Two-Year Clinical Follow-Up in 200 Patients Receiving Sirolimus-Eluting Stents in Lesions at a High Risk of Restenosis

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Introduction and objectives. Sirolimus-eluting stents (SESs) have been shown to reduce the rate of restenosis significantly in all types of coronary lesion. However, reports of late cases of thrombosis and restenosis have raised questions about long-term outcome in patients treated with these stents. Our aim was to evaluate long-term outcome in patients undergoing SES placement in lesions at a high risk of restenosis.

Patients and methods. Since SESs became available, we have used them to treat lesions at risk of restenosis. We studied clinical outcomes in consecutive patients treated with SESs who were followed up for more than 2 years.

Results. The study included 200 patients (age 60 ± 11 years, 22% diabetics) who were treated between June 2002 and April 2003 for 309 lesions: 16% were total occlusions, 16.8% in-stent restenoses, 28% diffuse lesions, and 30% small-vessel lesions. The total stent length per patient was 29 (16) mm and the mean diameter was 2.78 (0.27) mm. In a mean clinical follow-up period of 29 (3.2) months (range 24-34 months), there were 4 deaths, 2 (1%) of which were cardiac; 4 (2%) non-fatal infarctions; 4 (2%) in-stent thromboses (all occurred late, at 3, 7, 26 and 31 months), 4 (2%) cases requiring target lesion revascularization (at 3, 5, 14, and 15 months), and 6 (3%) requiring revascularization of a new lesion.

Conclusions. Long-term follow-up of patients undergoing SES placement in lesions at a high risk of restenosis revealed a very low restenosis rate. However, the incidence of late thrombosis appeared to be elevated and warrants further evaluation in larger studies.

Key words: Coronary lesion. Stent. Restenosis.

Seguimiento clínico a 2 años de 200 pacientes tratados con stent liberador de rapamicina en lesiones de alto riesgo de reestenosis

Introducción y objetivos. Los stents de rapamicina (SR) han demostrado reducir la tasa de reestenosis en múltiples estudios, pero se han descrito algunos casos de reestenosis y trombosis tardías que proyectan dudas sobre sus resultados a largo plazo (> 2 años). Nos plantearon estudiar retrospectivamente la evolución a largo plazo de pacientes tratados con SR en lesiones de alto riesgo de reestenosis.

Pacientes y método. Desde su introducción, hemos utilizado SR en los casos con lesiones de mayor riesgo de reestenosis. Estudiamos la evolución clínica de los pacientes en los que se implantaron SR y que cuentan con un seguimiento clínico superior a 2 años.

Resultados. Se estudió a 200 pacientes (edad 60 ± 11 años, un 22% diabéticos) tratados entre junio de 2002 y abril de 2003 en 309 lesiones: un 16%, oclusiones totales; un 16,8%, reestenosis intra-stent; un 28%, lesiones difusas, y un 30%, en vaso pequeño. La longitud total de stent por paciente fue de 29 ±16 mm y el diámetro del stent, de 2,78 ± 0,27 mm. En el seguimiento clínico de 29 ± 3,2 meses se produjeron los siguientes eventos: 4 muertes, de las que 2 (1%) fueron cardíacas; 4 infartos (2%); 4 trombosis de stent documentadas (2%), todas tardías a los 3, 7, 26 y 31 meses; 4 casos (2%) de revascularización por reestenosis del segmento tratado a los 3, 5, 14 y 15 meses, y 6 casos (3%) de revascularización de otra lesión.

Conclusiones. La evolución a largo plazo de los pacientes con SR en lesiones de alto riesgo reestenótico muestra una tasa de reestenosis clínica muy baja. La incidencia de trombosis tardía parece resultar algo elevada y debería ser evaluada en series más amplias.

Palabras clave: Lesión coronaria. Stent. Reestenosis.
INTRODUCTION

Sirolimus-eluting stents (SES) have been shown to dramatically reduce the incidence of restenosis in almost all lesions and clinical situations, with incidences of thrombosis comparable to those observed with conventional stents. 

Nonetheless, the studies and registries described in the literature typically report on clinical follow-up periods of 1 year, with only 2 studies providing much longer-term information, namely the FIM study (30 patients for 4 years) and the RAVEL study (120 patients for 3 years). These 2 studies were, however, small, highly controlled series that included carefully selected cases and excluded long lesions and those located in small vessels (<2.5 mm), as well as total occlusions, in-stent restenoses, ostial restenoses, bifurcations, grafts, and trunk lesions.

As a result, the long-term progress of patients treated with these stents in clinical practice, in particular in high-risk lesions and clinical situations, is not known. Isolated cases of restenosis and late thrombosis have been described, and these reports cast doubts on a clinical reality that is still uncertain.

The present study assesses the long-term (>2 years) clinical progress of a cohort of patients undergoing SES placement in lesions at a high risk for restenosis.

PATIENTS AND METHODS

Retrospective study including all patients referred to our unit from 1 June 2002 who had a clinical indication of coronary angiography, were eligible for percutaneous revascularization with SES and had one or more treated lesions meeting at least one of the following criteria:

1. In-stent restenosis.
2. Total obstruction at any time.
3. Diffuse lesion (>20 mm).
4. Small-vessel (<2.5 mm) lesion.
5. Ostial lesions.
7. Lesions in the trunk or dependent on a single vessel.
8. Saphenous or mammary grafts.

Patients who had undergone angioplasty (primary or rescue) for ST segment elevation infarction and those in cardiogenic shock were excluded. Patients with chronic occlusions were only included in the follow-up if dilatation was successful. Another 2 cases were excluded because SES placement was not possible. If the patient had other treatable lesions not meeting these criteria, SES were also used in these lesions. The method of stent placement was left to the discretion of the physician.

Although most patients with lesions having these characteristics received SES, logistic limitations made it impossible in some cases. Specifically, SES were used in 75% of the lesions treated in this period that met one or more of the criteria. The remainder were treated with conventional stents, either due to size availability or because the lesions had a more favorable profile (focal lesions in 2.5-mm vessels or 20-25-mm diffuse lesions in vessels ≥3 mm). All total occlusions and in-stent restenoses were treated with SES.

All procedures were performed using the femoral route and vascular closure devices. The use of glycoprotein IIb-IIIa inhibitors was left to the discretion of the physician. Angiographic success was defined as residual stenosis <25%, TIMI III flow, and no distal embolization or occlusion of collateral branches. Routine serial enzyme determinations were performed only in cases of suspected post-PTCA necrosis (procedure complication, ischemia, and/or post-PTCA symptoms), based on clinical or electrocardiographic criteria. All patients received an oral loading dose of clopidogrel 300 mg immediately after the procedure, and later a combination of acetylsalicylic acid (ASA) 100 mg and clopidogrel 75 mg for 3 months.

The clinical follow-up included consultation of the medical histories that contained records of the follow-up visits, which usually took place at 6 months and every 6-12 months thereafter, and the phone calls made to all patients at the time follow-up ended. The patients were monitored by their attending cardiologists, who ordered ischemia tests or coronary angiography at their discretion. In most of the patients, ischemia tests were performed to guide the indication of recatheterization.

Events were classified as follows:

1. Death (cardiac or noncardiac).
2. Q-wave myocardial infarction defined by the appearance of new Q waves in the electrocardiogram, whether preceded by clinical symptoms or not, or non-Q wave infarction defined as acute coronary syndrome associated with elevated enzyme levels (more than twice the upper limit of normality for the MB isoenzyme of creatine kinase) without the subsequent appearance of Q waves in the electrocardiogram.
3. Stent thrombosis defined as angiographic observation of a total or subtotal occlusion of the stent by thrombotic material preceded by acute clinical symptoms possibly accompanied by ST segment elevation.
4. Revascularization, either in the treated lesion (due to in-stent restenosis) or in a new lesion.
Statistical Analysis

Continuous variables are shown as mean ± standard deviation (SD) and categorical variables are expressed as percentages. MedCalc 8.0.2.0 was used for the statistical calculations.

RESULTS

Between June 2002 and April 2003, a total of 200 consecutive patients in whom 309 lesions had been treated were included in the study. This series accounted for 30% of all patients treated in the department during this period. The clinical characteristics of these patients are shown in Table 1. The angiographic characteristics of the 309 lesions are described in Table 2. Among these, 230 (74%) met one or more of the inclusion criteria, and all patients, as required for inclusion, had at least one of these higher-risk lesions. Fifty lesions were complete occlusions: based on clinical symptoms, 16 were recent (recent acute coronary syndrome, excluding primary angioplasty) and the remaining 34 were chronic. Aspects related to the revascularization procedure and the stent measurements are shown in Table 3. Total stent length per patient was 29±16 mm; direct stenting was attempted in 125 lesions, of which 117 (93.6%) achieved primary success and the remainder required predilatation. Angiographic success was achieved in 98% of the patients. Success was not obtained in 4 cases, with post-stent TIMI II flow in 1 (poor distal bed and competition with collateral circulation), residual stenosis >25% in 1 (fibrocalcified lesion), and occlusion of collateral branches (≤2 mm) in 2 cases.

Procedure and Hospitalization Complications

There were 3 (1.5%) non-Q-wave infarctions, one due to an occlusive retrograde dissection after stent placement in the middle segment of the right coronary that was resolved with an additional stent, and another two due to unresolvable occlusion of the diagonals (≤2 mm diameter) following stent placement in the left anterior descending artery and circumflex artery. However, failure to perform routine enzyme determinations in uncomplicated cases makes it impossible to assess the actual incidence of post-procedure non-Q-wave necrosis. One transient ischemic attack (0.5%) occurred in a 66-year-old man with hypertension (Table 4).

Events During Outpatient Follow-Up

During a follow-up of 29±3.2 months (range, 24-34 months) in which no patient was lost, there were 4 deaths (2 sudden, 1 cerebral hemorrhage, 1 complicated vascular disease of lower extremities), 4 (2%) late stent thromboses, 4 (2%) nonfatal infarctions, 4 (2%) revascularization procedures for restenosis in the treated segment, 6 (3%) revascularization procedures for new lesions, and 2 (1%) nonfatal strokes (Table 4).

At the end of follow-up, only 6 (3%) patients presented symptoms consistent with Class I or II stable angina; these patients were not referred for further study due to proper management of the symptoms, highly sporadic nature of the symptoms and/or negative (3 cases) or very slightly positive (2 cases) ischemia tests. In these last patients, there were other untreated lesions (very distal, occlusion precluding revascularization) that could also have explained the clinical symptoms.

Detailed Description of the Events

The deaths corresponded to 1 cerebral hemorrhage at 30 months, 1 case of valve disease complications in the lower
Nevertheless, the published studies focused specifically on lesions with a higher associated risk. Clinical trials, even though these studies did not evaluate restenosis and the resulting need for new revascularization had been done in all cases. Finally, in 6 patients who underwent revascularization for new lesions, no restenosis was observed in the drug-eluting stents.

**TABLE 3. Procedure Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated vessels/patient</td>
<td>2.9±0.5</td>
<td>1-12</td>
</tr>
<tr>
<td>Treated lesions/patient</td>
<td>1.5±0.6</td>
<td>1-12</td>
</tr>
<tr>
<td>Stents/patient</td>
<td>1.56±0.6</td>
<td></td>
</tr>
<tr>
<td>Stent length, mean±SD, mm</td>
<td>20.8±8</td>
<td></td>
</tr>
<tr>
<td>Stent diameter, mean±SD, mm</td>
<td>2.78±0.27</td>
<td></td>
</tr>
<tr>
<td>Total stent length/patient, mean±SD, mm</td>
<td>29.16±14</td>
<td></td>
</tr>
<tr>
<td>Direct stent, n (%)</td>
<td>177 (38)</td>
<td></td>
</tr>
<tr>
<td>Abciximab, n (%)</td>
<td>28 (14)</td>
<td></td>
</tr>
<tr>
<td>Triple-vessel stent treatment</td>
<td>5 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>Revascularization of treated lesion*</td>
<td>4 (2%)</td>
<td></td>
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<tr>
<td>Revascularization of other lesion</td>
<td>6 (3%)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>2 (1%)</td>
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</table>

*SD indicates standard deviation.

**TABLE 4. Clinical Events in a Follow-Up of 29±3.2 months (range, 24-34 months)**

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Non-CQ-wave infarction</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td></td>
</tr>
<tr>
<td>Clinical follow-up</td>
<td></td>
</tr>
<tr>
<td>Total deaths</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Nonfatal infarction</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Revascularization of treated lesion*</td>
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<td>6 (3%)</td>
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<tr>
<td>Nonfatal stroke</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

*For restenosis, excluding repeat surgeries for thrombosis.

_extremities at 24 months, and 2 sudden out-of-hospital deaths. In these last 2 deaths, 1 occurred at 20 months (70-year-old man with old inferior infarction with occluded right coronary precluding revascularization and large inferior-based aneurysm treated with 2 stents in the circumflex) and another at 15 days (80-year-old man with previous infarction, very diffuse atheromatous disease, triple-vessel disease with poor vascular beds, untreatable occluded right coronary, with 4 stents in the left anterior descending artery, circumflex and posterolateral branches).

One of the cases of late thrombosis was a 76-year-old man with previous occlusive, diffuse restenosis in a conventional stent in the proximal-medial left anterior descending artery. The distal bed of the vessel was perfectly visualized from the collaterals. After predilatation, a 33-mm stent, 2.75-mm in diameter was implanted; however, adequate flow (TIMI II) was not achieved. At 3 months, immediately after clopidogrel was discontinued, the patient experienced the onset of unstable angina. Coronary angiography showed complete occlusion of the stent, with filling of the distal vessel by excellent collateral circulation. Surgical revascularization was performed. The second case corresponded to a 76-year-old patient and occurred 7 months after an initial procedure in which a 2.5/33-mm stent was implanted on a de novo lesion in the proximal-medial left anterior descending artery. Percutaneous revascularization was performed. In the third case, a 47-year-old man with unstable angina and anterior hypokinesia showed a long left anterior descending artery occlusion in which 2.5/23 and 3/8-mm stents were implanted. The patient was admitted at 26 months with an anterior infarction; total occlusion was observed in the stent at this site and then treated with repeat angioplasty. The last case of thrombosis occurred in a 59-year-old man 31 months after a procedure in which a 2.75/13-mm stent was implanted in a de novo, nonocclusive lesion in the middle segment of the left anterior descending artery. He had normal ventricular function.

One suspected case of thrombosis, although not documented, concerned a patient with a 2.75/18-mm stent in the left anterior descending artery who presented an anterior infarction at 11 months. The reference hospital referred the patient for angiography several days later, but no restenoses or abnormal in-stent images were visualized and no severe lesions were observed in other areas of the vessel.

Revascularizations on treated segments were performed in 4 patients who presented anginal symptoms and in whom coronary angiography at 3, 5, 14, and 15 months disclosed focal in-stent restenosis. Percutaneous revascularization had been done in all cases. Finally, in 6 patients who underwent revascularization for new lesions, no restenosis was observed in the drug-eluting stents.

**DISCUSSION**

The main limitation of percutaneous revascularization is restenosis and the resulting need for new revascularization at mid-term. Drug-eluting stents have been shown to provide excellent results in important clinical trials, even though these studies did not evaluate lesions at a high risk for restenosis, as well as in registries of routine clinical use of these stents and in studies focused specifically on lesions with a higher associated risk. Nevertheless, the published studies and registries had clinical follow-up periods of less than 1 year, except for the FIM and RAVEL studies, which provide longer term information.

The present study assesses the long-term clinical progress of a cohort of patients undergoing SES placement in lesions at a high risk for restenosis.

**Stent Thrombosis**

No acute or subacute thrombosis was observed. In contrast, late thromboses occurred at 3, 7, 26, and 31 months. The first episode of late thrombosis corresponded to a case with a suboptimal initial result (TIMI II flow, competition with direct collateral circulation) in which occlusion occurred after clopidogrel was discontinued at 3 months following the procedure. The other case described as late thrombosis manifested as infarction at 7 months, which was apparently due to thrombosis; however, according to the angiographic image of the lesion distal to...
The total incidence in 2229 patients particularly after discontinuation was 0.8% 3.5%, and 6.3% at 1, 2, and 3 years, respectively. In our series, the treatment was required period for combined antiplatelet therapy, which varies from 2 months in the RA VEL study,1 3 months in the SIRIUS study,2 and 6 months in the Rotterdam group experience.2,3,6 In our series, the treatment was administered for 3 months, although it should probably be given for 6 months or more (empirically speaking) in patients with an in-stent restenosis, long stent length or multiple stents. Late thromboses should lead us to consider the required period for combined antiplatelet therapy, which varies from 2 months in the RA VEL study,1 3 months in the SIRIUS study,2 and 6 months in the Rotterdam group experience.2,3,6 In our series, the treatment was administered for 3 months, although it should probably be given for 6 months or more (empirically speaking) in patients with an in-stent restenosis, long stent length or multiple stents. Revascularization of Treated Lesions Patients who underwent revascularization of the treated segment had multiple stents, lesions that were very long and/or in a small vessel (<2.5 mm), or bifurcations. Two of the cases were observed later than usually seen in conventional stents (at 14 and 15 months). In all cases, the restenotic lesions were focal, facilitating and allowing in-stent treatment. In comparison to other clinical registries with drug-eluting stents, the Rotterdam series included 508 patients treated with SES, finding a mortality of 3.4% at one year, nonfatal infarction of 3.6% and clinically indicated revascularization of the treated vessel of 3.7%.6 This last figure is slightly higher than our figure of 2%, but should be considered within the clinical context of patients more prone to reoperation. In the only study with a very long follow-up (3 years), the RA VEL study6 observed a cumulative incidence of revascularization of the treated lesion in the SES group of 0.8%, 3.5%, and 6.3% at 1, 2, and 3 years, respectively, reaction to the polymer,12 particularly after discontinuation of combined antiplatelet therapy; however, on occasions they present characteristics that may indicate the involvement of lesions marginal to the stent that become complicated or the involvement of restenotic occlusive lesions. In this regard, the above study assessed the incidence of thrombosis with sirolimus- and taxol-eluting stents, including sudden death in the month after the procedure “not clearly attributable to another lesion” as a thrombosis event.19 The total incidence in 2229 patients with 9 months of follow-up was, as we have indicated, 1.3%, whereas the subacute incidence was 0.6% and late incidence was 0.7% (0.5% for SES and 0.8% for taxol). The predictive factors for late thrombosis were low ejection fraction, bifurcations and particularly, premature discontinuation (before 3 months for SES and before 6 for taxol-eluting stents) of combined antiplatelets. The Rotterdam group found an incidence of late thrombosis of 0.35% in drug-eluting stents. Late (>1 month) thrombosis does not occur only in drug-eluting stents, however, as an incidence of 0.6%-0.8% has been reported in some large series from the late 1990s using conventional stents without brachytherapy.20-21 Nevertheless, thrombosis reported after 6 months is an exceptional finding in conventional stents, when patients who received brachytherapy are excluded. Late thromboses should lead us to consider the required period for combined antiplatelet therapy, which varies from 2 months in the RA VEL study,1 3 months in the SIRIUS study,2 and 6 months in the Rotterdam group experience.2,3,6 In our series, the treatment was administered for 3 months, although it should probably be given for 6 months or more (empirically speaking) in patients with an in-stent restenosis, long stent length or multiple stents.
and in the conventional stent group of 24.1%, 24.1%, and 25% at 1, 2, and 3 years. The benefit clearly persists with drug-eluting stents; however, the late onset of clinical restenoses is also evident, as in our study. From 1 to 3 years, the incidence of recanalization for the treated lesion was 4.2% in the SES group and 1.7% in the conventional stent group. Both these results and our own uphold the possibility of a slower, less frequent restenosis process in these stents. In this study, the recanalization figures are probably relatively high due to angiographic follow-up. In clinical practice and in lesions at a high risk, such as those of the RAVEL study, the benefit of drug-eluting stents may be considerably lower.

It is questionable whether 2% for new recanalizations for restenosis with 3% of patients with Class IIIB stable angina at the end of the follow-up is a spectacular result in a group of patients with the lesion characteristics described. We have already mentioned in previous publications the reasons why lower incidences of recanalization are routinely reported in our setting, namely, clinical follow-up rather than clinical and angiographic, and the characteristics of the clinical setting. In this study, we observed that nonpreferred patients are generally asymptomatic or present very mild symptoms (3%) with negative or slightly positive ischemia tests at high loads, thus not requiring a different approach on the part of the clinician. Under these conditions, the incidences of recanalization with conventional stents, even with a less adverse lesion profile, are significantly higher than those obtained with drug-eluting stents.

Limitations
This observational study describes the results obtained in a selected, consecutive, nonrandomized series of patients with no control group. Because enzyme determinations were not performed after the procedure, the actual incidence of postangioplasty necrosis has been underestimated. Furthermore, no angiographic follow-up was carried out, which unquestionably means that the incidence has also been underestimated in the case of restenosis. The limited sample size prevents definitive conclusions about the incidence and characteristics of late thrombosis. Nevertheless, the study provides a thorough assessment of the long-term clinical progress of a large series of patients who underwent SES placement in high-risk lesions not previously addressed in the literature until now, but that reflects the harsher reality of actual clinical practice.

CONCLUSIONS
The long-term (2 to 3 years) clinical progress of patients treated with SES shows an acceptable incidence of thrombosis, in view of the types of lesions treated, all of them late. The need for recanalization of the treated lesion field is significantly low. However, larger studies should be conducted to confirm these findings and assess the incidence and characteristics of late thromboses.

REFERENCES


