Use of Sirolimus-Eluting Stents in Complex Lesions: Clinical and Angiographic Follow-Up

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Introduction and objectives. The RAVEL and SIRIUS studies have demonstrated important reductions in clinical and angiographic restenosis in lesions treated with sirolimus-eluting stents. However, inclusion criteria in both studies excluded complex lesions. We studied immediate and long-term results with this stent in these complex lesions.

Patients and method. Prospective, observational study with clinical and angiographic follow-up of patients who met the exclusion criteria used in the RAVEL and SIRIUS studies. All patients were treated in our catheterization laboratory between June 2002 and April 2003 with the Cypher stent, and 57 patients (68 lesions) were studied in all. The most frequent lesion characteristics were excessive length 26.5%; ostial lesions 25%, bifurcations 23.5%, and severe calcifications 22.1%. Almost half (47%) of the patients had diabetes and 68% had multivessel disease.

Results. PTCA was successful in all patients. There was one major adverse cardiovascular event (MACE) before discharge (1 acute Q-wave myocardial infarction). Two episodes of subacute thrombosis occurred during the first week. During long-term clinical follow-up (8.7 [3.1] months) of all patients, there were 4 MACE (7%): 1 cardiac death, 1 acute myocardial infarction and 2 revascularizations of the target vessel. Intrasegmental restenosis was observed by angiography in 4 lesions (8%).

Conclusions. Implantation of the Cypher stent in complex lesions is safe and is associated, after 6 months of follow-up, with a low incidence of clinical events and a very low percentage of angiographic restenosis.

Key words: *Stent. Restenosis. Prognosis. Coronary angiography.*

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Utilización del *stent* recubierto de rapamicina en la revascularización de lesiones complejas: estudio con seguimiento clínico y angiográfico

Introducción y objetivos. Los estudios RAVEL y SIRIUS han demostrado una importante reducción de la reestenosis clínica y angiográfica en lesiones tratadas con *stent* recubierto de rapamicina. Sin embargo, los criterios de selección de ambos ensayos clínicos excluyeron lesiones complejas. Estudiamos los resultados inmediatos y a medio plazo del *stent* de rapamicina en este tipo de lesiones complejas.

Pacientes y método. Estudio prospectivo y observacional con seguimiento clínico y angiográfico de pacientes tratados en nuestro servicio entre junio de 2002 y abril de 2003 con el *stent* Cypher que cumplían criterios de exclusión en los estudios RAVEL y SIRIUS. Se estudió a 57 pacientes (68 lesiones). Las características más frecuentes fueron: longitud excesiva en el 26,5%, lesiones ostiales en el 25%, bifurcaciones en el 23,5% y calcificación severa en el 22,1%. El 47% de los pacientes era diabético y el 68% presentaba enfermedad multivaso.

Resultados. La angioplastia coronaria transluminal percutánea se llevó a cabo con éxito en todos los casos. Hubo un evento cardíaco mayor durante el ingreso hospitalario (un infarto agudo de miocardio con onda Q) y 2 trombosis subagudas en la primera semana. Se realizó seguimiento clínico a medio plazo (8,7 ± 3,1 meses) en el 100% de los pacientes y acontecieron 4 eventos cardíacos mayores (7%): una muerte cardíaca, un infarto agudo de miocardio y 2 revascularizaciones del vaso diana. Se objetivó reestenosis angiográfica intrasegmentaria en 4 lesiones (8%).

Conclusiones. El implante del *stent* Cypher en lesiones complejas es seguro y se acompaña de una baja incidencia de eventos clínicos y muy bajo porcentaje de reestenosis angiográfica en el seguimiento a los 6 meses.

Palabras clave: Stent. *Reestenosis. Pronóstico. Coronariografía*.

ABBREVIATIONS

AMI: acute myocardial infarction.
PTCA: percutaneous transluminal coronary angioplasty.
SCAE: severe cardiovascular adverse events.

INTRODUCTION

Coronary interventions have evolved considerably since Andreas Gruntzig[1] carried out the first coronary angioplasty in 1968. The appearance of the stent and its widespread use in recent years has clearly involved change, with better short- and long-term[2–4] results and a large increase in indications for percutaneous revascularization. In recent years, many studies have demonstrated the superiority of the stent compared to balloon angioplasty in almost all fields, e.g., in *de novo* lesions, restenosis, long lesions, small vessels, saphenous vein grafts, etc.[2–11] Stents are thus the preferred procedure within the area of angioplasties, and 88.1% of angioplasties[12] carried out in Spain in 2001 used stents. However, the problem of angioplasty with stents continues to be restenosis, which in angiographic restenosis can range between 15% and 35%.[2-11] The recently published FIM and RAVEL[13,14] studies —where the ability of intracoronary sirolimus-eluting stents to diminish restenosis was studied for the first time in humans—opens a new and optimistic phase in interventionist cardiology. Sirolimus is a macrolide derived from samples of *Streptomyces* found on Easter Island. It is an immunosuppressive drug that binds to intracellular receptors and inhibits proliferation of vascular smooth muscle cells, blocking the progression of the cell cycle in the G1/S transition and, further, inhibiting the migration and proliferation of T[15] lymphocytes. Compared to standard drug-free stents, sirolimus-eluting stents have demonstrated their superiority in terms of reducing clinical and angiographic restenosis in favorable non-complex lesions.[13,14] The results of the SIRIUS[16] study were published recently, with the selection criteria expanded for lesions treated with sirolimus-eluting stents, although complex lesions continue to be excluded. These latter lesions involve a non-negligible percentage of the daily work in most cardiology centers.

Our aim was to study the effectiveness of sirolimus-eluting stents in the treatment of complex lesions not studied to date due to their fulfilling certain anatomical exclusion criterion in published clinical trials. We analyze immediate and mid-term results, in terms of clinical events and angiographic restenosis.

PATIENTS AND METHODS

Study Population

Between June 2002 and January 2003, we treated 57 patients with 68 complex lesions, that fulfilled the RAVEL[14] and SIRIUS[16] exclusion criteria, with sirolimus-eluting stents. We studied:

– The exclusion criteria that our lesions fulfilled in the RAVEL and SIRIUS studies.
– The clinical characteristics of the patients.
– The angiographic characteristics of the lesions.
– The angioplasty success rate (percentage) of sirolimus-eluting stents in this type of complex lesion.

Linear calcification on both sides of the target lesion and visible in the fluoroscopic still image was defined as “severe calcification.” Lesions which affected the coronary arteries in which both the principal branch and the lateral branch presented a diameter >2 mm were considered “bifurcated lesions.”

Procedure

Angioplasty with an implanted sirolimus-eluting stent (Cypher; Johnson & Johnson-Cordis Unit, Cordis Europa NV, Roden, Netherlands) was done according to the standard technique used in our center. Given the complexity of the lesions, predilatation with balloon was done before implantation and long stents were used to cover the entire length of the lesion. We implanted stents of a suitable diameter to obtain a 1.1-1.2:1 ratio regarding the reference diameter of the artery. Ablation techniques were not used prior to stent implantation. Bifurcated lesions were treated by the strategy of placing a stent in the main branch and a balloon in the lateral branch if the result was correct (provisional T stenting). When the use of balloon was not successful in the lateral branch, a sirolimus-eluting stent was implanted in this branch. All angioplasties were carried out via the femoral artery. Angioplasty was considered successful when post-implant residual stenosis was <20%, with TIMI III flow. If the patient had not been treated with tirofiban upon arrival in the theatre, abciximab was used at the discretion of the interventional cardiologist. All patients were given intravenous heparin sodium before beginning angioplasty at 100 U/kg when no glycoprotein IIb/IIIa inhibitor was used and at 70 U/kg if it was. All patients were treated with acetylsalicylic acid (100-200 mg/day) indefinitely and with clopidogrel (75 mg/day) for 9-12 months. If

they presented multivessel disease all subsidiary angioplasty lesions were treated with a Cypher stent when the diameter of the artery was ≤3 mm and with a standard stent when it was >3.5 mm.

Follow-Up

Clinical follow-up of all patients included in the study was done at the time of the hospital discharge, after 1 month and at 6 months. In addition, and given the absence of scientific information on these types of lesions, elective angiographic follow-up of the first 50 target lesions was done. Angiographic follow-up was carried out with 6 French catheters after the risks and benefits of the procedure were explained to the patient and they gave signed informed consent. Severe cardiovascular adverse events (SCAE) were studied, among which death due to cardiac causes, acute myocardial infarction and target vessel revascularization (both percutaneous and revascularization surgery) were included. In addition, hospital admissions due to cardiac causes were evaluated as well as the situation of the patient at baseline.

Quantitative Coronary Angiography

Quantitative coronary angiography was done before angioplasty, after stent implantation and during angiographic follow-up at 6 months. To this end, at least two orthogonal projections were done after the use of intracoronary nitroglycerine. Quantification was done with the edge-detection technique and Inturis Cardio Image (Philips Medical Systems) quantitative analysis program, and included the proximal and distal 5 mm to the implanted stent or stents. A stenosis ≥50% of the minimum luminal diameter was defined as angiographic restenosis at follow-up. We considered there was an in-stent restenosis when this occurred within the margins of the sirolimus-eluting stent, and an in-segment restenosis when the restenosis occurred within either the margins of the stent or in the proximal or distal 5 mm. Late loss was defined as the difference between the minimum luminal diameter immediately after the procedure and the minimum luminal diameter at 6-month follow-up.

Statistical Analysis

Data analysis was done with the SPSS statistical software program (version 10.0). Quantitative variables are expressed as mean±standard deviation and categorical variables as the absolute value and percentages. Survival was estimated with the Kaplan-Meier method.

TABLE 1. **The Exclusion Criteria of the RAVEL and SIRIUS Studies Fulfilled by the Lesions Included in Our Study**

Criterion	Percentage	Number
Long lesion, >30 mm	26.5	18
Severe calcification	22.1	15
Bifurcational lesion	23.5	16
Ostial lesion	25	17
Unprotected left main coronary artery disease	1.5	1
Total occlusions	22.1	15
Diffuse in-stent restenosis	8.8	6
Angiographic thrombosis	5.9	4
Two or more exclusion criteria	35.3	24

RESULTS

Between June 2002 and April 2003, we treated 57 patients with complex lesions (68 lesions) which fulfilled the anatomical exclusion criteria of the RAVEL[14] and SIRIUS[16] studies with the Cypher stent. The exclusion criteria that the lesions in our study fulfilled were mainly excessive length (26.5%), ostial lesions (25%), or bifurcated lesions (23.5%) (Table 1; Figure 1). Several of these lesions fulfilled two or more of these criteria. The clinical and angiographic characteristics of the lesions are presented in Table 2. It should be pointed out that 47.4% of the patients were diabetic (39% insulin-dependent) and 68.4% suffered from multivessel disease. Glycoprotein IIb/IIIa inhibitors (tirofiban or abciximab) were used in 39% of cases. Direct stent implantation was done in only 7.3% of the lesions. The mean deployment pressure of the stent was 13.7±2.21 atmospheres. Angioplasty was carried out successfully in all cases, although implantation of a Cypher stent was impossible in one patient and so a standard stainless steel stent was used instead. This involved an angioplasty of the left main coronary artery, with very severe calcification and moderate tortuosity. During hospital stay, one diabetic patient developed an acute Q-wave myocardial infarction (Table 3). A three-vessel angioplasty was done because she presented very poor caliber distal vessels for surgery. She developed postangioplasty inferior infarction, which led to a reassessment at 24 hours. Stent permeability was observed, but with TIMI II flow in a lateral branch. During the first month complications included two subacute stent thromboses. One was clearly related to stopping antiplatelet medication, with an ST-segment elevation infarction, which was treated with fibrinolysis (3×33-mm stents implanted in the proximal descending anterior artery in a 49-year-old woman with diabetes type 2). The other patient had angina (3×33-mm stents were also implanted in the

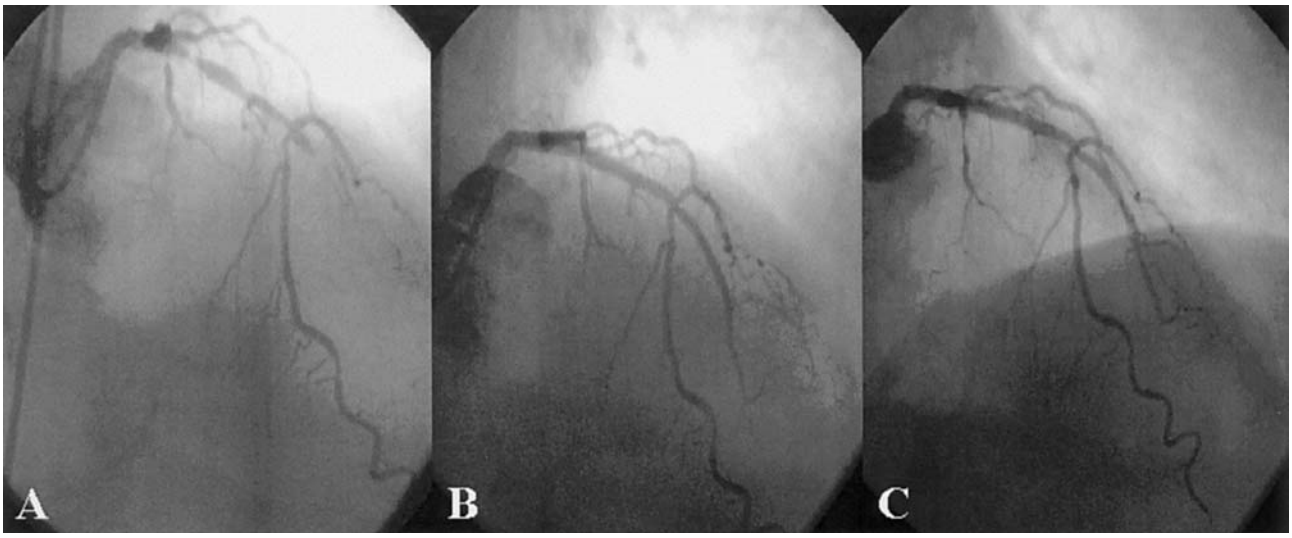

Fig. 1. Example of severe bifurcated lesion. A: left coronary arteriography in ROA 25°-cranial 30° projection where severe stenosis of the segments proximal and medial to the anterior descending artery and total occlusion of the second diagonal branch can be seen. B: the result after percutaneous transluminal coronary angioplasty with a 3.0×33 mm Cypher stent implant covering the segments proximal and medial to the anterior descending artery, and a 2.5×18 mm Cypher stent in the second diagonal branch (T stenting). C: angiographic 6-month follow-up in which an optimal result can be observed with minimum late loss in the 2 stents.

TABLE 2. **Clinical Characteristics of the Population and Target Lesion Angiographies**

Age, years	63.1±9.9	(range, 42-79)
Male gender	72%	
Previous infarction	24.6%	
Previous surgery	7%	
Diabetes mellitus	47.4%	
Hypertension	59.6%	
Smoking habit	40.3%	
Hypercholesterolemia	54.4%	
Reason for catheterization		
Angina		
Unstable	64.9%	
Stable	21.1%	
Infarction	14%	
Target vessel		
Anterior descending artery	58.8%	
Circumflex artery	10.3%	
Right coronary artery	29.4%	
Left main coronary artery	1.5%	
Type of lesion		
B_2	38.2%	
C	61.8%	
Lesion length	20.4±8.1 mm	(range, 5-42)
Stent length	24.7±8.5 mm	(range, 8-41)
Severe or moderate calcification	55.9%	
Severe or moderate tortuosity	29.4%	
Bifurcational lesions	23.5%	
Diffuse in-stent restenosis	8.8%	
Multivessel disease	68.4%	
Multivessel revascularization	26.3%	
Glycoprotein IIb/IIIa inhibitor use	39%	

proximal descending anterior artery in a 45-year-old woman with insulin-dependent diabetes after recanalization of a chronic total occlusion) and in whom, after locating a thrombosis at the ostium of the artery, surgical revascularization was done via a mammary artery graft. Clinical follow-up was achieved in 100% of the patients at 6 months and angiography of the first 50 treated lesions (42 patients). In addition to the two subacute thromboses, complications observed in clinical follow-up included cardiac death in one patient with diffuse and severe three-vessel disease who died of congestive heart failure (the same patient who developed AMI during her hospital stay) and a patient who presented angina at the fifth month, was diagnosed with proximal margin restenosis (Figure 2) and was treated with another Cypher stent. Two other patients presented effort angina which was attributed to other non-revascularized secondary vessels. The rest of the patients remained asymptomatic from a cardiological standpoint. Severe cardiac adverse events at 6-month follow-up are shown in Table 4. There were a total of four (7%) SCAE at clinical follow-up. At mid-term follow-up (8.7±3.1 months, with a 1-16 months

TABLE 3. **Cardiovascular Events During Hospital Stay***

Angioplasty success rate	100%
Mortality	0%
Q-wave infarction	1.75% (n=1)
Need for new revascularization	0%
SCAE	1.75% (n=1)

*SCAE indicates severe cardiovascular adverse event.

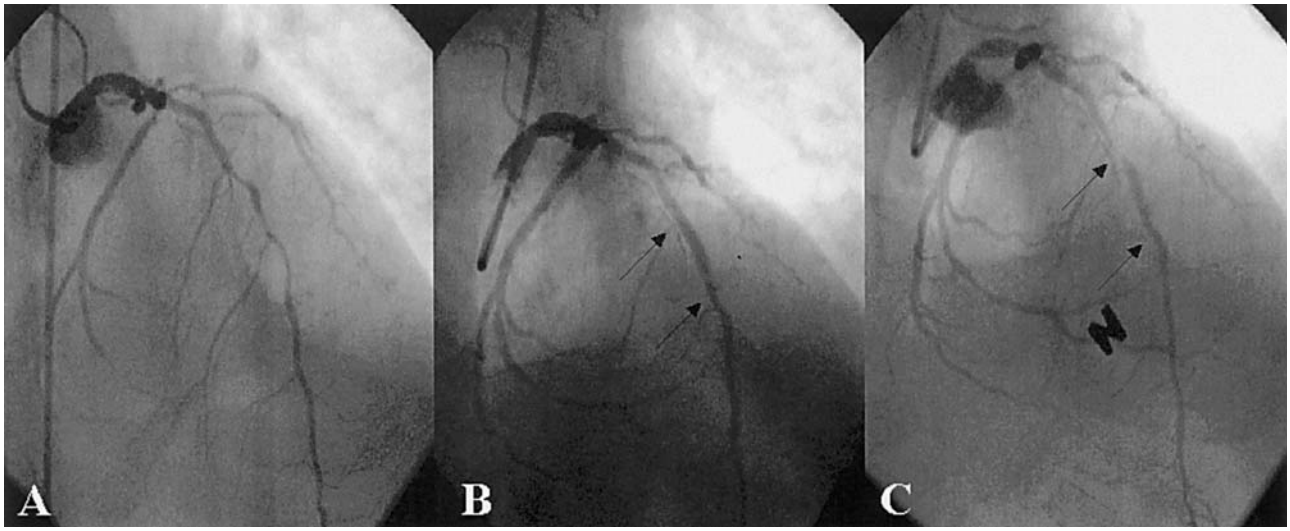

Fig. 2. Example of margin restenosis. A: left coronary arteriography in ROA 10°-cranial 40° projection where there is a long lesion in the medial segment of the anterior descending artery. B: result after implanting a 3.03×28 mm Cypher stent, deployed distal to the first septal branch. C: angiographic follow-up at 6 months in which very severe restenosis of the proximal margin of the stent can be seen. In images B and C, the arrows point to the proximal and distal extremes of the sirolimus-eluting stent.

TABLE 4. **Severe Cardiovascular Events at 6-Month Follow-Up***

Event	Percentage	Number
Cardiac death	1.75	1
Q-wave infarction	3.5	2
Need for new revascularization	3.5	2
Re-PTCA	1.75	1
Coronary surgery	1.75	1
SCAE	7	4

*PTCA indicates percutaneous transluminal coronary angioplasty; SCAE, severe cardiovascular adverse event.

interval) 90% of the patients were free of cardiac events and 93.5% were free from target vessel revascularization.

Of the 50 lesions electively reassessed angiographically (42 patients), we found only one in-stent angiographic restenosis (2%) in a patient who was asymptomatic and without ischemia during exercise testing, so we decided not to do a new angioplasty. Three patients presented margin restenosis, two in the proximal margin and one in the distal margin (a re-PTCA was done in one of these patients). Thus, in-segment restenosis appeared in four lesions (8%). The mean late loss was 0.27±0.59 mm. Data on angiographic quantification carried out during the procedure and at 6-month follow-up are shown in Table 5. There was no clinical or angiographic restenosis in the 6 diffuse or proliferative in-stent restenosis treated with the Cypher stent and this subpopulation remained asymptomatic and free of cardiovascular events.

TABLE 5. **Angiographic Quantification Data**

Reference diameter, mm		
Baseline	(n=68)	2.95±0.58
Postangioplasty	(n=68)	2.92±0.28
At 6 months	(n=50)	2.97±0.28
Minimum luminal diameter, mm		
Baseline	(n=68)	0.47±0.29
Postangioplasty	(n=68)	2.55±0.33
At 6 months	(n=50)	2.4±0.57
Percentage of stenosis		
Baseline	(n=68)	82.52±13.45
Postangioplasty	(n=68)	12.89±7.01
At 6 months	(n=50)	19.34±16.19
Late loss, mm	(n=50)	0.27±0.49
Percentage of restenosis, ≥50%	(n=50)	
In-stent		1 (2%)
Margin		3 (6%)
In-segment (total)		4 (8%)

DISCUSSION

Sirolimus-eluting stents have become available recently and there is no doubt that a large percentage of lesions and patients will be treated with this new therapeutic tool. The use of sirolimus has yielded such promising results in all the studies published that the number of patients who are considered potential beneficiaries of this type of stent is increasing and raises hope for an important and definitive reduction of in-stent restenosis. It is not unrealistic to think that, in the near future, the vast majority of coronary angioplasties will be done by implanting drug-eluting stents. However, until this becomes a reality the

number of drug-eluting stents available is limited, mainly due to their high cost, and thus it is necessary to select the patients who will benefit from them. When selecting the patients who will be revascularized with sirolimus-eluting stents, we have to take into account the clinical characteristics of the patient and the particular anatomical features of the target lesions. It seems reasonable to think that diabetic patients are a population who, due to their high rate of restenosis in angioplasties with standard stents, can benefit from these new devices.[14,16–18] However, in addition to this population, complex coronary lesions with an a priori high rate of restenosis with standard stents form another large group where the benefits of coated stents could yield better results. In our hospital we have been treating very long lesions, bifurcated lesions, total occlusions, ostial lesions and in-stent restenosis with the sirolimus-eluting Cypher stent, because the benefits of restenosis reduction are, in principle, higher than those in other more favorable lesions. However, these complex lesions are precisely the ones which have not been included in the clinical trials published up to the present.[13,14,16] Thus, the RAVEL study included very favorable lesions, and the SIRIUS study—although including a higher number of patients and complex lesions—also excluded the most complex lesions, which constitute an important percentage of interventions in cardiology centers.

In our study, the clinical results, both during hospital stay and especially in the mid-term, are genuinely positive with a very low incidence of severe cardiovascular events, which is the more striking as it concerns a population with a high risk of events, as assessed by their clinical characteristics (high percentage of diabetes and multivessel disease) and the angiographic characteristics of the lesions (very long and complex type B2 and C lesions). In our study, 90% of the patients revascularized with the Cypher stent were free of cardiovascular events at 6 months and 93.5% free from target vessel revascularization.

Regarding the results of the angiographies (carried out on the first 50 lesions), these were very positive, with a very low rate of angiographic in-segment restenosis (8%). Logically, due the complexity of the lesions, as well as the length and small diameter of the implanted stents (all the stents implanted were ≤3 mm diameter), the level of restenosis expected with standard stents would clearly have been higher.

With the advent of these new drug-eluting stents, the concept of "margin restenosis" has been created to refer to restenosis that can appear in the margins (5 mm) proximal and distal to the implanted stent. In the studies published to date, a percentage of lesions have been observed that show an absence of in-stent restenosis, but that present margin restenosis.[16] This means that, regarding restenosis in these types of stents, it would be more correct to refer to in-segment restenosis (a concept which includes in-stent restenosis and margin restenosis). In our series, three of the four in-segment restenoses were margin restenosis, and in-stent restenosis only appeared in one lesion (2%). The 3 patients with margin restenosis had similar characteristics: very long lesions where plaque was not completely covered despite using long stents (23-33 mm), and so a 20% residual lesion remained in the margins that seriously progressed over 6 months. All this indicates that, when treating complex lesions with sirolimus-eluting stents as well as more favorable lesions, the stent should not just cover the lesion but rather a slightly longer stent should be implanted. When analyzing the angiographic reevaluation, the most important finding is clearly the very low late loss, which is even more important when bearing in mind that all implanted stents were ≤3 mm diameter. We should point out that the angiographic reevaluation was carried out at 6 months and therefore does not provide any information on possible later restenosis.

We should also draw attention to subacute stent thrombosis. In our series, 2 patients presented subacute thrombosis (4%), which is, in principle, higher than expected. Although in one case there was a clear relationship with antiplatelet medication dropout, we should still exercise vigilance in this regard. Obviously, our series is very small, the lesions studied very complex and the implanted stents longer than those in ordinary practice. The Research study is a registry of 198 patients treated with the Cypher stent in which the incidence of subacute thrombosis with the sirolimus-eluting stent was studied, and was found to be similar to that of other stents.[19] This registry recommended double antiplatelet therapy for 6 months for the most complex lesions. After stopping this therapy, there were no cardiac events in our patients (at 9-12 months), although this information would have to be confirmed through longer follow-up and larger populations. Patients with more diffuse disease and more complex lesions can probably benefit from a more prolonged intense antiplatelet therapy, although this hypothesis should be substantiated in further studies.

It is doubtless that, in the not-too-distant future, coated stents will probably be used for most lesions in the field of coronary interventions.

It is to be expected that when most intracoronary stent manufacturers make drug-eluting stents available and demonstrate their effectiveness in reducing clinical restenosis and angiographies, competition will lead to price reductions and improvements in the platforms. Thus, the results published on paclitaxel-eluting stents are very positive, with restenosis at around 4%, although only very favorable lesions were studied.[20]

Obviously, we are dealing with a small series of patients and a descriptive study in which a random comparison of the treatment of these lesions with conventional stents has not been carried out. However, given this data, we consider that patients with complex lesions can greatly benefit from sirolimus-eluting stents, with very good clinical results in the mid-term and very low rates of angiographic restenosis.

CONCLUSIONS

Percutaneous treatment of patients with complex coronary lesions with sirolimus-eluting stents appears to be safe and yields a very high success rate, similar to that obtained with other uncoated stents. Patient evolution is very positive in the mid-term, with a very low incidence of cardiac events and a high survival rate free of cardiac events and target vessel revascularization. Furthermore, angiographic results at 6-month follow-up reveal a very low rate of angiographic restenosis and minimum late loss.

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