaneous transluminal coronary angioplasty (PTCA) in these lesions, due to the phenomenon of elastic retraction. Various studies have compared therapeutic strategies for these lesions, in which better results are generally observed after interventionist treatment (coronary revascularization surgery with internal mammary artery graft [IMA] or percutaneous revascularization versus conventional medical treatment). The present study evaluates the effectiveness and long-term safety of stent implantation in this type of lesions, and was undertaken due to the scarcity of studies on this topic in our area.

METHODS

Study population

A total of 98 consecutive patients referred to our laboratory between April 1995 and April 1998 were included for a prospective, non-randomized, clinical follow-up study. In this period, 1136 PTCA were performed and the study group represents 8.6% of all interventionist procedures carried out in our laboratory in this period. The follow-up concluded in May 2000.

Inclusion and exclusion criteria

Patients who presented significant pAD stenosis (stenosis of more than 70% by visual estimation) before the first septal branch and greater diagonal branch, with evidence of ischemia in the territory dependent on the pAD, were considered eligible for the study. The patients underwent scheduled percutaneous balloon revascularization and stent implantation. Patients referred in the course of acute myocardial infarction (AMI) were excluded, as were lesions with an unsuitable anatomy for the procedure in the judgement of the operator, particularly lesions with chronic occlusion and massive calcification. All patients signed an informed consent protocol before revascularization was performed. The study group included all the patients with pAD lesions treated in our laboratory in this period.

Protocol of procedure (PTCA+stent implantation)

In all the cases PTCA was performed by vascular access through the femoral artery and the stent was implanted (after balloon dilatation) by releasing it at high pressure (12-14 atmospheres). Palmaz-Schatz and NIR stents (the models most used) were mounted manually on the angioplasty balloon. In the last phase of the study, stents that were premounted on the balloon were used. «Angiographic success of the procedure» was defined as the existence of residual lesions of less than 30% by visual assessment of the segment where stent was implanted. «Depressed ejection fraction (EF)» was defined as the presence of an EF of less than 50% in visual assessments. «Multivessel disease» was defined as the presence of significant coronary lesions (stenoses of more than 70% by visual assessment) in two or more vessels. All patients received platelet aggregation inhibitor treatment with acetylsalicylic acid indefinitely and ticlopidine for one month after angioplasty. An i.v. bolus of 7500 to 10 000 IU of heparin was administered before the procedure, depending on the weight of the patient, to obtain partial thromboplastin activation times over 300 s.

Follow-up protocol

All patients participated in an annual clinical follow-up by personal or telephone interview. All of them underwent tests to detect ischemia as ordered by their attending cardiologists. In cases with dubious test results or discrepancies between the clinical symptoms and test results, we ordered new tests to detect ischemia (new exercise stress tests or radionuclide studies). The last visit was in person and a clinical history, physical examination, and ECG were performed. The patients in which angina persisted with clinical criteria of severity underwent angiographic re-evaluation directly in the laboratory. Angiographic restenosis was defined as the presence of stenosis of more than 50% in the pAD segment treated by stent implantation.

A series of variables were recorded in the study group for later analysis and determination of prognostic factors in the clinical evolution of patients. These variables were:
Clinical: age, sex, diagnosis before catheterization, presence of diabetes mellitus, arterial hypertension, smoking, dyslipidemia. Multiple risk factors were considered to exist when three or more classic risk factors were associated.

Anatomic: presence of multivessel disease, left ventricular dysfunction.

Procedure: length and diameter of stent, number of stents used, type of stent, and presence of ostial lesion.

Final events

During hospital admission and the later follow-up, a record was made of the incidence of major adverse cardiac events (MACE) or major complications, defined as: death of cardiac origin, appearance of new AMI, and need for a new pAD revascularization. Noncardiac deaths and the need for revascularization of vessels different from the pAD were recorded.

Statistical analysis

The different variables were compiled in a Microsoft Access® database and analyzed with the SPSS® statistical program, version 9.0. The qualitative variables are expressed as percentages and the quantitative variables as mean±standard deviation (SD). The actuarial curves of death-free survival, cardiac death-free survival, and event-free survival were estimated with the Kaplan-Meier method. In the univariate analysis, the different clinical, angiographic, and procedure variables specified were compared based on the presence or absence of major adverse events at the end of the follow-up, quantitative variables were compared with the Student t test, and qualitative variables with the Chi-square test. In addition, the curves of event-free survival were compared by the log-rank test for the variables that showed a tendency towards the presentation of events ($P<.25$). Multivariate analysis was made by constructing a Cox regression model with the progressive forward incorporation of variables in which independent variables that showed $P<.25$ in univariate analysis were introduced, as well as the variables of first and second-order interactions with the variables AHT, DM, dyslipidemia, and smoking in order to control the effect of the dichotomic variable «association of multiple risk factors». Statistical significance was $P<.05$.

RESULTS

Baseline characteristics

The clinical characteristics of the patients at the time of inclusion in the study and the anatomic characteristics found in coronary arteriography are shown in Table 1. Most patients were referred for unstable angina (87 patients unstable angina, 11 stable effort angina). Twenty-two patients had 3 or more cardiovascular risk factors; of them, 20 (91%) were hypertensive, 19 (86%) were diabetics, and 21 (95%) had dyslipidemia, whereas only 10 (55%) were active smokers. Seventy-one percent (71%) of the patients had a single lesion of the pAD and 70% of them did not evidence ventricular dysfunction in ventriculography.

Procedure

The variables of the procedure are shown in Table 2. Seventy-seven percent (77%) of the patients had short lesions of the pAD, as reflected by the percentage of short stents used (<16 mm). In 89 patients, only one stent was used during revascularization, and in 9 patients, two stents (in 2 cases for dissection and in the other seven, to cover the entire lesion) were both used for pAD treatment; a total of 107 endoprostheses were used. Major complications occurred during the procedure when the stent was dislodged (Palmaz-Schatz stents mounted manually on the undilated balloon) in the trunk of the left coronary artery. The patient was sent for emergency coronary revascularization surgery despite the absence of acute signs during the procedure. In the rest of the treated patients, angiographic success was obtained. This explains the implantation success rate of 98.9%. In another 10 patients, minor complication occurred during the procedure (2 cases of dissection resolved by implanting another stent, 1 balloon rupture without clinical repercussions, 7 cases of occlusion of a septal or diagonal branch with CPK elevation, which was less than 400 U/mL in only two of them). No local complication occurred at the puncture point or during the hospital stay up to discharge.
Evolution

The mean follow-up was 38 ± 11 months, being less than 24 months in only 2 patients who died (at 2 and 9 months of inclusion). No loss to follow-up occurred in the course of the study, as shown graphically in Figure 1. During the study up to finalization, 68 patients (69.4%) remained free of angina and presented no MACE during follow-up. Twenty-five patients (25.5%) had angina and were referred for a new coronariography. In 7 patients, angiographic restenosis was observed, but no new percutaneous or surgical revascularization procedure was decided on (4 patients had non-bridgeable distal vessels and anatomic lesions unfavorable for a new PTCA, and other 3 had restenosis of less than 70% and adequate clinical control with antianginal drugs). Twelve patients required a new revascularization of the target lesion: 6 by coronary artery surgery and IMA bypass 3, 6, 6, 9, 13, and 14 months, respectively, after stent implantation (in one, surgery was performed after a new PTCA of the pAD for early restenosis at 3 months), and 6 by a new PTCA between months 5 and 34 of follow-up (in one case the stent was removed due to intrastent restenosis). The other 7 patients with persistent angina were referred for a new revascularization by PTCA and stent implantation in vessels other than the pAD, 3 of them had 2 vessels treated (3 revascularizations of the right coronary artery, 3 of the middle anterior descending, and 4 of the obtuse marginal). Two patients had an anterior AMI (one silent) 2 and 4 months, respectively, after the procedure. Coronariography was not performed later because tests for residual ischemia were negative.

Five deaths occurred, 2 of cardiac origin at 2 and 38 months of inclusion in the study, and 3 of non-cardiac

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Table 2. Characteristics of the procedure

<table>
<thead>
<tr>
<th>No. of stents used</th>
<th>1 (90.8%)</th>
<th>2 (9.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent length &gt;16 mm</td>
<td>22 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>Stent diameter ≤3.0 mm</td>
<td>32 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Type of stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmaz-Schatz</td>
<td>61 (57%)</td>
<td></td>
</tr>
<tr>
<td>NIR</td>
<td>25 (23.4%)</td>
<td></td>
</tr>
<tr>
<td>Multilink</td>
<td>8 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>Wiktor</td>
<td>7 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Bestent</td>
<td>4 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>BARD</td>
<td>2 (1.9%)</td>
<td></td>
</tr>
</tbody>
</table>

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Fig. 1. Diagram of the evolution of patients (*asymptomatic at the end of the study, **death).
According to the Kaplan-Meier test, the probability of remaining free of MACE was 83.7% at 60 months of follow-up (Figure 2) and the overall probabilities not suffering cardiac or non-cardiac death were 98% and 94.8%, respectively (Figure 3).

The clinical, anatomical, and procedure variables, and their relation with the eventual appearance of MACE is shown in Table 3. Univariate analysis showed that the use of 2 stents was associated with a greater incidence of MACE ($P<.05$). Other clinical factors (AHT, DM, and the presence of multiple cardiovascular risk factors), angiographic factors (ostial location of the lesion), and procedural factors (stent diameter less than 3 mm or ostial lesion) showed a relation with a less favorable prognosis (in terms of MACE appearance), but did not reach statistical significance. The survival curves in relation to these variables are shown in Figure 4. In multivariate analysis, the only independent predictors of greater incidence of MACE were the use of 2 stents (odds ratio [OR]=3.8; 95% CI, 1.2-12.1; $P=.021$), and the AHT-DM-dyslipidemia interaction (OR=3.7; 95% CI, 1.3-10.3; $P=.011$). Ostial stenoses (OR=3.7; 95% CI, 0.8-16.6; $P=.09$) showed a greater tendency toward the occurrence of events.

The pharmacological treatments received by patients during the study are shown in Table 4. Platelet aggregation inhibitors (acetylsalicylic acid and/or ticlopidine) were often used during follow-up, in addition to the calcium antagonists and beta-blockers, which were taken by 48% and 46%, respectively, of the patients at the end of the study. The use of statins increased considerably, from 27% at the beginning of follow-up to 65% at finalization.

**DISCUSSION**

**Table 3. Statistical analysis of clinical, anatomical and procedural variables and their association with the presence of MACE in the follow-up**

<table>
<thead>
<tr>
<th>Free of MACE</th>
<th>Presence of MACE</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 62.1±9.3</td>
<td>64.5±8.5</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex 88.2%</td>
<td>87.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension 56.1%</td>
<td>75%</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes 24.4%</td>
<td>37.5%</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypercholesterolemia 81.7%</td>
<td>81.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking Active 18.3%</td>
<td>18.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Ex-smoker 50%</td>
<td>50%</td>
<td>NS</td>
</tr>
<tr>
<td>Presence &gt;2 CVRF 27.3%</td>
<td>13.2%</td>
<td>0.11</td>
</tr>
<tr>
<td>Multivessel disease 29.3%</td>
<td>25%</td>
<td>NS</td>
</tr>
<tr>
<td>Angina Stable 90.9%</td>
<td>9.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Unstable 82.7%</td>
<td>17.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Depressed EF 12.2%</td>
<td>6.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Use of 2 stents 6.1%</td>
<td>25%</td>
<td>0.012</td>
</tr>
<tr>
<td>Stent length &gt;16 mm 21.3%</td>
<td>31.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Stent diameter ≤3 mm 30.4%</td>
<td>50%</td>
<td>0.12</td>
</tr>
<tr>
<td>Ostial lesion 4.9%</td>
<td>12.5%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

MACE indicates major adverse cardiac events; EF, ejection fraction; CVRF, cardiovascular risk factors; NS, not significant.
The long-term outcome (mean and maximum follow-up of 38 and 60 months, respectively) of this prospective observational study of stenoses of the proximal segment of the pAD treated by stent implantation indicated that the procedure had a high success rate (98.9%), low rate of new revascularizations (12.2%), high probability of remaining free of MACE (83.7%), and low mortality. It should be noted that a
large percentage of patients had short, single-vessel lesions and without impaired left ventricular function.

Comparison with previous studies

Previous studies have demonstrated that interventionist treatment produces more benefits than pharmacological medical treatment in severe disease of the pAD or single-vessel coronary artery disease. Nevertheless, comparison of the two main revascularization techniques (PTCA and IMA graft) reveals a greater incidence of new revascularizations in the group treated with PTCA, more need for antianginal drugs, and worse exercise tolerance, with similar rates of reinfarction and mortality in the two groups. This greater incidence of new revascularizations after PTCA is due to the restenosis phenomenon, which occurs mainly in the first year post-PTCA. The incidence of restenosis after isolated PTCA varies in different series from 40% to 66%. The factors favoring restenosis include the presence of proximal lesions and descending anterior coronary involvement. The introduction of stent implantation has clearly modified these results, reducing the risk of restenosis by almost half, with a very low incidence of immediate complications and highly favorable short and midterm clinical evolution (similar to that achieved with IMA graft surgery). Previous studies have demonstrated a frequency of implant failure among stents that are manually mounted on the balloon of 1.5% to 3.1% with the Palmaz-Schatz stent and 1.5% to 6.6% with the NIR stent. Recent studies of second-generation stents, such as the SPORT-NIR registry, report implant failure rates of only 0.4%. In our study only one failure occurred, with implantation of the Palmaz-Schatz stent, which was mounted manually on the angioplasty balloon. This failure rate of 1% coincides with the results reported in previous studies.

The rates of restenosis and need for new stent revascularization vary in different series from 19% to 31%. Our findings confirm that new revascularizations of the pAD may occur up to two and a half years after the procedure, although most reinterventions took place in the first 12 months after stent implantation (66.6% of cases). We found an incidence of new revascularizations of pAD of 12.2%, although the real incidence of significant restenosis and the precocity in its appearance in our series is unknown since we did not systematically evaluate patients by angiography.

Predictors of evolution

Among the factors analyzed, only the use of two stents during the procedure was an independent risk factor for a less favorable clinical evolution, which coincides with the report by the group of Bauters et al.

Factors that traditionally suggest a worse prognosis after stent implantation, like DM, multivessel disease, hypertension, or left ventricular dysfunction in long-term follow-up were not confirmed in univariate analysis. In the case of DM, the phenomenon of restenosis was found to be due fundamentally to a process of excessive intimal hyperplasia compared with non-diabetic patients, in which this process developed less aggressively. This phenomenon is expressed by higher rates of restenosis and need for new revascularization procedures. Of the 23 diabetic patients in our study, most (20 of 23) were non-insulin-dependent, which may explain why DM was not an independent predictor, since recent studies have demonstrated a difference in the evolution of stent permeability depending on the type of diabetes. The prognosis is worse in insulin-dependent DM. Nevertheless, the association of DM, AHT, and dyslipidemia was identified as associated with a worse clinical evolution in multivariate analysis. This showed that although these factors were not clearly linked with the prognosis individually (at least samples of the size studied here), the concurrence of factors in a patient must be considered predictive of a less favorable evolution, as occurs in atherosclerotic disease in general.
There was heavy use of medications throughout follow-up, due fundamentally to the high prevalence in the study population of traditional cardiovascular risk factors like hypercholesterolemia and AHT, and multivessel disease manifested at the time of inclusion (31%) and during evolution (7 patients presented progression of coronary artery disease requiring revascularization of other vessels).

Clinical implications

The results of our study confirm the safety of stent implantation in lesions involving the pAD and a good long-term clinical response, which in some patients reached 5 years of follow-up. The figures obtained for survival and absence of MACE coincide with previous studies of stent implantation in pAD, and are comparable to those reported in other studies in which coronary revascularization with IMA graft surgery was performed.

In clinical practice the decision to choose IMA bypass surgery over PTCA and stent implantation must be made individually for each patient, taking into account the patient’s opinion after receiving information on both therapeutic alternatives, their results and risks, and considering the percutaneous alternative as the first choice in cases with a favorable coronary anatomy and in patients in which the need for future revascularizations can be foreseen (e.g., young patients).

Study limitations

The main limitation of the study was the absence of randomization, which precluded direct comparative analysis with other revascularization strategies. The fact that coronary arteriography was not performed systematically during follow-up does not allow us to determine the true rate of angiographic restenosis in the study group. The technology used was effective as of 1995. The use of new materials and designs in later-generation stents and new antiaggregant regimes with antagonists of the IIb-IIIa platelet receptors should improve the short-term and long-term results. However, the results obtained with these agents in our study do not seem to support their generalized use in stent implantation due to their high cost/benefit relation.

CONCLUSIONS

The treatment of stenosis of the proximal segment of the anterior descending coronary artery with stent implantation is safe in patients with a favorable coronary anatomy for this procedure. The percentage of complications is low and, in a prolonged follow-up, which in some cases in our study is 5 years, accompanied by a low incidence of new revascularization procedures and high survival rate.

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